# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-233**

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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|---|---|
| **Date** | (electronic stamp) |
| **From** | Joyce Korvick<br>Deputy Director<br>Division of Gastroenterology Products<br>Office of New Drugs III<br>Center for Drug Evaluation and Research |
| **Subject** | Division Director Summary Review |
| **NDA/BLA #**<br>**Supplement #** | NDA 22-233 |
| **Applicant Name** | Helsinn Healthcare SA |
| **Date of Submission** | 10/24/2007 |
| **PDUFA Goal Date** | 8/24/2008 |
| **Proprietary Name /**<br>**Established (USAN) Name** | Aloxi (Palonosetron) Capsules |
| **Therapeutic Class** | Serotonin subtype 3($5\text{-}HT_3$) receptor antagonist |
| **Dosage Forms / Strength** | Oral/ 0.5 mg |
| **Proposed Indication(s)** | prevention of acute (b) (4) nausea and vomiting associated with initial and repeat course of moderately emetogenic cancer therapy (MEC) |
| **Action/Recommended Action:** | **Approval of indication for prevention of <u>acute</u> nausea and vomiting associated with initial and repeat course of moderately emetogenic cancer therapy (MEC).** |

# 1. Introduction

Helsinn Healthcare SA seeks approval of a single oral dose of palonosetron hydrochloride 0.5 mg for the "prevention of acute (b) (4) nausea and vomiting associated with initial and repeat course of moderately emetogenic cancer therapy (MEC)." Palonosetron 0.25 mg I.V. was approved in 2003 for the same proposed indication. In addition, I.V. palonosetron is approved for the "prevention of acute and delayed nausea and vomiting associated with initial and repeat course of highly emetogenic cancer therapy (HEC)."

There are four antiemetics of the 5HT-3 receptor antagonist class currently marketed in the United States: ondansetron, granisetron, dolasetron and palonosetron. Palonosetron is the last in the class to develop the oral formulation.

# 2. Background

The sponsor proposed to support approval of the oral product by providing data from a single pivotal phase 3 trial based on the similar dose-response relationship between oral administration and intravenous administration observed in phase 2 and 3 trials. The phase 3 trial compared oral administration of 0.25 mg, 0.5 mg and 0.75 mg capsules to 0.25 mg IV dosing, and tested for non-inferiority with a pre-specified margin of -15%. The primary endpoint was Complete Response (no vomiting and no rescue medication) in the 0 to 24 time interval after administration of moderately emetogenic chemotherapy.

An end-of-phase 2 meeting was held December 15, 2003 during which the sponsor proposed one large Phase 3 pivotal efficacy trial and one large repeat-cycle open label safety and efficacy trial for the oral palonosetron clinical development program. Based on FDA feedback from the meeting the sponsor submitted a Special Protocol Assessment (IND 42,886) and two amendments for pivotal study PALO-03-13.

Study PALO-03-13 was completed in August 2006, and results and questions were submitted to DGP in a pre-NDA background package. Specifically, the sponsor asked about the adequacy of sole pivotal phase 3 study PALO-03-13, and supporting phase 3 repeat-cycle study PALO-03-14. DGP responded that the submission would need to justify the pivotal study and its results as providing substantial evidence of efficacy, and identify other data sources and studies used for supportive evidence.

On October 22, 2007 the sponsor submitted two phase 3 efficacy studies PALO-03-13 and PALO-03-14 and one Phase 2 dose-ranging study (2332) to support the clinical efficacy and safety of Palonosetron (Aloxi®) Capsules in the treatment of prevention of acute (b) (4) nausea and vomiting associated with moderately emetogenic chemotherapy. Both phase 3 clinical studies were multinational, multicenter studies, however, only PALO-03-13 was a double blind evaluation whereas PALO-03-14 was an open label, uncontrolled study. In addition, an historical pooled analysis (PALO-07-36) and an exploratory analysis (PALO-07-35) were also submitted.

The proposed dose is 0.50 mg, to be taken orally 60 minutes before the start of chemotherapy. It is intended to be used in patients 18 years and older.

## 3. CMC

The chemistry review recommends approval of this formulation and that the sponsor provided adequate information to assure identity, strength, purity and the quality of the drug product. The EES and EA were adequate.

