



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for palonosetron hydrochloride

Proprietary Product Name: Aloxi

Sponsor: Specialised Therapeutics Australia Pty
Ltd

January 2014

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to product submission

Submission details

<i>Type of Submission</i>	Major Variation (Dosage)
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	20 August 2013
<i>Active ingredient(s):</i>	Palonosetron hydrochloride
<i>Product Name(s):</i>	Aloxi
<i>Sponsor's Name and Address:</i>	Specialised Therapeutics Australia Pty Ltd Level 1, 711 High Street Kew East VIC 3102
<i>Dose form(s):</i>	Solution for injection
<i>Strength(s):</i>	250 µg / 5 mL
<i>Container(s):</i>	Vial
<i>Approved Therapeutic use:</i>	Aloxi is indicated for prevention of nausea and vomiting induced by cytotoxic chemotherapy.
<i>Route(s) of administration:</i>	Intravenous
<i>Dosage:</i>	The recommended dosage of Aloxi is 250 µg administered as a single dose approximately 30 minutes before the start of chemotherapy. Repeated dosing of Aloxi within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.
<i>ARTG Number (s)</i>	114185

Product background

This AusPAR describes a literature based submission (LBS) by the sponsor, Specialised Therapeutics Australia Pty Ltd, to vary the dosage for palonosetron hydrochloride (Aloxi) to a multiple dosage regimen. Aloxi injection is a sterile, clear, colourless, non pyrogenic, isotonic, buffered solution for intravenous (IV) administration. Palonosetron hydrochloride is an antiemetic and antinauseant agent. It is a selective serotonin subtype 3 (5-HT₃) receptor antagonist with a strong binding affinity for this receptor. Palonosetron hydrochloride is currently registered with the following indication:

Aloxi is indicated for prevention of nausea and vomiting induced by cytotoxic chemotherapy.

The **current** 'Dosage and Administration' recommendations are as follows:

Dosage for Adults

*The recommended dosage of Aloxi is 250 µg administered as a **single dose** approximately 30 minutes before the start of chemotherapy. **Repeated dosing of Aloxi within a seven day interval is not recommended** because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.*

Use in Geriatric Patients and in Patients with Impaired Renal or Hepatic Function

No dosage adjustment is recommended.

Dosage for Paediatric Patients

A recommended intravenous dosage has not been established for paediatric patients.

Administration

Aloxi is to be infused intravenously over 30 seconds.

The sponsor proposes to **delete**:

Repeated dosing of Aloxi within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

The sponsor proposes to **substitute** that text with the following:

Published clinical data indicate this dosage of Aloxi may be repeated on alternate days, in multiple day chemotherapy depending on the duration of chemotherapy.

The sponsor distinguishes acute (resolving within 24 h) and delayed (starting at or beyond 24 h) chemotherapy induced nausea and vomiting (CINV).

The TGA has adopted the relevant European Union guideline.¹

Regulatory status

Table 1 shows the international regulatory approval status for Aloxi at the time of the Australian submission. The sponsor's position is that a multiple dose regimen is approved in the EU and the US. The clinical evaluator considers that no Aloxi label recommends repeat dosing and that there is no explicit prohibition either.

¹ European Medicines Agency, "Committee for medicinal products for human use (CHMP): Guideline on non-clinical and clinical development of medicinal products for the prevention of nausea and vomiting associated with cancer chemotherapy (CPMP/EWP/4937/03)", 14 December 2006, Web, accessed 9 December 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017746.pdf>.

Table 1: International regulatory approval status for Aloxi at the time of submission.

Country	Date submitted	Approval date	Approved indications
EU	24.08.2008	29.01.2009	Multiple dose regimen
USA	31.07.2006	30.08.2007	Multiple dose regimen
Canada	31.03.2011	14.03.2012	Multiple dose regimen
New Zealand*	n/a	n/a	n/a
Switzerland	06.02.2009	10.06.2012	Multiple dose regimen

* The product is registered but not marketed in New Zealand.

