VI.2 Elements for a Public Summary

VI.2.1 Overview of disease

Palonosetron 250 micrograms solution for injection is indicated in adults for:

- the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy,

- the prevention of acute nausea and vomiting associated with moderately emetogenic cancer chemotherapy

Nausea and vomiting continues to be significant side effects of cancer therapy problem in patients receiving chemotherapy[ii].

Prevention and control of nausea and vomiting (emesis) are paramount in the treatment of cancer patients[2]. Nausea and vomiting can result in a number of clinical implications for patients: serious metabolic derangements, nutritional depletion and anorexia, deterioration of patients' physical and mental status, withdrawal from potentially useful and curative antineoplastic treatment and degeneration of self-care and functional ability[iii,iv]. CINV also significantly impairs patient daily functioning and health related quality of life (HRQoL).

Nausea and vomiting associated with chemotherapy can be acute, delayed, or anticipatory. Acute emesis is divided into acute (within 12 h of treatment) and late-acute (12–24 h).

Delayed nausea and vomiting occurs more than 24 h after treatment and can persist for up to 1 week. Anticipatory emesis occurs before chemotherapy in patients with poorly controlled emesis from a previous course of chemotherapy. The severity and pattern of chemotherapy-induced emesis depends on several factors associated with the patient as well as on the type of chemotherapy, dose schedule, and regimen[v,vi] . The most highly emetogenic agent is cisplatin, which at doses of 50 mg/m2 or more induces nausea and vomiting in more than 90% of patients who are not given prophylactic antiemetics. Other agents that have moderately high emetogenic potential include doxorubicin, cyclophosphamide, and carboplatin.

Evidence suggests that emesis is mediated mainly by several neurotransmitters in the gastrointestinal tract and central nervous system (CNS) including serotonin, dopamine, protachykinin 1 and gamma-aminobutyric acid (GABA), which act directly and indirectly on the center that controls emesis located in the medulla and on the postrema of the fourth ventricle. These neurotransmitters and their receptors have been the main targets of new antiemetic agents[vii].

It appears that 5-hydroxytryptamine (5-HT) receptors are particularly important in the pathophysiology of acute vomiting. Delayed emesis is observed in as many as 80% of patients, typically occurring 24 to 72 hours after high total doses of cisplatin (>100 mg/m2) have been administered. To date, the pathophysiology of delayed emesis remains unclear. The precise mechanism of action of the 5-HT-receptor antagonists is unknown; however, they may have both a central and a peripheral effect. The gastrointestinal tract contains 80% of the body's supply of serotonin. During chemotherapy, enterochromaffin cells that line the gastrointestinal tract are damaged resulting in the release of serotonin. Serotonin stimulates vagal afferent neurons that activates the vomiting center or directly activate the chemotherapy trigger zone[viii].

A number of antiemetic agents are currently available for the prophylaxis and treatment of CINV[4]. In addition to 5-HT3 receptor antagonists, substances used in the treatment of CINV include mainly steroids and dopamine D2 antagonists. Recently, a new antiemetic agent, aprepitant (an antagonist of the neurokinin 1 (NK1) receptors), has now been included in the recommendations for the prevention of emesis induced by chemotherapy of moderate and high emetic risk[6].

5-HT3 inhibitors block serotonin receptors and subsequently the neuronal cascade of events leading to nausea and vomiting is in effect blunted or blocked from further activation. Studies

have shown that the 5-HT3 receptor antagonists decrease emesis from several chemotherapeutic agents, including cisplatin, cyclophosphamide and doxorubicin[ix].

5-HT3 receptor antagonists used as antiemetic therapies available in some European countries include ondansetron, granisetron, tropisetron and dolasetron. Since their introduction, these agents have become the standard antiemetic agents for control of CINV and continue to provide effective management of nausea and vomiting with rarely requiring discontinuation of therapy.

VI.2.2 Summary of treatment benefits

Palonosetron is effective in controlling acute CINV in patients receiving highly (HEC) or moderately (MEC) emetogenic chemotherapy regimens.

Palonosetron is well tolerated; common adverse events include mild headache, and constipation[x].

Clinical trials have shown that as a single agent, palonosetron offers better control of CINV compared with currently available 5-HT3-RAs (ondansetron, granisetron, tropisetron and dolasetron). In two-phase III MEC trials, single-dose i.v. palonosetron have suggested possible higher efficacy compared with ondansetron or dolasetron for both acute and delayed CINV[xi,xii]. Even though they showed statistically better results for palonosetron, both studies were designed as non-inferiority trials. In a further phase III trial, palonosetron was reported to be as effective as ondansetron in preventing acute CINV in patients receiving HEC.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy in children have not been established. No recommendation on posology can be made. The dosing information for children and adolescents for prevention of acute chemotherapy-induced nausea and vomiting is based on clinical trials.