I concur with the conclusions reached by the chemistry reviewers. There are no outstanding issues.

## 4. Nonclinical Pharmacology/Toxicology

Nonclinical studies of palonosetron were reviewed under NDA 21,372. No new, nonclinical studies were submitted in the present application.

The reviewers recommended some wording changes to the proposed label in the following sections:
INFORMATION", "DRUG INTERACTIONS", "Pregnancy", "Nursing Mothers", "OVERDOSAGE", "Mechanism of Action", "Pharmacodynamics", and "NONCLINICAL TOXICOLOGY" (Carcinogenesis, Mutagenesis, Impairment of Fertility).

I concur with the recommendations made by the pharmacology/toxicology reviewer, and that there are no outstanding pharm/tox issues that preclude approval.

## 5. Clinical Pharmacology/Biopharmaceutics

The reviewers recommended that the dose be reduced to 0.25 mg from the proposed 0.5 mg. This recommendation was based upon data from the PALO-03-13 study: the dose of 0.25 mg was found to be effective and no dose-response relationship was demonstrated among the three dose levels of 0.25 mg, 0.5 mg and 0.75 mg. This recommendation is consistent with the finding that the absolute bioavailability of oral capsules was 97% and the approved dose for IV administration for the prevention of both acute and delayed CINV is 0.25 mg. The pharmacokinetics are linear over this dose range.

In phase 3 study PALO-03-13, the non-inferiority of all three oral doses 0.25, 0.5 and 0.75 mg was demonstrated to 0.25 mg palonosetron IV administration for CR0-24 i.e. the prevention of acute nausea and vomiting associated with moderately emetogenic chemotherapy. The percentage of patients with CR 0-24 was 73.5%, 76.3% and 74.1% for 0.25 mg, 0.50 mg and 0.75 mg oral doses, respectively. No formal statistical comparisons between the oral doses were pre-specified.

**PK parameters for palonosetron after a single-dose administration in healthy subjects and cancer patients.**

| Dose | Parameters | Healthy Mean (SD) | Cancer patients Mean (SD) |
|---|---|---|---|
| 0.25 mg[1] capsule | $C_{max}$ (ng/ml) | n/a | 0.55 (0.23) |
| | $T_{max}$[2] (h) | n/a | 6 (1-47.4) |
| | $AUC_{\infty}$ (ng·h/ml) | n/a | 34.2 (13.6) |
| 0.5 mg capsule | $C_{max}$ (ng/ml) | 0.81 (0.16) | 0.93 (0.34) |
| | $T_{max}$[1] (h) | 5.0 (2-8) | 3.5 (1-23.4) |
| | $AUC_{\infty}$ (ng·h/ml) | 38.2 (11.7) | 49.7 (12.2) |
| 0.75 mg capsule | $C_{max}$ (ng/ml) | 1.2 (0.32) | 1.42 (0.36) |
| | $T_{max}$[1] (h) | 4.5 (2-12) | 4 (1-23.3) |
| | $AUC_{\infty}$ (ng·h/ml) | 58.3 (18.1) | 103.3 (37.3) |

[1] PK following a 0.25 mg dose capsule administration was not studied in healthy subjects. The closest dose studied in healthy subject was 3 μg/kg which corresponds to 0.21 mg (70 kg BW) using an oral solution.
[2] median (min-max)

Study 2332, a phase 2 dose-response study for efficacy over doses 0.3, 1, 10, 30 ad 90 ug/kg was studied. Complete Response for the oral formulation was best for each of the highest groups, with 10 ug/kg having the highest response rate (approximately 50%). The lowest response was seen in the 3 ug/kg treatment group. The proposed single oral dose of 0.50 mg would be between the two doses tested. Therefore, it may have resulted in a higher response rate if it had been studied in this trial.

The reviewers commented that the DSI inspection was acceptable,

I have read the clinical pharmacology review and have a different recommendation. I recommend approval of the 0.5 mg dose. While the reviewers consider that the 0.25 mg dose is the lowest effective dose, from a clinical point of view several factors must be considered.