United States

The US Food and Drug Administration (FDA) has approved Aloxi for use in the CINV setting, recommending a single 0.25 mg IV dose. The indications endorse use with initial and repeat **courses** of chemotherapy. Alternate day dosing is not formally approved: only a single dose (prior to each course) is approved. To explore this in more detail, the US Product Information (PI) states, with regard to 'Dosage and Administration':

Chemotherapy Induced Nausea and Vomiting

Dosage for Adults – a single 0.25 mg IV dose administered over 30 seconds. Dosing should occur approximately 30 minutes before the start of chemotherapy.

The description in the 'Pharmacokinetics' section of the US PI of pharmacokinetic parameters refers to after single dosing, after alternate day dosing, and after daily dosing.

In the 'Clinical Studies' section, emphasis was on single dose palonosetron studies, with outcomes assessed through at least 120 h after administration of chemotherapy. Efficacy in prevention of acute and delayed nausea and vomiting (0 to 120 h) was established for initial and repeat **courses** of chemotherapy, presumably in the context of a single dose per course.

It is recognised that in 2007, the following information was deleted from the US PI:

Repeated dosing of Aloxi within a seven day interval is not recommended because the safety and efficacy of frequent (consecutive or alternate day) dosing in patients has not been evaluated.

European Union

In the EU, the situation is similar to that in the US. The Summary of Product Characteristics (SmPC) notes that Aloxi should not be used to prevent or treat nausea and vomiting in the days following chemotherapy if this is not associated with another chemotherapy administration.

Product Information

The approved PI current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The sponsor submitted a LBS to update the PI of Aloxi (palonosetron 250 µg/5 mL) solution for injection in relation to altering the dosage regimen (allowing multiple dosing).

The sponsor informed TGA that this submission presents published data from controlled and uncontrolled clinical studies to update the PI of Aloxi in the followings sections:

- 'Dosage and Administrations' section: to permit multiple dosing of palonosetron 0.25 mg IV for the prevention of CINV.
- 'Precautions General' section: additional statement that palonosetron use should only occur in association with chemotherapy.
- 'Pharmacokinetics' section: text related to some pharmacokinetic aspects of multiple dosing of palonosetron, based on two sponsor led studies.
- 'Clinical Trials' section: a brief summary of three randomised controlled trials submitted as published papers involving multiple administrations of palonosetron and intended to support the alternate dose schedule for palonosetron.

The proposed changes to the PI are associated with one amendment to the current Consumer Medicine Information (CMI).

The presented search strategy for this LBS has been approved by the TGA Library.

The dossier includes two pharmacokinetic studies and fourteen efficacy/safety studies presented as published papers.

The international sponsor for palonosetron, Helsinn Healthcare SA, has performed two clinical studies with repeated (< 7 days) palonosetron dosing with the aim of removing the warning on multiple dosing from the European SmPC; this variation was approved in the EU on 29 January 2009. Data supporting this variation included the two sponsor led studies:

- Phase I, double blind, randomised, placebo controlled trial to determine the pharmacokinetics and safety of multiple IV dosing of palonosetron in healthy subjects (n = 16); PALO-02-12 study.
- Phase II, open label trial to assess the safety and efficacy of Aloxi, administered as multiple doses, in patients (n = 41) receiving consecutive daily doses of cisplatin therapy for testicular cancer; PALO-04-09 study.

These two studies involved palonosetron 0.25 mg administered IV on 3 consecutive days in the PK PALO-02-12 study, and on 3 alternate days in the PALO-04-09 study.

The two studies were included as full study reports in an earlier submission and had been already evaluated by the TGA. The studies have subsequently been published by Hunt and colleagues² (PALO-02-12) and Einhorn and colleagues³ (PALO-04-09). These publications are submitted in current LBS as key supporting evidence for the multiple dose regimen proposed.

An earlier application to the TGA that sought approval for removal of the single dose restriction for Aloxi was rejected by the TGA on the basis of inadequate clinical efficacy and safety data for the proposed multiple dosing regimen. That application to amend the 'Dosage and Administration' section of the PI to allow for repeated dosing of palonosetron was based on the EU dossier.

The current submission differs from the previous one in that it includes results of a literature search for supportive clinical studies. The complete study reports for these studies are not included in this re-submission as the publications provide sufficient information for each study for the LBS.

