VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 OVERVIEW OF DISEASE EPIDEMIOLOGY

Acute nausea and vomiting from emetogenic cancer chemotherapy

Acute nausea and vomiting typically occurs within the first 24 hours after chemotherapy administration. It can begin within 1 or 2 hours after the start of chemotherapy and last for a number of hours. Chemotherapy agents may cause acute chemotherapy induced nausea and vomiting (CINV) that begins 8 to 10 hours after administration.

The use of antiemetic agents before chemotherapy can significantly lower the incidence of severe acute CINV. The essential tool for managing acute CINV is prevention, which is more effective than the treatment of established nausea and vomiting. In addition, the incidence and severity of delayed and anticipatory CINV can be lowered if acute CINV is prevented or minimized. Currently available antiemetic agents are most effective in prevention of acute CINV.

The primary risk factor for CINV is the intrinsic emetogenicity of the chemotherapeutic agent. Various emetic risks may result because different agents act at different sites or even multiple sites within the patient system.

The administration dose and schedule of a chemotherapeutic agent also are important treatment- related factors that affect risk for CINV. Administration of a low risk emetic drug in high doses over a short period of time may dramatically increase the risk for CINV. Although an agent may be associated with low emetic risk, the combined emetogenicity of individual agents can lead to an increased risk of nausea and vomiting that requires aggressive antiemetic therapy.

Although the extent of CINV depends largely on the emetogenic potential of the administered chemotherapy agents, patient characteristics such as previous experience with chemotherapy, sex, age, and alcohol intake history also have an impact. Patients who are at increased risk for CINV include women, patients younger than 50 years, patients prone to motion sickness and patients with pre-existing anxiety and nausea.

A patient's history of low alcohol consumption may indicate increased susceptibility to CINV. Chronic heavy alcohol dosage has been associated with improved control of emesis. Fewer women achieve complete emetic control than men, with differences as great as 20% to 30% between the sexes.[1] (Annex 12)

VI.2.2 SUMMARY OF TREATMENT BENEFITS

Palonosetron solution for injection has been studied in three main studies involving 1,842 adults receiving chemotherapy that was a strong or a moderate trigger of nausea and vomiting. Palonosetron, given at two different doses, was compared with Ondansetron and Dolasetron (other medicines of the same type).

Palonosetron solution for injection was as effective as the comparator medicines. With chemotherapy that was a strong trigger of nausea and vomiting, 59% of the patients receiving Palonosetron did not vomit in the 24 hours after chemotherapy (132 out of 223), compared with 57% of the patients receiving Ondansetron (126 out of 221). With chemotherapy that was a moderate trigger of nausea and vomiting, 81% of the patients receiving Palonosetron did not vomit in the 24 hours after chemotherapy (153 out of 189) compared with 69% of those receiving Ondansetron (127 out of 185). When it was compared with Dolasetron, these values were 63% for Palonosetron (119 patients out of 189) and 53% for Dolasetron (101 patients out of 191).[2] (Annex 12)

In double-blind randomised controlled trials, a single i.v. dose of Palonosetron 0.25 mg was effective in the prevention of nausea and vomiting with moderately emetogenic chemotherapy and in the control of acute nausea and vomiting with highly emetogenic chemotherapy. Single doses of Ondansetron 32 mg or Dolasetron 100 mg were used as comparators. In terms of efficacy, Palonosetron was non-inferior to the comparators in the acute phase of emesis both in moderately and highly emetogenic setting, independently of whether patients had been pre-treated or not.

From a clinical perspective, the benefit risk relationship was considered favorable. With a safety profile that was similar to the currently available 5-HT_3 receptor antagonists, Palonosetron was effective in the control of nausea and vomiting with moderately emetogenic chemotherapy and of acute nausea and vomiting with highly emetogenic chemotherapy. The efficacy of Palonosetron in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be enhanced by the addition of a corticosteroid administered prior to chemotherapy.[3] (Annex 12)

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

Not applicable

VI.2.4 SUMMARY OF SAFETY CONCERNS

Safety Concern	**What is known**	**Preventability**
Important Identified Risks		
Severe Constipation	Palonosetron treatment may increase large bowel transit time	Yes by monitoring of early symptoms. Do not take Palonosetron if you have acute bowel obstruction or a history of repeated constipation The patients with history of constipation or signs of sub-acute intestinal obstruction should be monitored following administration of Palonosetron.
Severe Hypersensitivity reactions	Allergic reactions or hypersensitivity may occur with Palonosetron treatment	Yes by monitoring of early symptoms. Tell doctor immediately if you notice signs of allergic reaction or hypersensitivity. Do not take Palonosetron if you are allergic to Palonosetron or any of the other ingredients of this medicine.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
QT/QTc prolongation	As for other 5-HT3 antagonists, caution should be exercised in the use of Palonosetron in patients who have or are likely to develop prolongation of the QT interval. These conditions include patients with a personal or family history of QT prolongation, electrolyte abnormalities, congestive heart failure, bradyarrhythmias, conduction disturbances and in patients taking anti-arrhythmic agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities. In addition, a doctor should be consulted before administration of Palonosetron in such cases. Hypokalaemia and hypomagnesaemia should be corrected prior to 5-HT3-antagonist administration.
Convulsive events	None proposed
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). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

Missing information

Risk	What is known
Effect in pregnancy	No clinical data is available on exposed pregnancies for Palonosetron. 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 is available regarding the placental transfer. It is not known whether Palonosetron will cause any harmful effects when used during pregnancy. Therefore, Palonosetron should not be used in pregnant women unless it is considered essential by the physician.
Effect in lactating women	There is no data concerning Palonosetron excretion in breast milk, so breast-feeding should be discontinued during therapy.
Effects on fertility	There is no data concerning the effect of Palonosetron on fertility. Patients concerned about their fertility while Palonosetron treatment should consult with their physician.

Use in paediatric population	Palonosetron Fresenius Kabi in pre-filled syringe is not recommended for use in children and adolescents. For this population, Palonosetron Fresenius Kabi in glass vials can be used. In addition, for paediatric population (children aged below 1 month), the safety and efficacy of Palonosetron has not been established. No data are available. There are limited data on the use of Palonosetron in the prevention of nausea and vomiting in children under 2 years of age.
Effects in patients with end stage renal disease undergoing haemodialysis	No data is available for patients with end stage renal disease undergoing haemodialysis.

VI.2.5 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

The Summary of Product Characteristics and the Package Leaflet for Palonosetron Fresenius Kabi 250 micrograms solution for injection and Palonosetron Fresenius Kabi 250 micrograms solution for injection in pre-filled syringe contains information about routine risk minimisation measures.

VI.2.6 PLANNED POST AUTHORISATION DEVELOPMENT PLAN

Not applicable.

VI.2.7 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable.