HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

31 January 2007

ALOXI 250 µg solution for injection
B/1 – CIP 375,482-8

Applicant: THERABEL LUCIEN PHARMA

palonosetron
List I

Date of marketing authorisation: 22 March 2005 (centralised marketing authorisation)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Palonosetron

1.2. Indications

- Prevention of nausea and vomiting associated with moderately emetogenic anti-cancer chemotherapy.
- Prevention of acute nausea and vomiting associated with highly emetogenic anti-cancer chemotherapy.

1.3. Dosage

Intravenous route.

Adults:
250 microgrammes of palonosetron in a single intravenous bolus injection given approximately 30 minutes before the start of chemotherapy. Aloxi must be administered in 30 seconds.

Co-administration of a corticoid prior to chemotherapy can improve the efficacy of Aloxi in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy.

Elderly patients:
No dose adjustment is necessary in elderly patients.

Children and adolescents:
This substance is not recommended for patients under 18 in view of the lack of sufficient data.

Patients with hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment.

Patients with renal impairment
No dosage adjustment is necessary for patients with renal impairment. No clinical data is available on patients receiving haemodialysis.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

A : Digestive tract and metabolism
A04 : Anti-emetics and antinausea drugs
A04A : Anti-emetics and antinausea drugs
A04AA : Serotonin antagonist
A04AA05 : Palonosetron

2.2. Medicines in the same therapeutic category

5HT3 receptor antagonists:
ANZEMET (dolasetron)
ZOPHREN (ondansetron)
KYTRIL (granisetron)
NAVOBAN (tropisetron)

2.3. Medicines with a similar therapeutic aim

Other pharmacological classes
- neurokinin 1 antagonist: EMEND (aprepitant)
- neuroleptic: PLITICAN (aliprazide), PRIMPERAN (metoclopramide)
- phenothiazine: VOGALENE (metoprimazine)

3 ANALYSIS OF AVAILABLE DATA

Three double-blind randomised phase III studies versus an active reference product (ondansetron or dolasetron) were carried out to assess the efficacy and tolerance of palonosetron in preventing nausea and vomiting associated with moderately and highly emetogenic anti-cancer chemotherapy.

- Two studies were carried out on patients receiving moderately emetogenic chemotherapy (study PALO-99-03 versus ondansetron[1], study PALO-99-04 versus dolasetron[2]).
- One study was conducted on patients receiving highly emetogenic chemotherapy (study PALO-99-05 versus ondansetron[3]).

[1] Gralla 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*;14:1570-77

[2] Eisenberg 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* ;98:2473-82

[3] Aapro MS, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA*, et al.* A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 2006;17(9):1441-9.

3.1. Efficacy

Study PALO-99-03

Study objective

To assess the efficacy and tolerance of palonosetron versus ondansetron in the prevention of nausea and vomiting associated with moderately emetogenic anti-cancer chemotherapy.

Methodology

Type of Study:

Phase III controlled, randomised, double-blind study comparing ALOXI 250 µg IV or 750 µg IV (single administration 30 minutes before chemotherapy, 30-second bolus) with ondansetron 32 mg IV (single administration, 15-minute perfusion).
No associated corticotherapy.

Duration: assessment after 24 hours for the primary endpoint
monitoring for 120 hours for the secondary endpoints

Inclusion criteria

Adult patients with cancer, either having undergone or not having undergone anti-cancer chemotherapy before, requiring a single administration of less than four hours of moderately emetogenic chemotherapy.

Primary endpoint:

Proportion of patients who are fully responsive in the 24 hours following the chemotherapy (non-inferiority hypothesis)
N.B.: 'Fully responsive' was defined as no vomiting and no rescue medication.
Non-inferiority was demonstrated if the lower limit of the 97.5% CI of the efficacy difference between ALOXI and ondansetron was less than -15%.

Secondary endpoints:

The main other criteria assessed were complete control (patients who were fully responsive and patients experiencing less intense nausea), the severity of nausea (Likert scale[4]) and the proportion of patients who were fully responsive in the later phase (monitoring for 120 hours).

Results:

571 patients were included.
ITT population: 563 patients (189 in the ALOXI 250 µg group, 189 in the ALOXI 750 µg group and 185 in the ondansetron group).
PP population: 517 patients (172 in the ALOXI 250 µg group, 174 in the ALOXI 750 µg group and 171 in the ondansetron group).

This opinion discusses only the results relating to the dosage referred to in the marketing authorisation (250 µg palonosetron).

