PUBLIC SUMMARY DOCUMENT

Product: PALONOSETRON HYDROCHLORIDE, solution for injection vial, 250 micrograms in 5 mL, Onicit®

Sponsor: Specialised Therapeutics Australia Pty Ltd

Date of PBAC Consideration: March 2010

1. Purpose of Application

The submission sought a Restricted benefit listing for the management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy which occurs within 48 hours of chemotherapy administration.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Palonosetron was registered by the Therapeutic Goods Administration (TGA) on 26 June 2006 for the prevention of nausea and vomiting induced by cytotoxic chemotherapy.

4. Listing Requested and PBAC's View

Restricted benefit

Management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy which occurs within 48 hours of chemotherapy administration.

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Nausea and vomiting can be a common side-effect of chemotherapy treatment. The prevention of acute nausea and vomiting associated with cytotoxic chemotherapy is currently managed with a combination of the drugs aprepitant, dexamethasone and a 5 HT_3 antagonist. Palonosetron would provide another 5-HT_3 antagonist option.

6. Comparator

The submission nominated ondansetron as the main comparator. Data was also provided for comparison with other 5-HT_3 receptor antagonists. The PBAC agreed that the appropriate comparator was ondansetron.

7. Clinical Trials

The submission presented seven randomised trials comparing palonosetron (250 microgram IV and/or 750 microgram IV) with other 5-HT_3 receptor antagonists, including ondansetron (32 mg IV, 8 mg IV followed by 8 mg orally twice daily, or 8 mg/m^2 IV every 8 hours while receiving chemotherapy during hospitalisation), dolasetron (100 mg IV) and granisetron (3 mg IV or 40 microgram/kg IV), in patients receiving moderately or highly emetogenic chemotherapy. The submission also presented one abstract of a meta-analysis of four randomised trials comparing palonosetron 250 microgram with other 5-HT_3 receptor antagonists (ondansetron, dolasetron and granisetron), and pooled the results from the seven individual trials for palonosetron (all doses) and other 5-HT_3 receptor antagonists combined (all doses). The dose regimens of the randomised therapies in the trials were not all within those recommended in the relevant product information documents or used in current clinical practice.

In two studies, ondansetron was administered at 32 mg intravenously (IV), which is a higher dose than that used in current clinical practice. Both these trials used a single dose of ondansetron.

The key trial in the submission was Bernardo et al. (2009), which was the only study comparing palonosetron 250 micrograms and ondansetron 8 mg IV followed by 8 mg orally twice daily for 3 days, was only available as an abstract, and a 2008 poster which appeared to be a subset of patients described in the 2009 abstract. This study was classified by the submission as a randomised trial, but the abstract made no mention of randomisation, referring only to 1:1 assignment to treatment groups.

The trials presented in the submission are shown below:

Trial ID / First author	**Protocol title / Publication title**	**Publication citation**
Direct randomised trials		
Palonosetron versus ondansetron		
Aapro et al. (2006) [Study PALO-99-05]	A phase III, double-blind, randomised trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy.	*Annals of Oncology* 2006; 17: 1441–1449
	Palonosetron is effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy.	*Support Care Cancer* 11(6): 391, abstract A-17, 2003 MASCC (Poster)
	Palonosetron (PALO) is a safe and well-tolerated 5-HT3 receptor antagonist (RA): safety results of a phase III trial.	*Proceedings of the American Society of Clinical Oncology* 22: 753, abstract 3028, 2003 ASCO (Poster)
Gralla et al. (2003) [Study PALO-99-03]	Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomised phase III trial comparing single doses of palonosetron with ondansetron.	*Annals of Oncology* 2003; 14: 1570–1577
	Single IV dose of palonosetron (PALO), a potent 5-HT3 receptor antagonist (RA), demonstrates sustained prevention of nausea and vomiting for 5 days following moderately emetogenic chemotherapy (MEC).	*Proceedings of the American Society of Clinical Oncology* 2003; 22: 760, abstract 3055, ASCO (Poster)
	Palonosetron (PALO) is more effective than ondansetron (OND) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy (MEC): results of a phase III trial.	*Proceedings of the American Society of Clinical Oncology* 2003; 22: 726, abstract 2918, ASCO (Abstract)
Bernardo et al. (2009) *(Abstract)*	Palonosetron compared to ondansetron in the prevention of chemotherapy-induced nausea and vomiting: Activity, safety, and cost-effectiveness evaluation.	*J Clin Oncol* 2009; 27 (15 Suppl): abstract e20573