1. While not statistically significant, there is a trend to increased efficacy of the 0.5 mg dose in PALO-03-13.
2. There is only one pivotal efficacy study. A future study powered to detect the differences between the various doses would need to be performed to definitively prove which dose is better.
3. Women had a lower response rate than men overall, however, the response was best in the 0.50 mg dose group (71%) and so choosing the 0.5 mg dose will bring the efficacy in women closer to that in men.
4. There are no apparent differences in the safety of the three doses tested. In addition, previous through QT studies have demonstrated safety to a maximum single dose of 2.25 mg. Therefore, the exposure to this single dose is expected to be safe.

Therefore I agree with the sponsor that the recommended dose should be 0.5 mg.

I concur with the other conclusions reached by the clinical pharmacology/biopharmaceutics reviewer regarding labeling and that there are no outstanding clinical pharmacology issues that preclude approval.

# 6. Clinical Microbiology

*NA- this is an oral formulation*

# 7. Clinical/Statistical-Efficacy

Study PALO-03-13 was the pivotal study. It was a multicenter, randomized, double-blind active control clinical trial of 635 patients set to receive moderately emetogenic cancer chemotherapy. A single-dose of 0.25 mg, 0.5 mg, or 0.75 mg oral ALOXI capsules given one hour prior to moderately emetogenic chemotherapy was compared to a single-dose of 0.25 mg I.V. ALOXI given 30 minutes prior to chemotherapy. Patients were randomized to either dexamethasone or placebo in addition to their assigned treatment. The majority of patients in the study were women (73%), white (69%), and naïve to previous chemotherapy (59%). The primary efficacy endpoint was Complete Response (no emetic episodes and no rescue medication) assessed in the acute phase (0-24 hours). A key secondary efficacy endpoint was Complete Response assessed in the delayed phase (24-120 hours). Other secondary endpoints included Complete Response for the acute plus delayed phases (0-120 hours) and No Nausea for the acute and delayed phases.

The medical review concluded the following:
"The medical reviewer recommends approval of 0.50 mg palonosetron oral capsules for the prevention of chemotherapy induced nausea and vomiting during the acute, 0 to 24 hour, time period."

"The sponsor is requesting the indication of prevention of acute (b) (4) nausea and vomiting associated with the administration of chemotherapeutic agents of moderate emetogenic potential, during initial and repeat administrations of chemotherapy for 0.50 mg palonosetron oral capsules. Acute CINV is defined as nausea and vomiting that occurs within 24 hours of receiving chemotherapy, and delayed CINV is nausea and vomiting that occurs from 24 to 120 hours after chemotherapy.)

"Efficacy in the acute phase was demonstrated for all 3 oral palonosetron dosages, based on a demonstration of non-inferiority to the active control, I.V. palonosetron with respect to the efficacy parameter of complete response. No oral dosages showed non-inferiority to the active comparator in the delayed phase, but 0.50 mg came closest to the NI margin."

**Table 3: Proportion of Patients Achieving Complete Response Post-Chemotherapy (**PALO-03-13**)**

| Time Period | Oral ALOXI 0.5 mg (N=160) | I.V. ALOXI 0.25 mg (N=162) | Difference [Two-sided 98.3% Confidence Interval]*: Oral ALOXI minus I.V. ALOXI Comparator |
|---|---|---|---|
| 0-24 hr | 76.3% | 70.4% | 5.9% [-6.5%, 18.2%] |
| 24-120 hr | 62.5% | 65.4% | -2.9% [-16.3%, 10.5%] |

* To adjust for multiplicity of treatment groups, a lower-bound of a two-sided 98.3% confidence interval was used to compare to -15%, the negative value of the non-inferiority margin.

"As indicated in the data above, analysis of the key secondary endpoint showed that a single dose of ALOXI Capsules 0.5 mg was numerically similar to a single dose of I.V. ALOXI 0.25 mg, however, statistical non-inferiority was not demonstrated. For ALOXI Capsules 0.5 mg versus I.V. ALOXI 0.25 mg, the proportion of patients with complete response at 0-120 hours was 58.8% versus 59.3%, respectively. The proportions of patients with no nausea at 0-24 and 24-120 hours were also numerically similar between oral and I.V. doses."

In other words, there were no statistical tests pre-specified to determine the differences between the oral doses. Therefore, I agree with the medical reviewer that the numerical trend for the 0.5 mg dose is favorable.