Patient characteristics

The populations were comparable between the two groups in terms of demographic characteristics (71% women and an average age of 55.6 ± 11). The main anti-cancer drugs being used were cyclophosphamide (63% of patients in both groups) and doxorubicin (approximately 50% of patients in both groups).

[4] The severity of nausea was assessed by the patients using the Likert scale (4 levels: no nausea, slight nausea, moderate nausea, severe nausea).

Most of the cytotoxic substances being used were moderately emetogenic according to Hesketh's classification.

Results for the endpoints
Table 1: Percentage of responsive patients in each treatment group

	Aloxi 250 µg	**Ondansetron 32 mg**	**CI of the difference [palonosetron 250µg - ondansetron 32mg]**
ITT population	*N = 189*	*N = 185*	
Fully responsive (no vomiting and no rescue medication)		**97.5% CI[a]**	
0 – 24 hours	81.0%	68.6%	[1.8%, 22.8%]
PP population	*N = 172*	*N = 171*	
Fully responsive (no vomiting and no rescue medication)		**97.5% CI[a]**	
0 – 24 hours	87.8%	70.8%	[6.9%, 27.2%]

[a] The aim of the study was to demonstrate non-inferiority. A lower limit greater than -15% demonstrates non-inferiority between Aloxi and the reference product.

Considering the main endpoint and the results of the PP and ITT analysis:
- ALOXI 250 µg was not inferior to ondansetron 32 mg in terms of full response (non-inferiority hypothesis: 97.5% CI of the difference [1.8%, 22.8 %]; threshold δ= -15%),
- There is a significant superiority difference in favour of palonosetron 250 µg compared to ondansetron 32 mg (p = 0.0085; 97.5% CI of the difference to the right of the decimal point).

With regard to the secondary endpoints that were explored but not investigated in depth, ALOXI 250 µg was not inferior to ondansetron 32 mg in terms of full response in the later phase (hour 24 to hour 120) (non-inferiority hypothesis: 97.5% CI of the difference [7.5%, 30.3 %]; threshold δ= -15%).
No statistically significant difference was observed between the two treatments in terms of complete control and in terms of absence of nausea during the 24 hours after the start of chemotherapy.

Study PALO-99-04

Study objective
To assess the efficacy and tolerance of palonosetron versus dolasetron in the prevention of nausea and vomiting associated with moderately emetogenic anti-cancer chemotherapy.

Methodology
Type of Study:
Phase III controlled, randomised, double-blind study comparing ALOXI 250 µg IV or 750 µg IV (single administration 30 minutes before chemotherapy, 30-second bolus) with dolasetron 100 mg IV (single administration, 30-second bolus).

Duration: assessment after 24 hours for the primary endpoint
monitoring for 120 hours for the secondary endpoints

Inclusion Criteria:
Adult patients with cancer, either having undergone or not having undergone anti-cancer chemotherapy before, requiring a single administration of less than four hours of moderately emetogenic chemotherapy.

Primary endpoint
Proportion of patients who are fully responsive in the 24 hours following the chemotherapy (non-inferiority hypothesis).
N.B.: 'Fully responsive' was defined as no vomiting and no rescue medication.
Non-inferiority was demonstrated if the lower limit of the 97.5% CI of the efficacy difference between ALOXI and dolasetron was less than -15%.

Secondary endpoints:
The main other criteria assessed were complete control (patients who were fully responsive and patients experiencing less intense nausea), the severity of nausea (Likert scale) and the proportion of patients who were fully responsive in the later phase (monitoring for 120 hours).

Results:
592 patients were included.
ITT population: 569 patients (189 in the ALOXI 250 µg group, 189 in the ALOXI 750 µg group and 191 in the dolasetron group).
PP population: 463 patients (156 in the ALOXI 250 µg group, 151 in the ALOXI 750 µg group and 156 in the dolasetron group).

This opinion discusses only the results relating to the dosage referred to in the marketing authorisation (250 µg palonosetron).

Patient characteristics
The populations were comparable between the two groups in terms of demographic characteristics (82% women and an average age of 54 ± 13). The main anti-cancer drugs being used were cyclophosphamide (75% of patients in both groups) and doxorubicin (48% of patients in both groups).
Most of the cytotoxic substances being used were moderately emetogenic according to Hesketh's classification.
Associated corticotherapy was administered to 5.8% of patients in the palonosetron 250 µg group and 4.2% of patients in the dolasetron group.