Since the completion of the two sponsor initiated studies listed above there have been many published reports of clinical studies involving multiple dose regimens for palonosetron for the prevention of CINV. These publications were retrieved via a comprehensive literature search strategy which has been approved by the TGA librarian.

Comments: The proposed efficacy statement for 'Clinical Trials' section is based on data from 246 patients from three published randomised controlled trials; out of these, 63 patients in two clinical trials received the proposed alternative day dosing of palonosetron of 0.25 mg administered IV in association with multi day chemotherapy.

In a study of 143 patients treated for acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS), 48 patients received the proposed alternate day dosing of palonosetron, 48 received different palonosetron dosing regimen, and 47 received an active comparator (ondansetron).

In a study of metastatic melanoma (MM), a total of 30 patients were treated: 15 patients received the proposed alternate day dosing of palonosetron, and 15 received a different palonosetron dosing regimen.

In a study of MM, a total of 73 patients were treated: 25 patients received 3 consecutive days of palonosetron, and 48 received shorter palonosetron dosing regimes.

Apart from the two sponsor led studies, and the three randomised controlled trials listed above, the rest of the submitted data, including the clinical guidelines, could be regarded as the background reading material.

Pharmacokinetics

The following conclusions were presented by the sponsor based on two studies:

- In the study by Hunt and colleagues⁴ involving healthy subjects, Aloxi 0.25 mg IV bolus over 10 seconds daily for 3 consecutive days resulted in a 2.1 fold accumulation (ratio

² Hunt TL, et al. (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol.* 45: 589-596.

³ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

⁴ Hunt TL, et al. (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol.* 45: 589-596.

of Day 3/Day 1 AUC_{0-24h} [area under the plasma concentration-time curve within time span t1 to t2]).

- Similarly, in the study by Einhorn and colleagues⁵ involving cancer patients, Aloxi 0.25 mg IV bolus over 30 seconds on Days 1, 3, and 5 resulted in a 1.42 fold accumulation (ratio of Day 5/Day 1 AUC_{0-t}). This is consistent with the plasma elimination half life of palonosetron (~40 h; see SmPC).
- Based on these two studies, AUC after daily IV doses of 0.25 mg over 3 days is expected to be similar to the AUC resulting from a single 0.75 mg dose. These pharmacokinetic data, therefore, support the proposal to use repeated daily dosing of Aloxi.

Comments (additional information):

The earlier submission to address the same issue of palonosetron multiple dosing regimens included the pharmacokinetic simulation study (PR-PALO-02-17).

The following were the comments of the clinical evaluator at that time:

Data were obtained from three studies; the 2 compartment model was used. The simulations calculated the plasma concentrations for several dosing regimens over a time interval of up to 216 h.

The following simulations were performed:

§ Single dose of 0.75 mg IV

§ 3 daily doses of 0.25 mg/day

§ 8 daily doses of 0.25 mg/day (to represent steady state).

The AUC_{0-∞} for the three daily doses was similar to that for the single dose of 0.75 mg. The model simulated no significant increase in the C_{max} (maximum plasma drug concentration) of palonosetron after the third daily dose.

The simulations did not predict the range of plasma concentrations that might be expected in a population of patients. The simulations used parameters estimated from mean values and did not simulate for the expected range of values. Hence, there is no way of knowing what proportion of the population might experience an AUC and/or C_{max} well in excess of the mean.

“The PK data were obtained for palonosetron 0.25 mg on Days 1, 2, 3 from a volunteer population and on Days 1, 3, 5 from a population of subjects with testicular cancer. These data did not indicate significant accumulation of palonosetron after Day 3.”

The simulations were rudimentary in that only mean plasma concentrations were simulated. The modelling did not use all the available data to develop the model and did not model the variability in plasma concentrations over time.”

“The modelling and simulations did not attempt to determine an optimal dosing strategy for multiple doses in a one week period.”

Pharmacodynamics

No new data submitted.

⁵ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

Efficacy

Overall, the available efficacy data to back up the multiple days of administration of palonosetron IV for prevention of CINV are inconclusive.