Regarding the Initial and Repeat dose language in the label, I have the following comments. The pivotal efficacy study PALO-03-13 included patients who were both naive and non-naive to MEC. The results in these sub-populations were similar, thus effective for initial and repeat doses.

**Complete Response by Cycle (full analysis set, N = 654)**

| | Palonosetron 0.75 mg (N=171) | | | Palonosetron 0.75 mg + Dexamethasone (N=483) | | | Total (N=654) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $CR_{0-24h}$ | $CR_{24-120h}$ | $CR_{0-120h}$ | $CR_{0-24h}$ | $CR_{24-120h}$ | $CR_{0-120h}$ | $CR_{0-24h}$ | $CR_{24-120h}$ | $CR_{0-120h}$ |
| Cycle 1 | (N=53) | | | (N=164) | | | (N=217) | | |
| | 66.0 | 60.4 | 54.7 | 78.0 | 63.4 | 57.3 | 75.1 | 62.7 | 56.7 |
| Cycle 2 | (N=49) | | | (N=137) | | | (N=186) | | |
| | 57.1 | 59.2 | 46.9 | 75.2 | 63.5 | 62.0 | 70.4 | 62.4 | 58.1 |
| Cycle 3 | (N=40) | | | (N=103) | | | (N=143) | | |
| | 67.5 | 65.0 | 57.5 | 73.8 | 62.1 | 61.2 | 72.0 | 62.9 | 60.1 |
| Cycle 4 | (N=28) | | | (N=79) | | | (N=107) | | |
| | 50.0 | 50.0 | 46.4 | 63.3 | 63.3 | 58.2 | 59.8 | 59.8 | 55.1 |

(Source: Clinical Study Report: Study PALO-03-14; Table 1, page 12)

Further the sponsor performed PALO-03-14 which was opened label. The response appeared numerically similar to that seen in the PALO-03-13. It was considered supportive due to the opened-label nature of the study. These two pieces of data support the approval of this wording in the current label. A similar strategy was used for the approval of the IV formulation. These studies show similar results. Finally, although PALO-03-14 used the 0.75 mg dose, given the similar efficacy of the 0.5 mg dose demonstrated in the PALO-03-13, it is appropriate to conclude that it would be effective in repeat cycles.

I agree with the medical reviewer regarding the approval of the indication for prevention of acute nausea and vomiting and have outlined my rationale for including the words "initial and repeat cycle" in label.

Additional statistical concerns regarding randomization and historical analyses were outlined in the reviews by Kate Dwyer and Wen-Jen Chen. For complete details please refer to their reviews. Their final recommendation was for approval of the indication as I have stated it.

# 8. Safety

The medical team commented that "The safety of palonosetron was demonstrated in trials supporting the I.V. formulation, and in post-marketing data. In the current submission adverse events are consistent with those already known to be associated with this drug. A dosage of 0.50 mg is recommended for marketing due to its favorable safety and efficacy profile." I agree with this conclusion.

- **Postmarketing data:**
  - No new safety signals were detected in the ISS which includes post-marketing data

- **DRisk Review:**
  - Comments from the DRisk regarding the Patient Package Insert (PPI) were acceptable to the medical review team. The review team discussed the Patient Package Insert and felt that the drug could be used safely without it. There are no significant safety issues which need to be conveyed tot ehpat8ient for safe use. Therefore, it does <u>not</u> need to be converted to a Med Guide and will not trigger FDAAA REMS program.

- **Trade Name:** Review of the Trade Name by Division of Medication Error Prevention and Analysis allowed the name, but they have a few concerns. Aloxi IV is currently approved and marketed; however, they felt that the name may result in "potential name confusion with the existing products, Adoxa, Alora and Olux-E. Although this finding would typically lead the DMEPA to object to the proposed proprietary name, FMEA of alternatives approaches to address this name confusion, including a new name for palonosetron capsules, a new name for all palonosetron HCL products, or use of a modifier with the name, also found potential opportunities for medication errors. As the FMEA noted some detectability of the medication errors resulting from name confusion, we will not object to the use of the name, Aloxi, for this product." They did provide the recommendation to be sent to the sponsor regarding the monitoring of medication errors related to Aloxi and report these errors to the Agency regardless of the severity of the adverse events. This was considered routine by DMEPA and did not require a communication plan which would trigger FDAAA.

