FINAL CDEC RECOMMENDATION

PALONOSETRON CAPSULE
(Aloxi — Eisai Limited)
Indication: Chemotherapy-Induced Nausea and Vomiting

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that oral palonosetron not be listed.

Reasons for the Recommendation:
1. There were no direct or indirect comparisons of oral palonosetron against other oral 5-HT_3 antagonists for the treatment of chemotherapy-induced nausea and vomiting.
2. Oral palonosetron failed to demonstrate non-inferiority against intravenous (IV) palonosetron for delayed chemotherapy-induced nausea and vomiting.

Background:
Palonosetron is a 5-HT_3 receptor antagonist. Oral palonosetron has a Health Canada indication for the prevention of acute nausea and vomiting associated with moderately emetogenic chemotherapy. Oral palonosetron is available as a 0.5 mg capsule and the dose recommended in the product monograph is 0.5 mg, administered one hour before the start of chemotherapy.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of oral palonosetron, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information
The following is a summary of information provided by the single patient group that responded to the CDR Call for Patient Input.
- The impact of the nausea and vomiting associated with chemotherapy can range from mild symptoms to severe disruption in the everyday lives of patients. It can also affect a patient's ability or desire to continue chemotherapy.
- Patients reported that currently available treatments to prevent nausea and vomiting associated with chemotherapy have not always been accessible or effective.

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Clinical Trials

The systematic review included one, double-blind, non-inferiority RCT of adult men and women who were scheduled to receive moderately emetogenic chemotherapy (PALO-03-13). Patients were randomized to a single dose of oral palonosetron 0.25 mg, 0.5 mg or 0.75 mg or IV palonosetron 0.25 mg administered before chemotherapy (N = 651). Patients were also randomized 1:1 to IV dexamethasone 8 mg or matching placebo administered immediately after palonosetron.

The trial was conducted in 46 centres in Europe, Mexico, and the United States. The majority of patients were women (> 70%) and the mean age was 56 years. Breast cancer was the most common type of cancer, followed by liver and lung cancers. The Karnofsky index was greater than 90%. More than half of the included patients had not received prior chemotherapy. Rescue antiemetic medication, other than a 5-HT_3 antagonist, was permitted after the start of chemotherapy.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Complete response in the acute phase — defined as no emesis and no rescue medication in the first 24 hours following the administration of chemotherapy.
- Complete response in the delayed phase — defined as no emesis and no rescue medication 24 hours to120 hours following the administration of chemotherapy.
- Complete control — defined as complete response and no more than mild nausea.
- Nausea, emesis, and use of rescue medication.
- Patient daily global satisfaction — measured using a 100 mm visual analogue scale with 0 corresponding to “not at all satisfied” and 100 to “totally satisfied.”
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome of PALO-03-13 was complete response in the acute phase. The prespecified criterion for non-inferiority between oral and IV palonosetron was a –15% difference in the proportion of complete responders using the lower bound of the two-sided 98.3% confidence interval (CI).

Results

Based on the Health Canada-recommended dosing, CDEC focused their discussion on the results comparing oral palonosetron 0.5 mg and IV palonosetron 0.25 mg.

Efficacy

- Oral palonosetron 0.5 mg was non-inferior to IV palonosetron 0.25 mg for the proportion of patients with a complete response in the acute phase in both the full-analysis set (80.3% versus 75.5%; risk difference [RD]: 4.8% [98.3% CI, –7.4 to 16.9]) and the per-protocol set (76.3% versus 70.4%; RD: 5.9% [98.3% CI, –6.5 to 18.2]).
- Oral palonosetron 0.5 mg did not demonstrate non-inferiority compared with IV palonosetron 0.25 mg for the proportion of patients with a complete response in the delayed phase, as the lower bound of the CI was below –15% for both the full-analysis set (RD: –2.9% [98.3% CI, –16.3 to 10.5]) and the per-protocol set (RD: –4.9% [98.3 CI, –18.6 to 8.7]).

