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# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-372

# Statistical Review(s)

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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| **NDA/Serial Number:** | 21- 372 / N000 |
| **Drug Name:** | Palonosetron HCl 0.25mg/5ml |
| **Indication(s):** | Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy |
| **Applicant:** | Helsinn Healthcare S.A. |
| **Dates:** | Submitted: 26 September 2002 |
| **Review Priority:** | Standard (10-month) |
| **Biometrics Division:** | Division of Biometrics 2 (HFD-715) |
| **Statistics Reviewer:** | Stella Grosser, Ph.D. |
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**Keywords:** minimization, active control trials, non-inferiority, meta-analysis.

## 1. Executive Summary

### 1.1 Conclusions and Recommendations

There is sufficient evidence and reasonable certainty that palonosetron 0.25 mg is efficacious in the prevention of acute nausea and vomiting following moderately and highly emetogenic cancer chemotherapy. There is also sufficient evidence that it is efficacious in the prevention of delayed emesis following moderately (but not highly) emetogenic chemotherapy. While the efficacy analyses are based on comparisons to approved anti-emetics (ondansetron and dolasetron), the efficacy conclusions and claims are relative to placebo; the label should reflect this distinction.

### 1.2 Brief Overview of Clinical Studies

The applicant proposes a single, intravenous injection of palonosetron 0.25 mg, given 30 minutes prior to moderately or highly emetogenic chemotherapy. Eighteen clinical trials were conducted to study the safety and efficacy of palonosetron. Of these, four are presented in support of the applicant's claim of efficacy of palonosetron 0.25 mg IV to prevent chemotherapy-induced nausea and vomiting (CINV) and are reviewed here. Two are for the prevention of CINV following moderately emetogenic chemotherapy (PALO-99-03 and PALO-99-04) and two are for the prevention of CINV following highly emetogenic chemotherapy (2330/PALO-00-01 and PALO-99-03).

Studies PALO-99-03, 99-04, and 99-05 were double-blind, multicenter, active-controlled studies enrolling 570, 592 and 680 patients respectively. They were conducted in Europe, including Russia, (99-03 and 99–05), and North America (99-04 and 99–05). Each study had three arms: 0.25 mg IV palonosetron, 0.75 mg IV palonosetron, and an active comparator (ondansetron 32 mg IV in 99-03 and 99-05, dolasetron 100 mg IV in 99-04). Allocation to treatment was a mixture of algorithms primarily relying on minimization rather than randomization. That is, the assignment of a new patient to a group was made to minimize differences among the treatment groups. Balance among the groups was in terms of the number of patients assigned to each stratum defined by prognostic criteria of gender, chemotherapy history (naïve or not naïve) and use of corticosteroids. This scheme does not correspond to what is usually thought of as randomization in a clinical trial. It most closely resembles a deterministic dynamic allocation procedure.

Study 2330 was designed as a phase 2 study using the IV formulation of palonosetron. It was a randomized, double-blind, multicenter, dose-ranging trial of palonosetron given to chemotherapy-naïve patients 30 minutes before the administration of highly emetogenic chemotherapy. The enrolled population consisted of 161 subjects. Palonosetron was administered at weight-based doses of 0.3, 1, 3, 10 or 30 μg/kg. Helsinn considers study 2330 supportive. It was a dose-ranging study conducted by the drug innovator Syntex. It used a weight-based dosing regimen, which was roughly translated into the eventual (fixed) dosing regimen.

### 1.3 Statistical Issues and Findings

A primary concern from a statistical point of view is the minimization allocation procedure used in studies PALO-99-03, PALO-99-04 and PALO-99-05. It is not randomization, but rather a deterministic allocation with the occasional random assignment. Several drawbacks of using minimization have been cited in the literature (Scott et al., 2002). The concern in this application is that standard statistical tests, or, equivalently, confidence interval calculations, make the assumption of random allocation: more generally, "the correct statistical analysis is complex and not yet clearly worked out." (Scott et al., 2002) Permutation methods can be used to check the results of standard analyses. The two approaches are likely but not guaranteed to yield similar conclusions; there are situations where the standard methods are very misleading. These situations have not been completely characterized and a permutation test is a good way to know whether the trials in this application fall into the problematic case. Apparently they do not: The results of the permutation analysis are in accordance with the primary, standard analysis.

None of the efficacy trials done as part of this application included a placebo control. To assess trial validity and justify the value of delta used to declare non-inferiority of palonosetron to ondansetron or dolasetron, an examination and meta-analysis of results from the anti-emetic literature was carried out. In the few studies where ondansetron or dolasetron was directly compared to placebo, the active treatment reliably out-performed placebo to a greater extent than seen between treatments in the trials in this application. A less direct comparison of the effects of setron treatments and placebo, achieved through logistic regression modeling by the applicant, yielded similar results and similar confidence in the assay sensitivity of the NDA studies. The magnitudes of the differences found or modeled in the meta-analysis also were large enough to justify a conclusion of non-inferiority of palonosetron in the current trials.

In studies PALO-99-03, 99-04, and 99-05, a higher proportion of the patients responded to palonosetron than to the comparator anti-emetics. Response rates ranged from a low of 57%, for ondansetron 32 mg following the administration of highly emetogenic chemotherapy, to a high of 81% for palonosetron 0.25 mg following moderately emetogenic chemotherapy

The applicant calculated the two-sided 97.5% confidence interval of the difference between the proportions of complete response in each dose of palonosetron and comparator (calculated as palonosetron minus comparator) to demonstrate non-inferiority of palonosetron to the comparators. In all cases, the lower boundary of the interval was above -10%, implying a reasonable certainty that the proportion of complete responders to palonosetron was no less than 10% less than the proportion among the comparators. Results of the permutation test confirmed these conclusions.

The applicant wishes to include a secondary outcome as part of the labeled indication, namely that palonosetron is effective for prevention of delayed nausea and vomiting. Following highly emetogenic chemotherapy (PALO-99-05), the rates of complete

response are consistently numerically higher for palonosetron 0.25 mg; however, there is no time period for which palonosetron is statistically significantly higher than the comparator ondansetron (as judged by the lower limit of the confidence interval of the difference). Following moderately emetogenic chemotherapy, the rates of complete response again are consistently numerically higher for palonosetron 0.25. It is statistically significantly higher than ondansetron at all time periods other than the final 96-120 hours, when there are high response rates in all three treatment arms; its performance against dolasetron is mixed, but is statistically significantly higher than for the overall time period 24-120 hours.

The results for the primary efficacy outcome for study PALO-00-01 (essentially the same as study 2330) support the choice of 0.25 mg as a threshold efficacy dose and confirm the results of 99-05 for highly emetogenic chemotherapy.

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