	Improving patient care while considering cost effectiveness of new active prophylaxis for chemotherapy-induced nausea and vomiting (CINV): Results of a prospective phase II trial.	ESMO – Stockholm. 2008 (Poster)
Sepúlveda-Vildósola (2008)	Palonosetron Hydrochloride Is an Effective and Safe Option to Prevent Chemotherapy-induced Nausea and Vomiting in Children.	*Archives of Medical Research* 2008; 39: 601-6
Palonosetron versus dolasetron		
Eisenberg et al. (2003) [Study PALO-99-04]	Improved Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting with Palonosetron, a Pharmacologically Novel 5-HT_3 Receptor Antagonist. Results of a Phase III, Single-Dose Trial Versus Dolasetron.	*Cancer* 2003; 98: 2473– 82
	Efficacy of palonosetron (RS-2529) compared with dolasetron in preventing acute and delayed moderately emetogenic chemotherapy-induced nausea and vomiting (CINV): results of a phase III randomized controlled trial.	*Blood* 2002; 100 (11 Suppl) (Part 2), 497b-498b, Abstract 5576
	Palonosetron is active in preventing acute and delayed emesis following moderately emetogenic chemotherapy: results of a phase III trial.	*Support Care Cancer* 2002; 10(4), abstract P-113, MASCC (Abstract)
	Safety and efficacy of fixed-dose palonosetron in preventing acute and delayed emesis following moderately emetogenic chemotherapy: a phase III study.	*International Pharmaceutical Abstracts* 2002; 39, abstract P-643E, ASHP (Poster)
	Safety of palonosetron (RS-25259) compared with dolasetron in preventing acute and delayed moderately emetogenic chemotherapy-induced nausea and vomiting (CINV): results of a phase III, randomized, controlled trial.	*Blood* 2002; 100(Suppl.1): 499b, abstract 5582, ASH (Abstract)
Palonosetron versus granisetron		
Saito et al. (2009)	Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial in the Japanese population.	*Lancet Oncol* 2009; 10: 115–24
Yu et al. (2009)	The efficacy and safety of palonosetron compared with granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multicentre, randomised, double-blind, parallel, comparative clinical trial.	*Support Care Cancer* 2009; 17: 99– 102
Meta-analyses of direct randomised trials		
Clark et al. (2009) *(Abstract)*	Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or	*Journal of Clinical Oncology*, 2009 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 27, No 15S (May

	highly emetogenic (MoHE) treatments: Systematic review and meta-analysis.	20 Supplement), 2009: e20620

8. Results of Trials

The proportions of patients achieving complete response during the acute phase (0 to 24 hours) in the key study Bernardo et al. (2009) are presented below. Results are presented by dose of palonosetron and overall where available, and co-administration of dexamethasone was noted. Complete response was defined as no emetic episode and no rescue medication use.

Trial ID	Palonosetron n/N (%)	Active comparator n/N (%)	Risk difference (95% CI)	Relative Risk (95% CI)
Bernardo et al (2009) (with dex)				
PALO 250 µg vs ONDA 8 mg IV then 8 mg orally twice daily for 3 days	106/117 (90.6)	91/118 (68.6)	0.13 (0.04, 0.23)	1.17 (1.05, 1.32)
HEC	NR (82)	NR (63.2)		
AC	NR (93.4)	NR (80.6)		
MEC	NR (100)	NR (94.4)		

Abbreviations: CI= confidence interval, Dex= dexamethasone, HEC= Highly emetogenic chemotherapy, IV= intravenously, MEC= moderately emetogenic chemotherapy, AC = anthracycline-cyclophosphamide based chemotherapy, ONDA= ondansetron, PALO= palonosetron, vs = versus, µg= microgram, NR = not reported

Complete response rates were numerically higher for palonosetron 250 microgram than the active comparators in all trials in the acute phase. Non-inferiority of palonosetron to the active comparator in the acute phase was concluded for Aapro et al. (2006), Gralla et al. (2003), Eisenberg et al. (2003), Saito et al. (2009) and Yu et al. (2009). There was no evidence of dose-response with palonosetron, as complete response rates were similar or higher for the 250 microgram dose compared to the 750 microgram dose.