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- Exploratory, post-hoc, analyses performed with the full-analysis set suggested that oral palonosetron 0.5 mg was non-inferior to IV palonosetron for the following secondary end points:
  - the proportion of patients without nausea in the acute and delayed phase
  - the proportion of patients without emesis in the acute and delayed phase
  - the proportion of patients without rescue medication in the acute and delayed phase
  - the proportion of patients with complete control in the acute phase.
- There were no significant differences between oral palonosetron 0.5 mg and IV palonosetron 0.25 mg with respect to patient satisfaction.

Harms (Safety and Tolerability)

- The proportion of patients with at least one serious adverse event was greater with oral palonosetron 0.5 mg group compared with IV palonosetron (6% versus 1%). A total of 19 serious adverse events were reported with the 0.5 mg oral dose compared with two events with the 0.25 mg IV dose. One patient in the 0.5 mg oral dose palonosetron group died.
- The proportion of patients with at least one adverse event was similar in the oral and IV palonosetron groups (47.2% versus 47.9%). Adverse events were commonly associated with the gastrointestinal tract and the central nervous system.
- No patients in either treatment group withdrew from the trial due to adverse events.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing oral palonosetron with oral ondansetron using data from two clinical trials for the IV form of palonosetron (PALO-99-03 and PALO-99-04). Two scenarios were considered for the treatment of chemotherapy-induced nausea and vomiting due to moderately emetogenic chemotherapy: two-drugs (5-HT_3 plus dexamethasone) and three-drugs (5-HT_3 plus dexamethasone plus aprepitant). The reference case time horizon in the model was set at five days to cover the average length of a single chemotherapy cycle. The manufacturer reported that for the two-drug regimen, palonosetron compared with ondansetron is associated with an incremental cost per QALY gained of $13,063, and $9,175 for the three-drug regimen.

A number of limitations were noted with the economic submission:

- The estimated difference in QALYs between the two treatment strategies is exceedingly small (~0.001 QALYs gained with palonosetron).
- There are areas of uncertainty in many of the model assumptions, which may influence results:
  - There are no direct comparisons of oral palonosetron and oral ondansetron, and no formal indirect comparison was performed.
  - The manufacturer used efficacy parameters from studies of IV palonosetron.
- The incremental costs are primarily related to drug costs. Where ondansetron is administered for two to three days as per clinical practice in Canada (compared with five days in the model), the incremental cost-utility ratio increases to $39,581 and $27,303 per QALY for the two-drug and three-drug regimens, respectively.
- The model assumed that the efficacy of oral palonosetron is the same as IV palonosetron; however, PALO-03-13 failure to confirm non-inferiority for oral versus IV palonosetron for nausea and vomiting in the delayed phase.

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- It has not been established that oral palonosetron is superior to oral ondansetron, and thus, there may be no incremental QALYs generated (i.e., no clinical benefit established, but higher costs of oral palonosetron).

The cost of oral palonosetron ($66 for 0.5 mg) is greater than that of other 5-HT_3 antagonists (dolasetron $29 [100 mg oral] and granisetron $27 [2 mg oral]), and greater than or similar to ondansetron depending on the duration of use ($31 for 2.5 days to $66 for 5 days).

Other Discussion Points:
CDEC noted the following:

- In PALO-03-13, patients who had experienced moderate to severe chemotherapy-induced nausea and vomiting (i.e., refractory patients) with past chemotherapy cycles were excluded. Hence, the results may only be generalizable to patients who are naive to chemotherapy and those with a better tolerance for chemotherapy.

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:

- There are no direct or indirect comparisons of oral palonosetron against other orally administered 5-HT_3 antagonists.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

February 20, 2013 Meeting

Regrets:

Two CDEC members did not attend the meeting.

April 17, 2013 Meeting

Regrets:
None

Conflicts of Interest:

None

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About this Document:
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The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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