Results for the endpoints
Table 2: Percentage of responsive patients in each treatment group

	Aloxi 250 µg	**Dolasetron 100 mg**	**CI of the difference [palonosetron 250 µg - dolasetron 100 mg]**
ITT population	*N = 185*	*N = 191*	
Fully responsive (no vomiting and no rescue medication)		**97.5% CI[a]**	
0 – 24 hours	63.0	52.9	[-1.7 %, 21.9 %]
PP population	*N = 156*	*N = 156*	
Fully responsive (no vomiting and no rescue medication)		**97.5% CI[a]**	
0 – 24 hours	71.8	59.6	[-0.4 %, 24.8 %]

[a] The aim of the study was to demonstrate non-inferiority. A lower limit greater than -15% demonstrates non-inferiority between Aloxi and the reference product.

ALOXI 250 µg was not inferior to dolasetron 100 mg in terms of full response (non-inferiority hypothesis: 97.5% CI of the difference [-1.7%, 21.9%]; threshold δ= -15%) in the 24 hours following chemotherapy.

With regard to the secondary endpoints that were explored but not investigated in depth, ALOXI 250 µg was not inferior to dolasetron 100 mg in terms of full response in the later phase (hour 24 to hour 120) (non-inferiority hypothesis: 97.5% CI of the difference [3.4%, 27.1%]; threshold δ= -15%).
No statistically significant difference was observed between the two treatments in terms of complete control and in terms of absence of nausea during the 24 hours after the start of chemotherapy.

Study PALO-99-05

Study objective

To assess the efficacy and tolerance of palonosetron versus ondansetron in the prevention of nausea and vomiting associated with highly emetogenic anti-cancer chemotherapy.

Methodology

Type of Study:

Phase III controlled, randomised, double-blind study comparing ALOXI 250 µg IV or 750 µg IV (single administration 30 minutes before chemotherapy, 30-second bolus) with ondansetron 32 mg IV (single administration, 15-minute perfusion).

Duration: assessment after 24 hours for the primary endpoint
monitoring for 120 hours for the secondary endpoints

Inclusion Criteria:

Adult patients with cancer, either having undergone or not having undergone anti-cancer chemotherapy before, requiring a single administration of less than four hours of highly emetogenic chemotherapy.

Primary endpoint

Proportion of patients who are fully responsive in the 24 hours following the chemotherapy (non-inferiority hypothesis).
N.B.: 'Fully responsive' was defined as no vomiting and no rescue medication.
Non-inferiority was demonstrated if the lower limit of the 97.5% CI of the efficacy difference between ALOXI and ondansetron was less than -15%.

Secondary endpoints:

The other criteria assessed were complete control (patients who were fully responsive and patients experiencing less intense nausea), the severity of nausea (Likert scale) and the proportion of patients who were fully responsive in the later phase (monitoring for 120 hours).

Results

680 patients were included.
ITT population: 667 patients (223 in the ALOXI 250 µg group, 223 in the ALOXI 750 µg group and 221 in the ondansetron group).
PP population: 572 patients (185 in the ALOXI 250 µg group, 191 in the ALOXI 750 µg group and 196 in the ondansetron group).

This opinion discusses only the results relating to the dosage referred to in the marketing authorisation (250 µg palonosetron).

Patient characteristics
The populations were comparable between the two groups in terms of demographic characteristics (approximately 51% women and an average age of 52 ± 14). The main anti-cancer drug used was cisplatin (82% of patients in both groups).
Most of the cytotoxic substances being used were highly emetogenic according to Hesketh et al.'s classification.
Associated corticotherapy (20 mg of dexamethasone prior to chemotherapy) was administered to 67.3% of patients in the palonosetron 250 µg group and 66.5% of patients in the ondansetron group.

Results for the endpoints
Table 2: Percentage of responsive patients[a] in each treatment group

	Aloxi 250 µg	**Ondansetron 32 mg**	**CI of the difference [palonosetron 250 µg - ondansetron 32 mg]**
ITT population	*N = 223*	*N = 221*	
Fully responsive (no vomiting and no rescue medication)		**97.5% CI[a]**	
0 – 24 hours	59.2%	57.0%	[-8.8 %, 13.1 %]
PP population	*N = 185*	*N = 196*	
Fully responsive (no vomiting and no rescue medication)		**97.5% CI[a]**	
0 – 24 hours	69.2%	63.3%	[-5.4 %, 17.3 %]

[a] The aim of the study was to demonstrate non-inferiority. A lower limit greater than -15% demonstrates non-inferiority between Aloxi and the reference product.

ALOXI 250 µg was not inferior to ondansetron 32 mg in terms of full response (non-inferiority hypothesis: 97.5% CI of the difference [-8.8%, 13.1 %]; threshold δ= -15%) in the 24 hours following chemotherapy.

