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Committee for Medicinal Products for Human Use (CHMP)

Aloxi

(Palonosetron)

Procedure No. EMEA/H/C/000563/A46/0016

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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Submission of a study in accordance with Article 46 of Regulations

RAPPORTEUR
ASSESSMENT REPORT

Aloxi
(Palonosetron)

EMEA/H/C/563

Scope of follow up measure:	**Submission of a study in accordance with Article 46 of Regulations (EC)**
Rapporteur:	**Dr. Patrick Salmon**
Clinical Assessor:	**Dr Patrick Salmon**
Procedure start date:	**15/02/2010**
Preliminary Assessment Report:	**23/03/2010**
CHMP members comments:	**09/04/2010**
Final Assessment Report:	**14/04/2010**

Assessor Summary

The report on this study performed in Russia and the Ukraine, in 7 patients aged over 28 days and up to 23 months, 96 patients between 2 years and 11 years, and 47 patients between the ages of 12 and 16 years, suggests no safety issue and also suggests efficacy up to 72 hours post operatively.
Currently the SmPC in section 4.2 states under Children and adolescents: Aloxi is not recommended for use in children below age 18 due to insufficient data.

The Guidance on the SmPC advises that when there is no indication in the paediatric population, available information should be summarised using the standard statements "The safety and efficacy in children have not been established. Currently available data are described in section 5.1, but no recommendation on posology can be made" and the assessors proposes that section 4.2 should be modified in this way with a summary of the study provided in section 5.1

The MAH is requested to propose a summary of the study indicating the age of the patients treated, the doses used, and the main findings regarding efficacy and safety.

MAH OVERVIEW OF NEW STUDY COMPLETED SINCE SUBMISSION OF THE ORIGINAL MAA

Studies in special groups: Paediatric populations
The Phase 3 study PALO-07-29 conducted in paediatric patients to investigate the prevention of post operative nausea and vomiting (PONV) extends the available clinical information for Palonosetron, and its findings are summarised below.

PALO-07-29: "A Multicentre, Double-blind, Randomised, Parallel Group, Stratified Study to Assess the Safety and Efficacy of Single IV Doses of Palonosetron to Prevent Postoperative Nausea and Vomiting in Paediatric Patients"
Postoperative nausea and vomiting (PONV) is a frequent and important cause of morbidity in children; occurring twice as frequently in children as in adults, increasing in incidence until puberty, and thereafter decreasing to adult incidence rates. (1)

Overall, an estimated 40% to 50% of children experience PONV after receiving general anaesthesia. (2) The incidence of PONV after tonsillectomy or strabismus surgery may be as high as 70% and 80%, respectively, in paediatric patients who have not received antiemetic prophylaxis. (3)(4)

Despite the introduction of new anti-emetic medications, PONV is still a frequent problem affecting the paediatric population. Anti-emetics of choice for PONV include but are not limited to, dexamethasone, dimenhydrinate, ondansetron, dolasetron and granisetron. The 5-HT_3 Receptor Antagonists are the anti-emetic drugs of choice for PONV in children because, as a class, they have proven efficacy in the prevention and treatment of PONV, with minimal adverse effects.
A clinical study was undertaken by Helsinn Healthcare to assess the safety and efficacy of intravenous palonosetron (Aloxi® solution for injection) in the prevention of PONV over a 72 hour postoperative period in children undergoing elective surgery.

The study design was a multicentre, double-blind, randomised, parallel and stratified study. Paediatric patients were given a single intravenous (IV) administration of palonosetron at one of two doses; either 1 mcg/kg or 3 mcg/kg, immediately before induction of general intravenous anaesthesia.