The proportions of patients achieving complete response during the delayed phase in the key study Bernardo et al. (2009) are presented below. The delayed phase usually referred to the time period of 24 hours to 120 hours. Complete response rates were numerically higher for palonosetron treated patients compared to comparator 5-HT_3 receptor antagonists in all trials except for the trial by Yu et al. (2009).

Trial ID	Palonosetron n/N (%)	Active comparator n/N (%)	Risk difference (95% CI)	Relative Risk (95% CI)
Bernardo et al (2009) (with dex)				
PALO 250µg vs ONDA 8mg IV then 8mg orally twice daily for 3 days	100/117 *(85.5)*	84/118 (71.2)	0.14 (0.04, 0.25)	1.20 (1.05, 1.38)
HEC	NR (74.4)	NR (63.2)		
AC	NR (90.2)	NR (71)		
MEC	NR (94)	NR (88.9)		

Abbreviations: CI = confidence interval, Dex = dexamethasone, HEC = Highly emetogenic chemotherapy, IV = intravenously, MEC = moderately emetogenic chemotherapy, AC = anthracycline-cyclophosphamide based chemotherapy, ONDA= ondansetron, PALO = palonosetron, vs = versus, µg = microgram, NR = not reported

Non-inferiority of palonosetron 250 micrograms to the active comparator in the delayed phase was concluded in Aapro et al. (2006), Gralla et al. (2003) and Eisenberg et al. (2003). However, it was difficult to interpret the clinical relevance of the conclusion of non-inferiority in delayed chemotherapy induced nausea and vomiting (CINV) due to the short half-life of the active comparators, the potential administration of inadequate doses of active comparator for delayed CINV, and the possibility that the 100 mg dose of dolasetron may have been suboptimal for some patients. Gralla et al. (2003) and Eisenberg et al. (2003) also had limited usage of concomitant corticosteroids (e.g. dexamethasone), which is recommended by the guidelines for delayed CINV.

Saito et al. (2009) was the only trial which nominated complete response rate in the delayed phase as one of the primary outcomes. In this trial, the authors concluded that when administered with dexamethasone, palonosetron 750 microgram was superior to granisetron 40 microgram/kg in delayed phase CINV (Risk difference 12.2 % (95 % CI 6.4 %, 18.0 %)). However, the dosage of palonosetron was higher than the TGA-approved dose and patients were not taking aprepitant, which is recommended for the patient population recruited.

Three trials reported the use of rescue anti-emetic medications in the 'delayed phase' of CINV (Aapro et al. (2006), Gralla et al. (2003), Bernardo et al. (2009)). Despite the differences in data presented, fewer palonosetron treated patients required rescue medications.

The submission pooled the results from the individual trials for palonosetron (all doses) and other 5-HT_3 receptor antagonists combined (all doses). The results are tabulated below:

Pooled results	Palonosetron (all doses) n/N (%)	Other 5-HT_3 antagonists n/N (%)	Relative Risk (95% CI)	Odds Ratio (95% CI)	p-value
Acute phase	1453/2028 (71.6)	966/1428 (67.6)	1.11 (1.05, 1.17)	1.47 (1.17, 1.86)	0.001
Delayed Phase	1182/2028 (58.3)	668/1428 (46.8)	1.26 (1.18, 1.34)	1.68 (1.41, 2.00)	<0.0001
Overall phase	1077/2028 (53.1)	614/1428 (43.0)	1.26 (1.17, 1.35)	1.62 (1.39, 1.88)	<0.0001

Abbreviation: 5-HT_3 antagonist = selective serotonin subtype 3 receptor antagonist, CI = confidence interval

The results of the meta-analysis suggested palonosetron is more effective than other 5 HT_3 receptor antagonists in the acute, delayed and overall phases. The PBAC noted that these analyses should be interpreted with caution. For PBAC's comments on these results, see *Recommendation and Reasons*.

The safety of palonosetron was similar to the active comparators (ondansetron and dolasetron). The Periodic Safety Update Reports identified cardiac events, convulsions/seizure events, cases of "lack of efficacy" and hypersensitivity reactions including anaphylactic shock as areas for close monitoring and re-evaluations.

9. Clinical Claim

The submission described palonosetron administered as a single IV dose as therapeutically equivalent to other 5-HT3 receptor antagonists administered as an IV bolus and oral doses for 2 to 3 subsequent days.

The key trial in the submission was Bernardo et al (2009), which was the only study comparing palonosetron 250 micrograms and ondansetron 8 mg IV followed by 8 mg orally twice daily for 3 days and the PBAC considered this the most relevant to current use of 5-HT3 receptor antagonists in Australia. However, as this study was only available in poster and abstract format, the PBAC agreed that a sound, critical evaluation of the data could not be performed, and as such uncertainty remains around the submission's claim of therapeutic equivalence of palonosetron 250 micrograms as a single IV dose to other 5-HT3 receptor antagonists administered as an IV bolus and oral doses for 2 to 3 subsequent days.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as palonosetron 250 microgram as a single IV dose and ondansetron 8 mg IV followed by 8mg orally twice daily for 3 days.

The table below summarises the cost-minimisation analysis of palonosetron and ondansetron:

Parameter	Palonosetron		Ondansetron	
	Dosage	Cost	Dosage	Cost
Day 1	250µg IV	$121.95	8mg IV	$32.49*
Day 2	NA	NA	8mg orally twice daily	$28.45
Day 3			8mg orally twice daily	$28.45
Day 4			8mg orally twice daily	$28.45
Total cost per cycle	$121.95 $117.84^		$117.84	

Abbreviation: NA = not applicable; µg = microgram

* The dispensed price for maximum quantity of ondansetron 8 mg/4mL injection was updated to reflect the price effective 1 December 2009

^ The proposed price for palonosetron was adjusted during the evaluation to account for a price reduction for ondansetron, effective 1 December 2009

The PBAC noted that the incremental cost of palonosetron compared with other 5-HT3 receptor antagonists ranges from a cost saving of $8.48 per cycle (when compared with granisetron), to an additional cost of $12.47 per cycle (when compared with dolasetron or tropisetron). This approach assumed the non-inferiority of palonosetron with all other 5 HT3 receptor antagonists administered as IV bolus plus an oral regimen for 3 days, however the clinical data presented only provided information on comparators other than ondansetron as a single IV dose.

11. Estimated PBS Usage and Financial Implications

During the evaluation a number of errors of methodology were identified in the submission's estimates of use and financial implications, to the extent that the submission's estimates were not reliable to inform PBAC's decision making. Therefore a re-analysis was conducted during the evaluation. The number of prescription from this re-analysis was in the range of 10,000 – 50,000 prescriptions in Year 5.

The financial cost/year to the PBS was estimated as a cost savings of less than $15,000 in Year 5 from the re-analysis.

The PBAC noted that the estimated financial implications are highly sensitive to the projected reduction in usage of oral 5-HT3 receptor antagonists should palonosetron be listed on the PBS. The PBAC considered that this was unlikely to be realised and therefore the submission may have substantially underestimated the costs to the PBS.

12. Recommendation and Reasons

The PBAC recommended the listing of palonosetron on the PBS on a cost-minimisation basis compared with intravenous ondansetron. The PBAC considered that the equi-effective doses to be palonosetron 250 micrograms and intravenous ondansetron 12 mg.

The PBAC agreed that the appropriate comparator was ondansetron. The PBAC noted that the submission presented seven randomised trials comparing palonosetron (250 microgram IV and/or 750 microgram IV) with other 5-HT3 receptor antagonists, including ondansetron (32 mg IV, 8 mg IV followed by 8 mg orally twice daily, or 8 mg/m^2 IV every 8 hours while receiving chemotherapy during hospitalisation), dolasetron (100 mg IV) and granisetron (3 mg IV or 40 microgram/kg IV), in patients receiving moderately or highly emetogenic chemotherapy. The submission also presented one abstract of a meta-analysis of four randomised trials comparing palonosetron 250 microgram with other 5-HT3 receptor antagonists (ondansetron, dolasetron and granisetron), and pooled the results from the seven individual trials for palonosetron (all doses) and other 5-HT3 receptor antagonists combined (all doses). The PBAC noted that the dose regimens of the randomised therapies in the trials were not all within those recommended in the relevant product information documents or used in current clinical practice.

The key trial in the submission was Bernardo et al (2009), which was the only study comparing palonosetron 250 micrograms and ondansetron 8 mg IV followed by 8 mg orally twice daily for 3 days and the PBAC considered this the most relevant to current use of 5-HT3 receptor antagonists in Australia. However, as this study was only available in poster and abstract format, the PBAC agreed that a sound, critical evaluation of the data could not be performed, and as such uncertainty remains around the submission's claim of therapeutic equivalence of palonosetron 250 micrograms as a single IV dose to other 5-HT3 receptor antagonists administered as an IV bolus and oral doses for 2 to 3 subsequent days.

The PBAC agreed that based on the supporting data, palonosetron 250 microgram administered as a single IV dose is at least non-inferior to other 5-HT3 receptor antagonists administered as a single IV bolus in preventing CINV in the acute and delayed phases. However, the PBAC considered that while allowing comparison of bolus IV doses, the supporting studies did not inform the comparative efficacy of palonosetron single IV dose to other 5-HT3 receptor antagonists administered as an IV bolus followed by oral administration for 2-3 subsequent days. Further, it was noted that two of the supporting studies used ondansetron at a dose of 32 mg IV, which the TGA considered as no more effective than 8 mg except following cisplatin chemotherapy, and is not commonly used in Australia.

The PBAC did not consider that palonosetron 250 microgram IV and ondansetron 8 mg IV followed by 8 mg orally twice daily for 3 days was equi-effective given the lack of evidence to support this claim. The PBAC concluded that given the uncertainty around the data presented to support the use of 5-HT3 antagonists for delayed nausea except that which was presented in Bernardo et al 2009, in abstract form, that a pragmatic approach was to allow cost-minimisation of palonosetron with ondansetron 12 mg intravenous which would reflect current best clinical practice and was in accordance with the National Comprehensive Cancer Network guidelines.

The submission proposed cost minimisation of palonosetron against any 5HT3 receptor antagonist IV and 3 days oral therapy. The PBAC noted that the incremental cost of palonosetron compared with other 5-HT3 receptor antagonists ranges from a cost saving of $8.48 per cycle (when compared with granisetron), to an additional cost of $12.47 per cycle (when compared with dolasetron or tropisetron). This approach assumes the non-inferiority of palonosetron with all other 5-HT3 receptor antagonists administered as IV bolus plus an oral regimen for 3 days, however the clinical data presented only provide information on comparators other than ondansetron as a single IV dose. The PBAC also noted that the estimated financial implications are highly sensitive to the projected reduction in usage of oral 5-HT3 receptor antagonists should palonosetron be listed on the PBS. The PBAC considered that this was unlikely to be realised and therefore the submission may have substantially underestimated the costs to the PBS.

Recommendation:
PALONOSETRON HYDROCHLORIDE, I.V injection, 250 microgram in 5 mL

Restriction:	<u>Restricted benefit</u> Management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy which occurs within 48 hours of chemotherapy administration. <u>NOTE</u>: No applications for increased maximum quantities will be authorised. Palonosetron is not PBS-subsidised for administration with oral 5-HT_3 antagonists.
Maximum quantity:	1
Repeats:	0

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Specialised Therapeutics Australia understands the analysis performed by the PBAC, and accepts the outcome. We welcome the opportunity to provide Palonosetron therapy to Australians.