- **Final safety labeling recommendations:**

Safety recommendations were centered on the PPI. Comments were incorporated which described the signs and symptoms for the rare allergic reactions that have been reported with the IV formulation.

- **REMS/RiskMAPs/PMRs**
  The only PMR includes the PREA commitments (see pediatric section).

- **Advisory Committee Meeting:**
  *NA- no AC was held for this application because it presented now new issues, and was a routine change in formulation from the IV Aloxi currently marketing.*

# 9. Pediatrics

There are currently 2 PMCs (post-marketing commitments) for study of pediatric patients in the IV NDA 21372 for MEC and HEC. The Pediatric committee recommended that we request studies with oral formulations in the age range similar to that of the IV formulations 1 month and above. In this case we agree, however, it was noted that the capsule formulation is not appropriate for pediatric patients less than 4 years of age. However, we waived studies less than one month and deferred studies in pediatric patients greater than 1 month. The reason for this recommendation from the pediatric group is that the IV studies are not completed, at that time the IV formulation may be considered the age appropriate formulation for the under 4 years of age group. At that time the deferral for the oral formulation can be re-addresses regarding the age ranges.

We waived pediatric studies less than 1 month of age due to the impracticability and the small number of pediatric patients available for study.

A written request for this molecular entity is currently being developed.

# 10. Other Relevant Regulatory Issues

- **DSI Audits:** DSI clinical audits were conducted at 4 centers which participated in the pivotal clinical trial. The written review comments on 3 centers since the forth inspection was pending at that time. Verbal communications today with Dr. Malek were conducted (RPM – Jagjit Grewal). He noted that he had been in contact with the field investigator who finalized his review. This did not differ from the draft the field had sent Dr. Malek. Based upon these communications, Dr. Malek felt that we could proceed with approval and that there would be no significant deficiencies precluding approval.

- **Financial Disclosure:** form submitted and acceptable.
- **SEALD:** *N/A*

# 11. Labeling

- **Physician labeling:**

The major areas of discussion centered on the indications and clinical trials sections of the label.

1. The indication which was supported by the application was for prevention of **ACUTE** nausea and vomiting in **INITIAL** and **REPEAT** course moderately emetogenic chemotherapy. (See clinical trials section for my discussion of this issue)

2. The results from the pivotal trial were described in detail beyond what the clinical and statistical reviewers felt were appropriate given the multiplicity issue and the lack of pre-specification. The focus was to provide physicians information without over representing the data. (b) (4)

Refer to the final label included in the approval letter for further details.

- **Carton and immediate container labels:** Recommendations from DRISK were acceptable to the sponsor who made the appropriate changes.
- **Patient labeling:** This included a Patient Package Insert (see above).

## 12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** I recommend approval of this supplement with the agreed upon labeling changes. This is agreement with review team recommendations, with one exception. (b) (4)

- **Risk Benefit Assessment:**
  The Risk Benefit has not changed with reformulation to the oral form of palonosetron for the redefined indication as described in the approval recommendations. The safety profile has not changed.

- **Recommendation for Postmarketing Risk Management Activities:**
  No REMS were recommended.

- **Recommendation for other Postmarketing Study Commitments (PMC)**
  No PMCs were recommended by the team.

| **Material Reviewed/Consulted:** OND Action Package | **Reviewer** |
|---|---|
| Medical Officer Review | Nancy Snow |
| Medical Team Leader Review | Hugo Gallo-Torres |
| Statistical Review | Kate Dwyer (8/22/08), Wen-Jen Chen |
| Pharmacology Toxicology Review | David Joseph |
| Clinical Pharmacology Review | Insook Kim |
| CMC Review | Zhengfang Ge |
| DSI Clinical Site Inspection summary | Khairy Malek |
| OSE/Division of Risk Management Review | Sharon Mills |
| OSE/Division of Medication Error Prevention Review | Richard Abate |

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
SEALD=Study Endpoints and Label Development Division

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Joyce Korvick
8/22/2008 05:24:44 PM
MEDICAL OFFICER