CDEC FINAL RECOMMENDATION

PALONOSETRON INJECTION
(Aloxi IV – Eisai Limited)
Indication: Chemotherapy-Induced Nausea and Vomiting

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that intravenous (IV) palonosetron not be listed at the resubmitted price.

Reason for the Recommendation:
At the confidential resubmitted price, the cost of treatment with palonosetron (*[confidential price removed at manufacturer's request]*) is greater than dolasetron ($29 for 100 mg oral), granisetron ($27 for 2 mg oral), and ondansetron ($31 for moderately emetogenic chemotherapy [MEC] and $42 for highly emetogenic chemotherapy [HEC], for a single IV dose followed by 2.5 days of oral therapy). Given the differences in the administration of ondansetron in the included clinical trials (single IV dose on day 1) compared with the economic model (2.5 days of oral doses), CDEC concluded that there was considerable uncertainty in the cost-effectiveness analyses for both HEC and MEC.

Background:
Palonosetron is a 5-HT_3 receptor antagonist. Palonosetron IV has Health Canada indications for the prevention of acute and delayed nausea and vomiting associated with MEC; and acute nausea and vomiting associated with HEC, including high-dose cisplatin. Palonosetron IV is available as an injectable solution of 0.25 mg per 5 mL. The Health Canada-recommended dose is 0.25 mg administered by IV 30 minutes before the start of chemotherapy.

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

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. Nausea and vomiting can also affect a cancer patient's ability or desire to continue chemotherapy.
- Patients reported that currently available treatments are not always accessible or effective.

Clinical Trials

The systematic review included four double-blind, parallel, non-inferiority RCTs of adults planned to receive cancer chemotherapy. Studies PALO-99-05 (N = 667) and Yu et al. (N = 208) were conducted in patients receiving HEC, while studies PALO-99-03 (N = 570) and PALO-99-04 (N = 592) were conducted in patients receiving MEC. The PALO studies compared IV palonosetron 0.25 mg or 0.75 mg with IV ondansetron 32 mg (PALO-99-03 and PALO-99-05) or IV dolasetron 100 mg (PALO-99-04). In Yu et al., IV palonosetron 0.25 mg was compared with IV granisetron 3 mg.

The PALO studies were conducted in North America and various European countries; whereas, the Yu et al. study was conducted exclusively in China. PALO-99-03 and PALO-99-04 included a large proportion of women (> 70%); whereas, the Yu et al. study included mostly men (> 60%). The study population in PALO-99-05 included an equal proportion of men and women. The mean age ranged from 50 to 56 years across all trials. The mean Karnofsky index in all studies was greater than 87%. Approximately 40% to 66% of patients had not received prior chemotherapy. Rescue antiemetic medication 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 to 120 hours following the administration of chemotherapy.
- Complete control – defined as complete response and no more than mild nausea.
- Patient daily global satisfaction – measured using a 100 mm visual analog scale with 0 corresponding to "not at all satisfied" and 100 to "totally satisfied."
- Functional Living Index-Emesis questionnaire – consisted of nine questions related to nausea and nine questions related to vomiting. A visual analog scale of 1 to 7 was used for each question.
- The proportion of patients with nausea, emesis, and requiring rescue medication.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome in all of the RCTs was complete response in the acute phase following the administration of MEC or HEC. In the PALO trials, the pre-specified criterion for non-inferiority between IV palonosetron and the comparator groups (i.e., ondansetron, granisetron, or dolasetron) was a –15% difference in the proportion of complete responders using the lower bound of a two-sided 97.5% confidence interval (CI). In the trial conducted by Yu et al., the non-inferiority criterion was a –10% difference in the proportion of complete responders using the lower bound of a two-sided 95% CI.

Results

Based on the Health Canada recommended dosing, CDEC focused their discussion on the results for palonosetron IV 0.25 mg.

Efficacy

Moderately Emetogenic Chemotherapy:

- For the proportion of patients with complete response in the acute phase, per-protocol analyses demonstrated that palonosetron was superior to ondansetron (risk difference [RD] 17%; [97.5% CI: 6.9 to 27.2]) in PALO-99-03 and non-inferior to dolasetron (RD [97.5% CI], 12.2 [–0.4 to 24.8]) in PALO-99-04.
- For the proportion of patients with a complete response in the delayed phase, palonosetron was superior to ondansetron (RD [97.5% CI], 19% [7.5 to 30.3]) and dolasetron (RD [97.5% CI], 15.3% [3.4 to 27.1]).
- Fewer patients experienced nausea, vomiting, or required rescue medications with palonosetron in the acute and delayed phases compared with ondansetron or dolasetron (statistical significance not reported).
- Quality of life during the 24 to 96-hour time interval was statistically significantly better with palonosetron compared with both ondansetron and dolasetron.