None of the three randomised controlled trials, submitted as published papers and intended to back up the proposed alternate day dosing of palonosetron, convincingly demonstrated the benefits of this regimen, or in fact the benefits of multiple day dosing of palonosetron.

Only two of these randomised controlled trials investigated the alternate day dosing of palonosetron (Mattiuzzi et al.⁶ and Noor et al.⁷). This equates to a total of 63 patients exposed to alternate days of administration of palonosetron in these two studies.

The sponsor led PALO-04-09 study published by Einhorn and colleagues⁸ was an open label uncontrolled study that investigated an alternate days dosing regimen in 41 patients with testicular cancer which was assessed not to be an adequate efficacy study design. In this study, regarded as key study for this submission, half of the patients (51.2 %) had no emetic episodes for the 1-5 days study period, 12.2 % of patients had no nausea and no rescue medications during the first 5 days, and 34.1 % of patients were recorded as having complete response during the 5 days of treatment.

On Days 4 and 5, when a complex overlap of acute and delayed cisplatin induced emesis was most likely present, 68 % and 71 % of patients, respectively, reported no emetic episodes.

Overall, efficacy outcomes from this trial were not impressive, but probably in line with what one can expect from a combination of a 5-HT₃ receptor antagonist + dexamethasone in this setting.

The rest of the efficacy data represented a mixture of studies in a heterogeneous patient population with a variety of dosing schedules of palonosetron, and provided equally equivocal results.

Overall, some trends indicating possible benefits of repeating the doses of palonosetron were described in the published studies, however, often the studies were underpowered, or not evaluable.

The submitted guidelines representing the opinions of the learned cancer societies are cautiously supportive of the repetitive dosing of palonosetron, in specific circumstances.

There is a scarcity of good quality data.

Conclusion

Based on the sponsor led PALO-04-09 study, the submitted three randomised controlled trials, the rest of published papers involving alternate days dosing of palonosetron, and on the basis of extrapolation from indirect evidence involving different dosing schedules of palonosetron, the evaluator believes that there is likely to be some benefit in repeating the dosing of palonosetron for up to 3 doses/cycle.

⁶ Mattiuzzi GN, et al. (2010) Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. *Cancer* 116: 5659-5666.

⁷ Noor R, et al. (2012) Comparison of two dosing schedules of palonosetron for the prevention of nausea and vomiting due to interleukin-2-based biochemotherapy. *Support Care Cancer* 20: 2583-2588.

⁸ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

These data are, however, not sufficiently robust to be included in the 'Clinical Trials' section of the Aloxi PI.

Safety

The submitted data does not raise any specific safety concerns for the evaluator.

The clinical evaluator dealing with a previous submission relating to multiple dosing of palonosetron expressed the following concerns:

"There were insufficient numbers of subjects exposed to multiple dosing within one week period in clinical trials to support Variation 1 in the absence of adequate PK data."

The current clinical evaluator has made an assessment that the inclusion of the published papers in current submission has mitigated this concern to some extent, bearing in mind that the safety data available from the published studies is scanty.

List of questions

None.

Clinical summary and conclusions

Following review of the submitted data, the evaluator has made the assessment that there are no evident safety concerns compelling to uphold the previously present single dose restriction on palonosetron injection, within 7 days of the first dose.

Removal of this restriction will bring the Australian PI of Aloxi in line with the other international labels, namely the EU SmPC of Aloxi, the FDA label, and the Product Monograph for Canada, none of which carry the single dose restrictions.

Of note, none of the Aloxi international labels clearly recommend repeated dosing of palonosetron, but neither is there an explicit prohibition from doing so.

The evaluator rejected the proposed text to the 'Clinical Trials' section and the 'Dosing and Administration' section based on insufficient clinical data. The proposed text to the Pharmacology section of the PI is acceptable.

-The optimal dosing regimen for repeated doses of palonosetron is yet to be defined.

The evaluator recommended additional text for 'Dosage and Administration' section advising that there is limited safety data on repeated dosing of palonosetron, particularly beyond 3 doses. The text is similar to one already present for Aloxi Product Monograph in Canada.