With regard to the secondary endpoints that were explored but not investigated in depth, ALOXI 250 µg was not inferior to ondansetron 32 mg in terms of full response in the later phase (hour 24 to hour 120) (non-inferiority hypothesis: 97.5% CI of the difference [-4.6%, 17.3 %]; threshold δ= -15%).

No statistically significant difference was observed between the two treatments in terms of complete control and in terms of absence of nausea during the 24 hours after the start of chemotherapy.

3.2. Adverse events

In clinical studies performed at a dose of 250 µg (633 patients in total), the most frequent adverse events which it was thought might be related to ALOXI were headache (9%) and constipation (5%).
In studies, tolerance was comparable to tolerance of the benchmark products used (ondansetron or dolasetron).

3.3. Conclusion

ALOXI 250 µg IV has been shown not to be inferior to ondansetron 32 mg IV and dolasetron 100 mg IV in terms of complete response (defined by the absence of vomiting and no need for rescue medication) during the first 24 hours in patients who have received moderately emetogenic chemotherapy. As far as superiority is concerned, the results show a significant difference in favour of palonosetron 250 µg compared to ondansetron 32 mg.

In patients who have received highly emetogenic chemotherapy, ALOXI 250 µg IV was found to be not inferior to ondansetron 32 mg IV in terms of complete response (defined as above) in the acute post-chemotherapy phase.

The studies submitted were not designed in order to assessing the efficacy of palonosetron in late-onset nausea and vomiting.

In studies, tolerance of ALOXI was comparable to tolerance of the benchmark products used (ondansetron and dolasetron).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual Benefit

- Nausea and vomiting induced by **moderately** emetogenic chemotherapy are disabling and bring about a marked deterioration in the quality of life.

ALOXI is intended to be used for prophylaxis.
The efficacy/adverse effects ratio of this product is high in this indication.
This proprietary drug is intended for first-line therapy.
There are alternative drugs available.

The public health burden of nausea and vomiting associated with moderately emetogenic chemotherapy is moderate.
Improving overall cancer treatment is a public health imperative. The therapeutic need to prevent late-onset nausea and vomiting caused by anti-cancer chemotherapy is not adequately met at present. In contrast, existing drugs are largely sufficient to meet the needs in the acute phase.
Given the results of the PALO-99-03 study in terms of complete response, ALOXI is likely to have at best a minor impact compared to ondansetron on reducing morbidity associated with acute vomiting and nausea caused by moderately emetogenic anti-cancer chemotherapy.
However, no impact is likely in the later phase. There is also no guarantee that experimental data will be transposed into clinical use. Corticotherapy was not used at all or only rarely in the studies, whereas in practice it is often used in moderately emetogenic chemotherapy.
Consequently, ALOXI is not expected to have an impact on public health in this indication.

The actual benefit of this proprietary product is substantial.

- Nausea and vomiting induced by **highly** emetogenic chemotherapy are disabling and bring about a marked deterioration in the quality of life.

ALOXI is intended to be used for prophylaxis.
The efficacy/adverse effects ratio of this product is high in this indication.

This proprietary drug is intended for first-line therapy.
There are alternative drugs available.

> The public health burden of nausea and vomiting associated with highly emetogenic chemotherapy is moderate.
> Improving overall cancer treatment is a public health imperative. The therapeutic need to prevent late-onset nausea and vomiting caused by anti-cancer chemotherapy is not adequately met at present. In contrast, existing drugs are largely sufficient to meet the needs in the acute phase.
> The data available indicates that ALOXI is unlikely to have any impact compared to ondansetron on reducing morbidity associated with acute or late-onset vomiting and nausea caused by highly emetogenic anti-cancer chemotherapy.
> Consequently, ALOXI is not expected to have an impact on public health in this indication.

The actual benefit of this proprietary product is substantial.

4.2. Improvement in actual benefit

The Transparency Committee is of the opinion that ALOXI offers a minor improvement in actual benefit (IAB IV) in terms of efficacy compared to ondansetron when used to prevent nausea and vomiting associated with **moderately** emetogenic anti-cancer chemotherapy.

ALOXI offers no improvement in actual benefit (IAB V) compared to ondansetron when used to prevent acute vomiting and nausea associated with **highly** emetogenic anti-cancer chemotherapy.

4.3. Therapeutic use

There is no official recommendation in France for the treatment of nausea and vomiting associated with chemotherapy. Therapeutic strategy is based on the international recommendations described below.