No data are available for patients with end stage renal disease undergoing haemodialysis. No pharmacokinetic data in haemodialysis patients are available. Severe renal impairment reduces renal clearance, however total body clearance in these patients is similar to healthy subjects. No dosage adjustment is necessary in patients with renal insufficiency.

No clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer. Therefore, palonosetron should not be used in pregnant women unless it is considered essential by the physician.

No pharmacokinetic data on excretion in breast milk are available. Therefore, breastfeeding should be discontinued during therapy.

There are no data concerning the effect of palonosetron on fertility.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Constipation in patients with a history of constipation or signs of subacute intestinal obstruction	In clinical studies at a dose of 250 micrograms (total 633 patients) the most frequently observed adverse reactions, at least possibly related to palonosetron, were headache (9 %) and constipation (5 %).	Preventable. As palonosetron may increase large bowel transit time, patients with a history of constipation or signs of subacute intestinal obstruction should be monitored following administration of palonosetron.
Hypersensitivity	Hypersensitivity reactions were reported as very rare (<1/10,000) adverse reactions from post-marketing data.	Preventable. Hypersensitivity to the active substance or to any of the excipients of the formulation of the finished product is a contraindication of the use of the medicinal product.

Important potential risks

Risk	What is known
Electrocardiogram QT prolonged	The effect of palonosetron on QTc interval was evaluated in a double blind, randomised, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of IV administered palonosetron at single doses of 0.25, 0.75 or 2.25 mg in 221 healthy subjects. The study demonstrated no effect on QT/QTc interval duration as well as any other ECG interval at doses up to 2.25 mg. No clinically significant changes were shown on heart rate, atrioventricular (AV) conduction and cardiac repolarisation.
Serotonin syndrome	There have been reports of serotonin syndrome with the use of 5-HT3 antagonists either alone or in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs).

Missing information

Risk	What is known
Use in pregnant	No clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Only limited data from animal studies are available regarding the placental transfer.
Effect in lactation	There are no data concerning palonosetron excretion in breast milk.
Effect in children aged less than 1 month	The safety and efficacy in children aged less than 1 month have not been established. Currently available data are based on clinical trials but no recommendation on posology can be made.
Effects in patients with end-stage renal disease undergoing haemodialysis	No data are available for patients with end stage renal disease undergoing haemodialysis. No pharmacokinetic data in haemodialysis patients are available.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the product information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

Palonosetron 250 micrograms solution for injection has no additional risk minimisation measures. Routine pharmacovigilance should be sufficient for post-marketing safety monitoring of the risks.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

SUMMARY OF CHANGES TO THE RMP		
DATE	**VERSION NUMBER**	**CHANGES**
July 2015	01	As per RMS preliminary assessment report, the following changes to the RMP have been addressed in order to align the safety concerns to those of the originator 1. The indication for paediatric patients 1 month of age and older has been included. 2. The posology en paediatric population has been

		modified. 3. The identified risk SOC: Gastrointestinal disorders has been changed by Severe constipation. 4. The identified risk SOC:Investigations (PT: Electrocardiogram QT prolonged has been changed by QT/QTc prolongation as important potential risk. 5. The identified risk SOC:Immune system disorders (PT: Anaphylactic reaction) has been removed. 6. The identified risk SOC: Immune sustem disorders (PT: Anaphylactoid reaction) has been removed. 7. The identified risk SOC: Immune system disorder (PT: Hypersensitivity reactions) has been changed by severe hypersensitivity reactions. 8. The identifies risk SOC: Vascular disorders (PT: Shock) has been removed. 9. The potential risk: Effects on ability to drive and use machines has been removed. 10. The potential risk:Convulsive events Serotonin syndrome has been added. 11. The missing information: Use in paediatric population has been changed by effect in children aged less than 1 month (potential off-label use for CINV prevention). 12. The missing information:Use in pregnancy and lactation has been changed by two safety concerns:effect in lactating women and effect in pregnancy. 13. The missing information:Effect in fertility has been removed. 14. The missing information: use in end-stage renal disease patients undergoing haemodialysis has been changed by effects in patients with end stage renal disease undergoing haemodialysis. 15. The SmPC and Package leaflet has been changed according to the originator.
January 2016	02	As per RMS assessment report, the following changes to the RMP have been addressed: 1. the reference to the product name "Aloxi" should be replaced by "palonosetron" in the SmPC text for paediatric population included in the RMP