Recommendation

The evaluator recommends the approval of this submission by Specialised Therapeutics Australia Pty Ltd to update the PI for Aloxi (palonosetron hydrochloride) injections in relation to removal of single dose restriction, conditional upon the sponsor addressing the recommendations as outlined in the clinical evaluation report.

V. Pharmacovigilance findings

Risk management plan

There was no requirement for a Risk Management Plan evaluation in a submission of this type.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The evaluator recommends approval of the deletion of the single dose restriction, with some modifications to the sponsor's proposed PI changes.

Overview of data

This was a literature based submission. The literature search strategy was approved after review by the TGA Library. There were 2 pharmacokinetic studies, and 14 efficacy/safety studies, all being published papers (including abstracts).

The two pharmacokinetic studies (PALO-02-12, corresponding to Hunt et al.⁹ and PALO-04-09, corresponding to Einhorn et al.¹⁰) were presented to the TGA as Clinical Study Reports.

In the current submission, the evaluator regards as influential the above mentioned two pharmacokinetics studies *and* three randomised controlled trials. Other submitted data are regarded as "background reading".

Pharmacokinetics

Palonosetron has a plasma half life of 40 h, significantly longer than that of other 5-HT₃ receptor antagonists (typically 4-8 h). The company's 'core safety information' document notes that 10% of patients have a terminal elimination half life of >100 h. Palonosetron is mainly metabolised by CYP2D6, and it is known that poor metabolisers (as well as extensive and ultrarapid metabolisers) exist for this isoform. In a 2006 new chemical

⁹ Hunt TL, et al. (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol.* 45: 589-596.

¹⁰ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

entity study of 3 poor and 3 extensive metabolisers, pharmacokinetic results were similar. It is not clear which study or studies identified the subset of 10% with prolonged half life.

PALO-02-12, corresponding to Hunt et al.¹¹

This study examined the pharmacokinetics and safety of palonosetron 0.25 mg IV once daily for 3 consecutive days (n = 12), compared to placebo (n = 4), in healthy volunteers. There was a 2.1 fold increase in AUC_{0-24h} from Day 1 to Day 3. Change in C_{max} was similar. The sponsor noted that even these Day 3 levels were lower than levels after a single IV 0.75 mg bolus dose. The 0.75 mg dose is not approved in Australia. The sponsor compares AUC_{0-24h} results but in this study, pharmacokinetic parameters were measured well beyond 24 h; thus, AUC_{0-t[*last*]} was much higher than AUC_{0-24h}.

PALO-04-09, corresponding to Einhorn et al.¹²

This study examined pharmacokinetics in a subset of 11 subjects with testicular cancer. Palonosetron 0.25 mg IV was given on Days 1, 3 and 5 in patients given cisplatin on Days 1-5. There was no control arm for pharmacokinetic comparison. There was a 1.4-fold increase in AUC_{0-t} from Day 1 to Day 5; AUC_{0-t} refers to plasma concentration-time curve to the last measured time point, which appears to be 2.5 h. Given that palonosetron's half life is about 40 h, this 'AUC' is a snapshot of initial exposure (compared to the plasma concentration-time curve for Hunt et al.¹³). Dosing did not extend beyond Day 5 and it is likely accumulation would continue with additional dosing. C_{max} rose by a slightly lower proportion.

While C_{max} results were similar across these studies, AUC results were widely different (reporting units across studies were the same, that is, ng.hr/L) and this is possibly due to the practice in the Einhorn study¹⁴ of measuring pharmacokinetic parameters only to 2.5 h.

Both pharmacokinetics studies had relatively small sample sizes and pharmacokinetics results were not accompanied by alarmingly high coefficients of variation (at least for AUC). Possibly, no patients with outlying pharmacokinetics (that is, in the subset with half life >100 h) were included.

Efficacy

Sources of efficacy evidence included:

- PALO-04-09 (Einhorn et al.¹⁵)
- Three comparative randomised controlled trials found by literature search (Noor et al.¹⁶; Giralt et al.¹⁷; and Mattiuzzi et al.¹⁸)

¹¹ Hunt TL, et al. (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol.* 45: 589-596.

¹² Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

¹³ Hunt TL, et al. (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol.* 45: 589-596.