	Highly emetogenic chemotherapy		**Moderately emetogenic chemotherapy**	
	Prevention of acute vomiting and nausea	*Prevention of late-onset vomiting and nausea*	*Prevention of acute vomiting and nausea*	*Prevention of late-onset vomiting and nausea*
ASCO [Gralla, 1999[5]]	Anti-$5HT_3$ + corticotherapy	- Chemotherapies including cisplatin : Corticotherapy + metoclopramide or anti-$5HT_3$ - Chemotherapies not including cisplatin : Corticotherapy ± metoclopramide ± anti-$5HT_3$	Corticoids	-
ASCP [Kris, 2006[6]]	Anti-$5HT_3$ + aprepitant + corticotherapy	Corticotherapy + aprepitant	Anti-$5HT_3$ + corticotherapy	aprepitant
MASCC [Kris, 2004[7] ; Herrstedt, 2005[8] ; Roila, 2005[9]]	Anti-$5HT_3$ + corticotherapy + aprepitant	Corticotherapy + aprepitant	Anti-$5HT_3$ + corticotherapy	Oral corticotherapy or Anti-$5HT_3$
ESMO [ESMO,2005[10]]	Anti-$5HT_3$ + corticotherapy + aprepitant	Corticotherapy + aprepitant	Anti-$5HT_3$ + corticotherapy	Anti-$5HT_3$ or corticotherapy
NCCN [NCCN, 2005[11]]	Aprepitant + Corticotherapy + Anti-$5HT_3$ ± lorazepam		Corticotherapy + Anti-$5HT_3$ (palonosetron) ± lorazepam	

ASCO: American Society of Clinical Oncology
ASCP: American Society for Clinical Pathology
MASCC: Multinational Association of Supportive Care in Cancer
ESMO: European Society for Medical Oncology
NCCN: National Comprehensive Cancer Network

[5] Gralla RJ et al. Recommendations for the use of anti-emetics: evidence-based clinical practice guidelines. Journal of clinical oncology 1999; 117:2971, 1999.
[6] Kris MG et al. American society of clinical Oncology Guideline for Antiemetics in Oncology: Update 2006. J Clin Oncol 2006; 24: 2932-47.
[7] Kris MG. Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic-risk chemotherapy Support Care Cancer 2004; 13: 85-96.
[8] Herrstedt J. Acute emesis: moderately emetogenic chemotherapy. Support care Cancer 2005; 13: 97-103.
[9] Roila F. Delayed emesis: moderately emetogenic chemotherapy. Support Care Cancer 2005; 13: 104-108.
[10] ESMO minimum clinical recommendations for prophylaxis of chemotherapy-induced nausea and vomiting. Annals of Oncology 2005; 16: i77-i79.
[11] National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Antiemetics. V1.2005

In the absence of French recommendations and given the clinical data available, ALOXI could be used as first-line therapy as an alternative to other anti-$5HT_3$ drugs in the prevention of nausea and vomiting associated with moderately and highly emetogenic chemotherapies.

4.4. Target population

The target population must take account of the number of cycles which cancer patients receiving moderately or highly emetogenic chemotherapy undergo.
An epidemiological study performed in France in 2005 at the firm's request by IMS (Oncology Analyzer) found that 279,302 cancer patients had undergone chemotherapy. Of these, 202,993 patients were treated with highly or moderately emetogenic chemotherapy. It is thought that approximately 80% of these patients (around **162,000 individuals**) were treated with a setron and/or aprepitant.

Patients undergoing highly emetogenic chemotherapy have on average 4.5 cycles of chemotherapy, and patients undergoing moderately emetogenic chemotherapy have on average 5.6 cycles. This means that the number of cycles of highly or moderately emetogenic chemotherapy requiring anti-emetic treatment with setron can be estimated at **700,000 to 900,000**.

4.5. Transparency Committee Recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the marketing authorisation.

4.5.1. Packaging: suitable for the conditions of prescription
4.5.2. Reimbursement rate: 65%
4.5.3. Exception drug status

The committee is in favour of awarding this product exception drug status.

The Transparency Committee requests that a study be set up on patients being treated with ALOXI for the indication "Prevention of nausea and vomiting associated with moderately emetogenic anti-cancer chemotherapies". This study should describe the following aspects under actual treatment conditions:

- the characteristics of patients being treated (sex, age, etc.) and their chemotherapy (indication, protocol, cycles and dosage regimens);
- the characteristics of anti-emetic ALOXI treatment (administration site, dosage and concomitant medication);
- the impact of the use of ALOXI on the occurrence of late-onset nausea and its treatment (consumption of anti-emetic drugs, especially 5-HT3 receptor antagonists).

The duration of the study, to be determined by a scientific committee, should be explained, and it should be sufficient to meet the Committee's request.