Use of an IV line facilitates rapid onset of loss of consciousness, relaxation and analgesia, and since IV access is already available for the induction and maintenance of anaesthesia, the preferred route of administration of the palonosetron study drug was intravenously prior to surgery, thus avoiding additional needle sticks for the patient.
The study, conducted at 4 sites in Russia and 8 sites in the Ukraine, involved 150 evaluable paediatric patients, aged >28 days up to 16 years undergoing surgical elective procedures requiring general intravenous anaesthesia.
The safety parameters evaluated included the recording of adverse events, physical examination, vital sign measurements, 12-lead ECG, and clinical laboratory (haematology, blood chemistry and urinalysis) assessments.
Efficacy was evaluated based on emetic episodes, severity of nausea (only for patients aged 6 up to 16 years inclusive) and intake of rescue medication.
The efficacy parameter of major interest in the study was the proportion of patients with no emetic episodes during the overall time period 0-72 hours post-operatively. Additional efficacy parameters assessed included the proportion of patients with no emetic episodes, the severity of nausea (in patients aged 6-17 years), the time to first emetic episode, the time to first administration and need for rescue medication, the time to treatment failure (based on time to the first emetic episode or time to the first administration of rescue medication, whichever occurred earlier), the proportion of patients without rescue medication use, and the Complete Response (CR, defined as no emesis and/or retching and no rescue medication). The above-mentioned parameters were evaluated during the 0-6 hour, 6-24 hour, 24-48 hour, 48-72 hour, 0-24 hour, 0-48 hour, 0-72 hour and 24-72 hour time intervals.

Safety analysis was performed for the safety cohort, defined as all patients who received palonosetron and had at least one safety assessment after treatment and all the statistical analyses were descriptive.
The number of patients who experienced at least one treatment emergent adverse event (TEAE), including related, severe, severe related, serious, and serious related TEAE randomisation techniques, deaths, the number of patients withdrawn due to TEAE and the number of patients withdrawn due to related TEAE were recorded by treatment dose and overall.
Clinical laboratory assessments were analysed in the central laboratory with reference ranges differentiated by gender and/or age group. Clinical laboratory data results were recorded by treatment group and test name.
For all ECGs, heart rate (HR) and PR, QRS, QT and QTc intervals were analysed. For each parameter, the number of patients with at least one abnormality after baseline was recorded.

The total number of subjects initially planned for inclusion in study PALO-07-29 and actually randomised to the study, including numbers by age, gender and race, is provided in Table 1 below.

Table 1: Breakdown of Total numbers of Patients, PALO-07-29

Patient Demographic	Number of Patients
Total number of patients initially planned for the study	150
Total number of patients who entered in the study	150
Total numbers by gender	
Males	92
Females	58
Total numbers by age	
>28 days up to 23 months	7
2 years up to 11 years	96
12 years up to 16 years	47
Total numbers by race	
Caucasian	150
Total number who dropped out of the study for any reason	0

A total of 150 Caucasian paediatric patients [92 (61.3%) males; 58 (38.7%) females] ranging in age from 0.7 to 16.7 years, received palonosetron and were analysed as a safety set.

Randomisation was stratified by age group (>28 days up to 23 months; 2 years up to 11 years; 12 years up to 16 years inclusive) and by country. Within each stratum, patients were randomised to receive one of the two treatment doses.

Summary of safety results:

A total of 92 treatment emergent adverse events (TEAEs) were experienced by 61 (40.7%) patients, of which 38 events occurred in 29 (39.2%) patients in the palonosetron 1 mcg/kg group and 54 events in 32 (42.1%) patients in the palonosetron 3 mcg/kg group.
TEAEs were most commonly reported in the "injury, poisoning and procedural complications, and respiratory, thoracic and mediastinal disorders" System Organ Class (SOC) in both treatment groups. The most frequently reported TEAEs in both treatment groups were procedural pain (palonosetron 1 mcg/kg: 27.0% of patients; palonosetron 3 mcg/kg: 25.0% of patients), pharyngolaryngeal pain (palonosetron 1 mcg/kg: 6.8%; palonosetron 3 mcg/kg: 2.6%), and rhinalgia (palonosetron 3 mcg/kg: 5.3%).
In the gastrointestinal disorders SOC, vomiting and nausea occurred in the palonosetron 3 mcg/kg group only (6.6% and 5.3%, respectively), in 5 and 4 patients respectively.
Adverse events were analyzed by subgroups based on country, gender, and age group.
Within subgroups, the percentage of patients with TEAEs was comparable between treatment groups, except for patients >28 days to 23 months old. In this age group, the low number of patients precluded meaningful interpretation of data.
In the youngest patients (>28 days – 23 months), the only TEAEs reported were procedural pain, pyrexia, and nasopharyngitis. Procedural pain was reported for all 4 patients with TEAEs in this subgroup.
None of the TEAEs was judged to be related to the study drug, and all TEAEs were classified as being of mild or moderate intensity. The percentage of patients reporting at least one TEAE of moderate intensity was somewhat lower for the low dose group (18.9%) than for the high dose group (27.6%); however, the percentage of patients with mild TEAEs was comparable between the treatment groups (palonosetron 1 mcg/kg: 23.0%; palonosetron 3 mcg/kg: 25.0%).

No risk for cardiac safety issues was determined in the study population and no safety concerns were raised for the administration of palonosetron in both treatment groups on examination of vital signs or laboratory data, or on physical examination. No deaths occurred, no SAEs were reported, and no patients were withdrawn from the study due to the occurrence of TEAEs.

Summary of efficacy results:

A similar pattern of response was observed between the two treatment groups for the efficacy endpoint of major interest (i.e. the proportion of patients without emesis during the 0-72 hours interval post-operatively) as well as for the additional efficacy parameters recorded.
Efficacy results are summarised in Table 2.

Table 2: Proportion of Patients With/Without Emetic Episodes During 0-72 hours post-operatively

		Palonosetron 1 mcg/kg (N=75)			Palonosetron 3 mcg/kg (N=75)	
		Emetic Episode			Emetic Episode	
Time Interval		Yes	No		Yes	No
0-72 hours	n (%)	9 (12.0)	66 (88.0)		12 (16.0)	63 (84.0)
	95% CI		[78.4, 94.4]			[73.7, 91.4]

The proportion of patients without emetic episodes during 0-72 hours post-operatively was 88.0% in the low dose group and 84.0% in the high dose group. Within subgroups, the proportion of patients without emetic episodes was comparable between treatments during the 0-72 hours.
In the low dose group, the proportion of patients without nausea was 69.2% during the 0-72 hours interval and ranged from 71.2% (0-6 hours) to 98.1% (48-72 hours) at further time intervals. The proportion of patients without nausea in the high dose group was 66.7% during the 0-72 hours time period and ranged from 68.5% (0-6 hours) to 100% (48-72 hours) during further intervals.
Only 2 (2.7%) patients in the low dose group and 1 (1.3%) patient in the high dose group were administered rescue medication.

MAH CONCLUSIONS on BENEFIT AND RISK

The evaluation of study PALO-07-29 revealed no significant change to the established risks/benefit profile of palonosetron. The good tolerability of palonosetron at both doses, and its proven efficacy for protection against vomiting and nausea up to 72 hours postoperatively, support the use of intravenous palonosetron as an optimal therapeutic alternative to other drugs to prevent PONV in paediatric patients undergoing surgical procedures.

In light of the above conclusions no changes to the safety information for palonosetron are proposed. The data from study PALO-07-29 on the clinical use of palonosetron for the prevention of post operative nausea and vomiting in children aged >28 days up to 16 years are likely to be of interest to prescribers even though cannot be considered as conclusive. However since these data do not influence the benefit-risk balance for Aloxi 250 micrograms solution for injection approved in EU for the prevention of CINV, no regulatory changes to the marketing authorisation are proposed.

Assessor comment

The report on this study performed in Russia and the Ukraine, in 7 patients aged over 28 days and up to 23 months, 96 between 2 years and 11 years, and 47 patients between the ages of 12 and 16 years, suggests no safety issue and also suggests efficacy up to 72 hours post operatively.

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2.5.7 REFERENCES

1. Kovac AL. *Management of postoperative nausea and vomiting in children*. Pediatric Drugs 2007; 9(1): 47-69

2. Watcha MF, White PF. *Postoperative nausea and vomiting: Its etiology, treatment and prevention*. Anesthesiology 1992; 77: 162-84

3. Ferrari LR and Donlon JV. *Metoclopramide reduces the incidence of vomiting after tonsillectomy in children.* Anesthesia and Analgesia Journal 1992; 75: 351-4

4. Madan R, Bhatia A, Chakithandy S, Subramaniam R et al. *Prophylactic Dexamethasone for Postoperative Nausea and Vomiting in Pediatric Strabismus Surgery: A Dose Ranging and Safety Evaluation Study*. Anesthesia and Analgesia 2005; 100:1622-1626

2.5.8 CROSS REFERENCE LIST OF CLINICAL STUDY REPORT

Report Number	**Date**	**Report Title**	**Location Module**
PALO-07-29	July 2009	A Multicenter, Double-blind, Randomized, Parallel Group, Stratified Study to Assess the Safety and Efficacy of Single IV Doses of Palonosetron to Prevent Postoperative Nausea and Vomiting in Pediatric Patients	5.3.5.4