¹⁴ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

¹⁵ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

- Retrospective comparative studies and studies with historical controls (n = 2)
- Abstracts and conference proceedings regarding controlled studies (n = 4)
- Uncontrolled studies (n = 5, including Einhorn et al.¹⁹)
- Guidelines on antiemesis (n = 4)
- A review paper (Schwartzberg et al.²⁰)

Noor et al.²¹

This study compared palonosetron 0.25 mg IV on Days 1 and 4 (n = 15) versus Days 1, 3 and 5 (n = 15). Patients had metastatic melanoma and were treated with dacarbazine (Day 1), cisplatin + vinblastine + IL2 (Days 1-4) and IFN- α 2b (Days 1-5). Several of those agents are considered highly emetogenic according to EviQ.

- A primary endpoint was not described yet multiple comparisons were made (for example, episodes of nausea by Day 7, nausea by Day 21, vomiting by Day 7, vomiting by Day 21 and use of rescue medicines by Day 7; average and median number of patients with nausea at any day to Day 7 and with vomiting at any day to Day 7; interference of nausea and vomiting with appetite, sleep, physical activity, social life and enjoyment of life). For only one of these endpoints was a statistically significant difference across arms obtained (number of patients with nausea at any day during Days 1-7); the test was not corrected for multiple comparisons.
- Comparison of the alternate day schedule is not with a single dose schedule or with another established treatment.
- Presence of liver metastases may affect risk of CINV. There was an imbalance across arms regarding presence of liver metastases (9/15 with two dose, 4/15 with alternate day dosing). The argument that the fraction of patients with major involvement (>3 metastases or metastases >3 cm) was similar does not address all confounding that might arise from the imbalance.
- The study was supported by a grant from Eisai Pharmaceuticals.
- The Delegate does not consider that this study supports efficacy of an alternate day dosing regimen relative to the current single dose regimen or another established regimen.

¹⁶ Noor R, et al. (2012) Comparison of two dosing schedules of palonosetron for the prevention of nausea and vomiting due to interleukin-2-based biochemotherapy. *Support Care Cancer* 20: 2583-2588.

¹⁷ Giralt SA, et al. (2011) Three palonosetron regimens to prevent CINV in myeloma patients receiving multiple-day high-dose melphalan and hematopoietic stem cell transplantation. *Ann Oncol.* 22: 939-946.

¹⁸ Mattiuzzi GN, et al. (2010) Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. *Cancer* 116: 5659-5666.

¹⁹ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

²⁰ Schwartzberg LS, et al. (2012) The role of second-generation 5-HT₃ receptor antagonists in managing chemotherapy-induced nausea and vomiting in hematological malignancies. *Crit Rev Oncol Hematol.* 83: 59-70.

²¹ Noor R, et al. (2012) Comparison of two dosing schedules of palonosetron for the prevention of nausea and vomiting due to interleukin-2-based biochemotherapy. *Support Care Cancer* 20: 2583-2588.

Giralt et al.²²

73 patients with multiple myeloma were given palonosetron 0.25 mg on Day -2, Days -2 and -1, or Days -2, -1 and 0, where melphalan (presumably IV) was given on Days -2 and -1 prior to HSCT on Day 0. IV melphalan is listed as moderately emetogenic in EviQ.

- One cohort can be considered single dose palonosetron, but there is no alternate day dose regimen. Dexamethasone was used.
- There was no difference in the primary endpoint of proportion of patients without emesis during Days -2 to +4, across arms (41.7-44.0%). Being emesis free without rescue was less likely in the single dose arm (8.3% versus ~20%; but $p = 0.14$).
- Functional impact of nausea/vomiting was least with two doses, most with a single dose.
- Some results favoured the multiple dose arms, yet this was the case even on day -2 when treatments were identical (for example, at day -2, 75% of 1-day patients, 83.3% of 2-day patients and 96% of 3-day palonosetron patients had no emesis with no use of any rescue medicine).
- Mean hours with nausea were 42.4 h for 1-day and 20-22 h for 2-3 day patients.
- Confounding baseline factors such as renal impairment or hypercalcaemia (in this MM cohort) were apparently not assessed, although vomiting from organic aetiology was an exclusion criterion and prior nausea/vomiting was balanced across arms.
- The study was sponsored by Helsinn (the US sponsor of palonosetron) and was funded, designed, conducted and supervised in full by Eisai Inc. Writing/editorial assistance for the paper was funded by Eisai Inc. Eisai staff analysed data and oversaw preparation of the clinical study report. Several authors were employees of Eisai.
- The Delegate does not consider that this study provides formal support for the alternate day regimen.