Highly Emetogenic Chemotherapy:

- Palonosetron was non-inferior to ondansetron for the proportion of patients with a complete response in the acute phase in the per-protocol (69% versus 63%; RD [97.5% CI], 5.9% [–5.4 to 17.3]) and intention-to-treat (RD [97.5% CI], 2.2 [–8.8 to 13.1]) analyses.
- Palonosetron was non-inferior to granisetron for the proportion of patients with a complete response to treatment in the acute phase in the intention-to-treat analysis (83% versus 72%; RD [95% CI], 11% [1.11 to ∞]). There was no per-protocol analysis reported.
- For complete response, palonosetron was non-inferior to granisetron in the acute phase as well as on each of the subsequent three days.
- Fewer patients vomited, experienced nausea, or required rescue medications in the palonosetron group in the acute phase compared with the ondansetron group (statistical significance not reported).
- Patient satisfaction with treatment was similar with palonosetron and ondansetron.
- There were no statistically significant differences between palonosetron and ondansetron in quality of life at 0 to 24 hours and at 24 to 96 hours.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was similar between palonosetron and the comparator groups. Gastrointestinal and central nervous system adverse events were the most commonly reported.
- The proportion of patients with at least one serious adverse event was greater with dolasetron compared with palonosetron (5% versus 2%) and similar between palonosetron and ondansetron.
- Withdrawals due to adverse events were infrequent in all of the included studies (i.e., less than 1%).

Cost and Cost-Effectiveness

The manufacturer submitted a confidential reduced price during the embargo period for palonosetron of *[confidential price removed at manufacturer's request]*.

The manufacturer submitted a cost-utility analysis comparing palonosetron with ondansetron using data from three clinical trials (PALO-99-03 and PALO-99-04 for MEC, and PALO-99-05 for HEC). The reference case time horizon in the model was set at five days to cover the average length of a single chemotherapy cycle. Analyses were conducted separately for MEC and HEC. In addition, two scenarios were considered for both MEC and HEC: two-drug (5-HT_3 plus dexamethasone) and three-drug (5-HT_3 plus dexamethasone plus aprepitant). The manufacturer assumed that the cost of treatment would be one dose of palonosetron IV, and 2.5 days of treatment with oral ondansetron to align with clinical practice. For MEC, the manufacturer reported that the incremental cost per quality-adjusted life-year (QALY) gained for palonosetron compared with ondansetron for the two-drug regimen was $38,135, and $27,489 for the three-drug regimen. For HEC, the incremental cost per QALY gained for palonosetron compared with ondansetron for the two-drug regimen was $22,128, and $22,466 the three-drug regimen.

A number of limitations were noted with the economic submission:

- Differences in the administration of ondansetron from the included RCTs (single IV dose on day 1) and the economic model (2.5 days of oral treatment) raise questions around the relative accuracy of the modelled efficacy of palonosetron versus ondansetron. Incorporation into the model of the costs associated with oral ondansetron in the absence of additional clinical benefits may have biased cost-effectiveness results in favour of palonosetron.
- The estimated differences in QALYs between the treatment strategies were exceedingly small (approximately 0.001 QALYs gained with palonosetron).
- For MEC, there was uncertainty around clinical efficacy. If equal efficacy was assumed in the delayed phase, the incremental cost-utility ratio increased to $304,330 and $89,104 per QALY for the two-drug and three-drug regimens respectively.
- For HEC, if equal efficacy (non-inferiority) was assumed in both the acute and delayed phases, the incremental cost per QALY increased to $1,748,000 and $1,199,377 for the two-drug and three-drug regimens, respectively.

The cost of treatment with palonosetron (*[confidential price removed at manufacturer's request]*) is greater than dolasetron ($29 per 100 mg oral), granisetron ($27 per 2 mg oral), and ondansetron depending on the duration of use ($31 for 2.5 days with MEC to $91 for 5 days with HEC).

Other Discussion Points:

CDEC noted the following:

- The efficacy estimates reported in the included trials may not be reflective of current clinical practice for the following reasons:
  - Retreatment with ondansetron on days two and three is common due to the short half-life of this compound. A regimen allowing for repeated dosing of ondansetron may have attenuated the observed differences in the included trials on delayed chemotherapy-induced nausea and vomiting. Hence, the generalizability to clinical practice of the findings of non-inferiority for delayed chemotherapy-induced nausea and vomiting in HEC (study PALO-99-05) and superiority in MEC (PALO-99-03 and PALO-99-04) is uncertain.

  - There was no standardized use of dexamethasone in the included trials. In the PALO studies, the concomitant administration of a corticosteroid was permitted; however, none of the patients in PALO-99-03 received a corticosteroid and only 6% of patients in PALO-99-04 received a corticosteroid. Usage was higher in PALO-99-05 with approximately 60% of patients receiving a corticosteroid.
  - In the PALO studies (PALO-99-03, PALO-99-05, and PALO-99-04), 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.
- The comparator group medication used in PALO-99-04 (IV dolasetron 100 mg) is not available in Canada.

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.

Regrets:
February 20, 2013: Two CDEC members did not attend the meeting.

April 17, 2013: None

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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