Scottish Medicines Consortium

palonosetron 250 micrograms solution for injection (Aloxi®)
Cambridge Laboratories No. (208/05)

New chemical entity

4 October 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

Palonosetron (Aloxi®) is accepted for use within NHS Scotland for the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

It is as effective as other $5HT_3$ antagonists in preventing emesis when given as a single intravenous injection following highly emetogenic chemotherapy (HEC) in the acute phase and moderately emetogenic chemotherapy (MEC) in the acute and delayed phases post–chemotherapy.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

palonosetron 250 micrograms solution for injection (Aloxi®)

Indication

Prevention of acute nausea and vomiting associated with highly-emetogenic cancer chemotherapy (HEC) and the prevention of nausea and vomiting associated with moderately - emetogenic cancer chemotherapy (MEC).

Dosing information

250 micrograms as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Repeated dosing within a seven-day interval is not recommended.

UK launch date

June 2005

Comparator medications

Dolasetron, granisetron, ondansetron, tropisetron.

Cost of relevant comparators

The costs below represent the range of costs for a single course of each of the $5HT_3$ antagonists licensed for prevention of chemotherapy-induced nausea and vomiting taking account of each of the recommended regimens. Unless otherwise specified, the same regimens are used with MEC and HEC.

Single dose regimen for palonosetron*

Palonosetron (Aloxi®) 250 micrograms as a single intravenous bolus **£56**
* with HEC, palonosetron is licensed for prevention in the acute phase only

Costs for a single course of other 5HT3 antagonists in the acute phase (0-24 hours after the first dose of chemotherapy) and the delayed phase (24-120 hours)

Prevention in acute phase	Cost	Prevention in delayed phase	Cost
Dolasetron (Anzemet®) 100mg IV infusion	£13	200mg oral once daily to a maximum of 3 further days	£14 to £42
Dolasetron (Anzemet®) 200mg oral	£14	200mg oral once daily to a maximum of 3 further days	£14 to £42
Granisetron (Kytril®) 2mg oral	£13	2mg daily	£13/day+
Granisetron (Kytril®) 3mg IV, 1-3 doses within 24 hours	£26 to £77	Nil++	Nil

Ondansetron(Zofran®)			
MEC			
8mg oral x 2	£14	8mg orally twice daily for up to 5 days	£14 to £72
8mg IV bolus	£12	8mg orally twice daily for up to 5 days	£14 to £72
HEC			
Ondansetron (Zofran®) 8mg bolus IV for 1-3 doses	£12 to £36	8mg orally twice daily for up to 5 days	£14 to £72
Ondansetron 32 mg IV infusion	£48	8mg orally twice daily for up to 5 days	£14 to £72
Tropisetron (Navoban®) 5mg IV bolus	£12	5mg orally daily for 5 days	£54

+ Duration unspecified in licence
++ SPC mentions that there is clinical experience in patients using daily administration for up to five consecutive days in one course of therapy.

For ease of comparison, costs incurred during the acute and delayed phases have been separated for 5HT3 antagonists other than palonosetron. These costs must be combined to obtain the full cost of a course of treatment. For example, in the first row of the table, the cost of a course of dolasetron would be £13+(£14 to £42) = £27 to £55.

Summary of evidence on comparative efficacy

Palonosetron is an anti-emetic belonging to a group which act as antagonists at $5HT_3$ (serotonin) receptors. It has high binding affinity and selectivity for the $5HT_3$ receptor, and an elimination half-life of about 40 hours. It is licensed for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately emetogenic chemotherapy (MEC). In patients receiving highly emetogenic chemotherapy (HEC) it is licensed for the prevention of CINV in the acute phase (0-24 hours after administration of chemotherapy). MEC causes emesis in about 30-90% of patients and HEC in 90% or more. CINV is also characterised by retching and by nausea.

At the licensed dose of 0.25 mg, palonosetron has been compared to other $5HT_3$ receptor antagonists in three randomised double-blind controlled trials. Two trials involved patients receiving MEC in whom palonosetron was compared with single doses of ondansetron 32 mg or dolasetron 100 mg. In the third, palonosetron was compared with ondansetron 32 mg in patients receiving HEC.

In the trial involving HEC, anti-emetic therapy could be supplemented, at the investigator's discretion, with a single pre-treatment dose of corticosteroid and this was recorded in about 67% of patients. In the comparison with ondansetron in MEC, no patients received pre-treatment corticosteroids, while in the comparison with dolasetron it was permitted as a late amendment to the protocol, and was recorded for about 5% of patients.

Efficacy analyses were conducted on an intention-to-treat (ITT) sample involving all patients who received at least one dose of chemotherapy and study medication. The primary end-point in all trials was the proportion of patients achieving a complete response (CR), defined as no emetic episode (vomiting or retching) and no rescue anti-emetic medication, during the

first 24 hours following administration of chemotherapy. The primary analysis investigated non-inferiority of palonosetron to the comparator, with a threshold of -15% for the difference, palonosetron minus competitor, while secondary analyses investigated statistical significance for differences between treatments. After the acute phase, follow-up for efficacy was continued for a further period of four days which was defined as the delayed phase.

For the primary analysis, the difference between palonosetron and competitor met the defined criteria for non-inferiority in all trials. The difference was significantly in favour of palonosetron in the comparison with ondansetron in patients receiving MEC, but not in the other two trials. Palonosetron was significantly superior to the competitor in achieving CR in the delayed phase in the two trials involving MEC, but not in patients receiving HEC. Complete response rates (acute and delayed) are summarised below.

Patients achieving complete response (CR) in three phase III trials in acute phase (0-24 hours after the first dose of chemotherapy) and the delayed phase (24-120 hours)

Type of chemotherapy	No. (%) patients achieving CR 0-24 h			No. (%) patients achieving CR 24-120h		
	Palonosetron 0.25mg	Ondansetron 32mg	Dolasetron 100mg	Palonosetron 0.25mg	Ondansetron 32mg	Dolasetron 100mg
MEC	153/189 (81%) p=0.008	127/185 (69%)		140/189 (74%) p<0.001	102/185 (55%)	
MEC	119/189 (63%) NS (p>0.05)		101/191 (53%)	102/189 (54%) p=0.004		74/191 (39%)
HEC	132/223 (59%) NS (p>0.05)	126/221 (57%)		101/223 (45%) NS (p>0.05)	86/221 (39%)	

MEC= moderately emetogenic chemotherapy
HEC= highly emetogenic chemotherapy

Treatment difference in favour of palonosetron over comparator for the proportion of patients achieving complete response (CR) in three Phase III trials

Type of chemotherapy	**Comparator**	**Treatment difference palonosetron minus comparator (97.5% Confidence Intervals)**	
		0-24 hours	24-120 hours
MEC	ondansetron	12% (1.8% to 23%)	19% (7.5% to 30%)
MEC	dolasetron	10% (-1.7% to 22%)	15% (3.4% to 27%)
HEC	ondansetron	2.2% (-8.8% to 13%)	6.4% (CI not reported)

Secondary end-points included the proportion of patients achieving complete control, defined as a complete response with nausea being absent or no greater than mild in the acute and delayed phases. This favoured palonosetron numerically in all analyses, but the difference was significant only during the delayed phase in the two trials involving patients receiving MEC. There were significant differences in favour of palonosetron for the proportion of patients remaining free of emesis in the delayed phase and (except for the HEC trial) in the acute phase, and time to first emesis also favoured palonosetron. There were non-significant advantages for palonosetron in the proportion of patients requiring rescue medication during the acute and delayed phases.

Patients enrolled in the three main studies who were scheduled to receive further courses of chemotherapy could continue in a single-arm, open-label extension study investigating response to single doses of palonosetron 0.75 mg ± corticosteroid during subsequent cycles. A total of 875 patients received 1667 cycles of chemotherapy, predominantly MEC, and complete response rates were generally maintained over repeated cycles.

Summary of evidence on comparative safety

The adverse events most commonly judged to be related to palonosetron were those associated with other $5HT_3$ antagonists and were similar in incidence to comparator products. The most common adverse events in all groups were headache and constipation.

Summary of clinical effectiveness issues

The three main trials were similar in design, with the main differences being in the choice of comparator and in the chemotherapy regimens administered. However, there were differences between trials in the use of corticosteroids as adjuvant anti-emetic therapy. Where relevant, corticosteroid use was reported and subject to sub-group analysis. The palonosetron Summary of Product Characteristics states that efficacy in patients receiving HEC may be enhanced by the administration of corticosteroids as is the case with other 5HT3 receptor antagonist.

The primary end-point was based on emesis and / or retching and use of rescue medication, and did not assess nausea. Thus, at least in theory, patients with nausea of any severity could be classed as complete responders. Nausea was considered in the secondary end-point complete-control, which showed a significant advantage for palonosetron during the delayed phase in patients receiving MEC, but not in other analyses.

In trials, both palonosetron and the comparator $5HT_3$ receptor antagonists were administered as a single dose prior to chemotherapy. This reflects UK dosage recommendations for palonosetron and USA Federal Drug Administration recommendations for the competitors. However, in the UK, $5HT_3$ receptor antagonists other than palonosetron are recommended to be given before chemotherapy, then continued for a variable period afterwards.

The European Public Assessment Report expressed concerns about the quality of evidence for the efficacy of palonosetron in preventing delayed CINV, based on the choice of competitor regimens, particularly for the HEC trial. In this setting it is licensed only for prevention of acute symptoms.

The manufacturer provided a review of the literature for ondansetron and for granisetron, another $5HT_3$ receptor antagonist commonly used in the UK. On the basis of indirect comparison, they conclude that the response rates achieved with ondansetron in the trials reported in the submission were similar to those reported in the literature for a variety of 'real-life' ondansetron regimens and that the efficacy of granisetron is equivalent to ondansetron. They acknowledge the limitations of such indirect comparison.

There was a high incidence of adverse events in trials, but most were considered to be related to the underlying chemotherapy rather than to the anti-emetic therapy.

Summary of comparative health economic evidence

The manufacturers submitted a cost-utility analysis of palonosetron administered as a single pre-chemotherapy intravenous (IV) dose compared to ondansetron administered as pre-chemotherapy IV dose followed by oral administration in the post chemotherapy period for the prevention of chemotherapy induced nausea and vomiting (CINV) for patients receiving either moderately or highly emetogenic chemotherapy (MEC and HEC).

Data in the economic analysis for the efficacy of palonosetron versus ondansetron were derived from head to head randomised trials, one for patients receiving MEC, and one for patients receiving HEC. Three outcomes were defined in the economic model: treatment success (equivalent to the Complete Control sub-group in the trials), partial success (equivalent to the Complete Response minus Complete Control patients in the trials) and treatment failure. Separate analyses were conducted for a hypothetical cohort of patients receiving MEC or HEC and within each cohort for the acute and delayed CINV phases, and overall (both phases combined). Based on expert opinion, utilities and resource use estimates for breakthrough CINV were attached to each outcome. Palonosetron demonstrated superior treatment success outcomes and in all but one scenario was found to dominate ondansetron (higher QALY outcomes, lower net costs once resource savings are taken into account). For the acute phase for MEC an incremental cost per QALY of £18,000 was estimated.

Overall cost-effectiveness for both acute and delayed CINV phase for both HEC and MEC cohorts was established in the analysis. However, the main concerns with the analysis were the reliance on non-statistically significant treatment differences in the HEC trial and for the complete control group in the MEC trial, the crude estimation of utilities (based on a survey of oncologists), and assumptions about the dose and efficacy of the comparator product in HEC which may mean cost has been overestimated and/or efficacy underestimated for this arm. These uncertainties were not clearly tested in the one way sensitivity analysis.

A reasonable case can be made that, despite deficiencies in some of the data inputs to the economic model, if the acute and delayed phases are considered together the cost-effectiveness of palonosetron in patients in MEC is demonstrated. For HEC the weaknesses do not significantly undermine the case.

Patient and public involvement

A Patient Interest Group Submission was not made.

Budget impact

The manufacturers estimated a one-year budget impact of £190,000 for the use of palonosetron for patients receiving MEC, and cost savings of £220,000 for the use of palonosetron for patients receiving HEC. These costs and savings are based on 100% uptake by switching from current $5HT_3$ receptor therapy. However, there is a possible overestimate of the savings associated with HEC.

Guidelines and protocols

The UK National Comprehensive Cancer Network (NCCN), an alliance of 19 leading cancer centres, develops, updates and disseminates clinical practice guidelines in oncology. Version 1 (2005) of the antiemesis clinical practice guideline recommends dexamethasone plus a $5HT_3$ antagonist for acute prevention of nausea and vomiting following MEC and has been updated to specify palonsetron as the preferred $5HT_3$ antagonist. For acute prevention following HEC it recommends a $5HT_3$ antagonist (of which palonosetron is an option) combined with aprepitant, and dexamethasone and it gives five options for days 2-4 post chemotherapy.

The Multinational Association for Supportive Care in Cancer (MASCC), an international multidisciplinary organisation, hosted a consensus conference on antiemetic therapy in March 2004. In the first edition of the guideline process a $5HT_3$ antagonist plus dexamethasone was recommended for prevention of acute nausea and vomiting in MEC, then oral dexamethasone or a $5HT_3$ antagonist for prevention of delayed CINV (dexamethasone preferred). Palonosetron is listed alongside other $5HT_3$ antagonists but the guideline expressed no preference for an individual agent. A combination of $5HT_3$ antagonist, dexamethasone and aprepitant was recommended for the prevention of acute nausea and vomiting following chemotherapy of high emetic risk.

Additional information

In November 2004, following consideration of a full submission, SMC advised that:

Aprepitant is accepted for restricted use within NHS Scotland for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy.

The antiemetic regimen incorporating aprepitant was superior to one regimen (where dexamethasone alone was used in the delayed phase of treatment), for the prevention of cisplatin-induced nausea and vomiting in the acute and delayed phases. It should be initiated only by appropriate hospital based specialists.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 19 September 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

Gralla R, Lichinitser M, Van Der Vegt S et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol* 2003; 14(10): 1570-7.

Eisenberg P, Figueroa-Vadillo J, Zamora R et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: results of a phase III, single-dose trial versus dolasetron. *Cancer* 2003; 98(11): 2473-82.

Aapro M, Bertoli L.F, Lordick Fet al. Palonosetron is effective in preventing acute and delayed chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Poster presented at the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) 2003; 11.

Cartmell AS, Ferguson R, Yanagihara Vet al. Protection against chemotherapy-induced nausea and vomiting (CINV) is maintained over multiple cycles of moderately or highly emetogenic chemotherapy by Palonosetron (PALO), a potent 5-HT3 receptor antagonist (RA). American Society of Clinical Oncology 2003;22:Abstract number 3041.

European Medicines Agency. Aloxi, Palonosetron. European Public Assessment Report: Scientific Discussion. 28/04/05.
http://www.emea.eu.int/humandocs/Humans/EPAR/aloxi/aloxi.htm