Mattiuzzi et al.²³

In this study, patients were given palonosetron 0.25 mg IV daily for 5 days, or 0.25 mg IV on Days 1, 3 and 5, or an ondansetron regime (8 mg IV then 24 mg continuous infusion over 12+ h). The population studied had AML and were receiving high dose cytarabine (moderately emetogenic according to EviQ).

- The ondansetron dosage is consistent with an approved regimen. The Zofran PI states:

Highly emetogenic chemotherapy. A single dose of ondansetron 8 mg by slow intravenous injection in not less than 30 seconds, immediately before chemotherapy has been shown to be effective in many patients. Higher doses may be required in some patients, particularly those on high dose cisplatin, and the doses should be adjusted according to the severity of the emetogenic challenge. If required, additional intravenous doses may be given up to a maximum of 32 mg in 24 h.
- Therefore, this study does compare alternate day palonosetron with a registered regimen for prevention of CINV. However, with ondansetron, the PI notes:

²² Giralt SA, et al. (2011) Three palonosetron regimens to prevent CINV in myeloma patients receiving multiple-day high-dose melphalan and hematopoietic stem cell transplantation. *Ann Oncol.* 22: 939-946.

²³ Mattiuzzi GN, et al. (2010) Daily palonosetron is superior to ondansetron in the prevention of delayed chemotherapy-induced nausea and vomiting in patients with acute myelogenous leukemia. *Cancer* 116: 5659-5666.

Initial treatment may be followed by oral ondansetron 8 mg 12-hourly or rectal ondansetron 16 mg once daily for up to 5 days to protect against delayed emesis.

This additional ondansetron was not offered in the study.

- The study does not allow comparison of alternate day palonosetron with a single dose regimen.
- The study arms were relatively large (n = 47-48).
- The primary endpoint was ‘no emesis and no use of rescue medicines over 7 days’ and this was achieved in 21% (ondansetron), 31% (palonosetron Days 1-5) and 35% (palonosetron Days 1, 3, 5) (p=0.32).
- Research support in this paper was from “GI Pharmaceuticals”.
- The Delegate does not consider this paper provides robust support for an alternate day regimen.

PALO-04-09 (Einhorn et al.²⁴)

This study was open labelled and uncontrolled, so does not add much to understanding of alternate day palonosetron dosing relative to approved or established approaches.

Other efficacy data

These studies lack the bias-minimising advantages of prospective randomised controlled trials.

Feinberg and colleagues²⁵ reported promising results for alternate day palonosetron in cisplatin and carboplatin exposed subgroups. The ondansetron arm included a single dose of palonosetron on the last day of antiemetic dosing, however this would tend to narrow differences between arms if palonosetron were superior to ondansetron. The study was sponsored by Eisai Inc; two authors were Eisai employees.

Abstracts of papers are not evaluable in any formal sense, although the sponsor’s view that these abstracts demonstrate that multiple dosing is used widely in other countries is noted. Guidelines provide context but cannot be considered pivotal information.

Safety

Safety data are mainly derived from PALO-02-12 and PALO-04-09, since these studies had the most detailed safety monitoring.

In PALO-02-12 (Hunt et al.²⁶) there was no increase in incidence of AEs at Day 3 relative to Day 1. The number of subjects exposed was small.

In PALO-04-09 (Einhorn et al.²⁷) there was no evidence of cumulative toxicity. In particular, electrocardiogram (ECG) testing on Days 1 and 5 was performed in a subset (n = 11); there was no evidence of a cumulative effect on ventricular repolarisation. Sample

²⁴ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

²⁵ Feinberg B, et al. (2012) Impact of initiating antiemetic prophylaxis with palonosetron versus ondansetron on risk of uncontrolled chemotherapy-induced nausea and vomiting in patients with lung cancer receiving multi-day chemotherapy. *Support Care Cancer* 20: 615-623.

²⁶ Hunt TL, et al. (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol.* 45: 589-596.

²⁷ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

size was limited, making detection of toxicity due to outlying pharmacokinetics responses to multiple dosing less likely.

Risk management plan

There was no requirement for a RMP evaluation in a submission of this type.

Risk-benefit analysis

Delegate considerations

Efficacy

There is existing evidence for efficacy of a single dose, to 120 h. There is no value in establishing non inferiority of a multi dose regimen, so improvement in the benefit-risk profile with alternate day dosing should be demonstrated.

The studies provided in this submission have design weaknesses and/or do not show clinically meaningful improvement in primary efficacy endpoints related to prevention/treatment of nausea/vomiting. Collectively, an impression is generated that multiple dosing may offer 'some' advantage, but this has not been demonstrated conclusively or robustly. Therefore, the Delegate's approach is to allow the sponsor to delete from the PI text that actively recommends against multiple dosing, but to include text that makes it clear that robust data do not exist to support alternate day dosing, relative to single dosing.

Safety

Safety data are not emphasised in published studies provided in the submission. There is some reassurance from the sponsor's studies that multiple dosing is not generating additional safety issues. In particular, there is no signal that QT prolongation is a major issue with multiple dosing, despite the drug accumulation seen in pharmacokinetic studies. However, the two studies with detailed safety monitoring were quite small (for example, n = 12 for Hunt et al.²⁸; n = 41 for Einhorn et al.²⁹ but only 11/41 with ECG testing); it is possible that no or few subjects with outlying pharmacokinetics were well studied for safety after alternate day or multiple dosing.

Proposed action

The Delegate proposes to approve the application but vary the proposed PI changes.

Advice from the Advisory Committee on Prescription Medicines (ACPM) was not requested for the previous, similar application. Then, a key element of the application was rejected (the recommendation in the PI against multiple doses was retained). In the current application this may also happen. Therefore, advice of the ACPM is requested. Specifically:

- Does the ACPM consider that there is sufficient evidence to remove the current recommendation against multiple dosing?

²⁸ Hunt TL, et al. (2005) Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol*. 45: 589-596.

²⁹ Einhorn LH, et al. (2007) Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. *Support Care Cancer* 15: 1293-1300.

- Does the ACPM consider that, beyond this, there is sufficient evidence to endorse alternate day dosing in the PI, in the 'Clinical Trials' section and/or the 'Dosage and Administration' section?
- Does the ACPM have any further suggestions about how to improve the PI/CMI for this product?

Response from sponsor

The sponsor does not wish to make further comment on the issues raised by the TGA Delegate and has accepted the revisions to the proposed PI suggested by the clinical evaluator and Delegate.

Advisory Committee considerations

The ACPM, taking into account the submitted limited evidence of efficacy and safety, agreed with the delegate and considered Aloxi solution for injection containing 250 µg/5 mL of palonosetron (as hydrochloride) to have an overall positive benefit-risk profile for the amendment to the 'Dosage and Administration' section to allow the text:

Drug accumulation was observed in subjects administered Aloxi on consecutive days or once every two days for three doses (see 'Pharmacokinetics'). Safety and efficacy data available regarding repeated dosing of Aloxi within a course of multi-day chemotherapy are limited (see 'Clinical Trials').

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the 'Precautions' section of the PI to reference the 10% of patients who cannot as yet be identified but have a markedly extended drug half life and therefore presumably in danger of excess accumulation.
- A statement in the relevant section of the PI and the CMI to clarify safety data on interactions with other antiemetic agents.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Aloxi containing palonosetron hydrochloride for the revised dosage regimen. Drug accumulation was observed in subjects administered Aloxi on consecutive days or once every two days for three doses (see 'Pharmacokinetics'). Safety and efficacy data available regarding repeated dosing of Aloxi within a course of multi-day chemotherapy are limited (see 'Clinical Trials').

The full indications remain as follows:

Aloxi is indicated for prevention of nausea and vomiting induced by cytotoxic chemotherapy.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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