There were some weaknesses in the study. The exclusion criteria for this study excluded non-naïve patients who had moderate to severe nausea with prior chemotherapy. This could have led to bias with a more favorable response in the non-naïve group. However, the results do not demonstrate such a bias. If a site only had one drug available, the patient was automatically enrolled in that treatment arm. This does not reflect true randomization. However, this only occurred in five patients (2 in each of the palonosetron arms, and 1 in the ondansetron arm) Although the palonosetron seems to demonstrate some efficacy at 120 hours, some factors need to be considered. The p-values were not adjusted for multiple endpoints. Since there were multiple secondary endpoints, there may be issues with multiplicity. In addition, the comparator arm ondansetron is not indicated for prevention of CINV at 120 hours. Thus, what the results may be demonstrating is that the nausea from the chemotherapy is simply wearing off.

B. Safety

In general, the palonosetron was well tolerated in this study. There was a high rate of treatment adverse events in all three study arms. The rate was highest for the patients in the palonosetron 0.75 mg group. Cancer patients undergoing chemotherapy generally have a high rate of complications and co-morbid illness so the high rate is not unexpected. The number of serious adverse events was equal in all groups.
Adverse events of the blood and lymphatic system were most common in all treatment groups. These were equally spread out in all treatment groups and were secondary to chemotherapy. Following the blood and lymphatic disorders, headache was the most frequently reported adverse event. This also was balanced in all treatment arms. The majority of adverse events in all treatment arms were of mild intensity. The rate of severe adverse events was slightly higher in the palonosetron groups compared to the ondansetron group. The body system most frequently involved for severe adverse events was neutropenia (2/187, 1.1%) for the 0.25 mg palonosetron group and leukopenia (2/188, 1.1%) for the 0.75 mg palonosetron group. All the serious adverse events in the palonosetron group were judged to be unrelated or unlikely to be related to the study drug. One patient in the 0.75 mg palonosetron arm had to withdraw from the study due to debility. This adverse event was described as severe was thought to be possibly related to the study drug. There were 4 deaths reported during the study. Three occurred in the palonosetron 0.75 mg group and 1 in the ondansetron group. All deaths were judged as either unlikely or unrelated to the study drug.

No significant safety issues were seen in vital signs, blood, or urine laboratory parameters. The majority of patients had no change in ECG. The 0.25 mg palonosetron group had the least number of patients with worsening ECG's. There were no significant differences seen between treatment groups on QTc. The 0.25 palonosetron group showed a slight decrease in QTc in some intervals when corrected with Bazett's formula. Ondansetron arm had the highest QT/QTc mean maximum change in duration. A subset of patients had underwent Holter monitor. A similar percentage of abnormalities (15% vs 14.3%) were seen in the 0.25 mg palonosetron group compared to the ondansetron group.

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Narayan Nair
7/2/03 12:04:52 PM
MEDICAL OFFICER

Joyce Korvick
7/2/03 12:53:00 PM
MEDICAL OFFICER

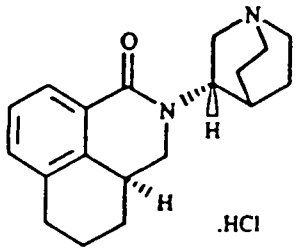
CLINICAL REVIEW

Medical Officer Review of NDA 21-372
Palonosetron

Date Submitted: 26 September 2002
Date Received: 27 September 2002
Date Assigned: October 1 2002
Date Completed: 6 June 2003

Applicant: Helsinn Healthcare SA
Via Pian Scairolo
6912 Pazzallo (Lugano) - Switzerland

Drug: Generic Name - Palonosetron
Molecular Weight - 332.87
Molecular formula - $C_{19}H_{24}N_2O.HCl$
Molecular structure –



Drug Class: 5-HT_3 antagonists

Formulation: 5-ml vial of palonosetron injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate and citrate buffer in water

Route of Administration: Intravenous

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