VI.2 Elements for a Public Summary

VI.2.1 *Overview of Disease Epidemiology*

Acute Nausea and Vomiting (N&V)

Incidence:

The incidence of acute and delayed N&V was investigated in highly and moderately emetogenic chemotherapy treatment regimens. Patients were recruited from 14 oncology practices in six countries. Overall, more than 35% of patients experienced acute nausea, and 13% experienced acute emesis. In patients receiving highly emetogenic chemotherapy, 60% experienced delayed nausea, and 50% experienced delayed emesis. In patients receiving moderately emetogenic chemotherapy, 52% experienced delayed nausea, and 28% experienced delayed emesis. Chemotherapy-induced nausea and vomiting (CINV) was a substantial problem for patients receiving moderately emetogenic chemotherapy in ten community oncology clinics. Thirty-six percent of patients developed acute CINV, and 59% developed delayed CINV.

Etiologies:

Chemotherapy is the most common treatment-related cause of N&V. The incidence and severity of acute emesis in persons receiving chemotherapy varies according to many factors, including the particular drug, dose, schedule of administration, route, and individual patient variables. In most cancer patients, these symptoms can be prevented or controlled.

Risk factors for acute emesis include:

- Poor control with prior chemotherapy.
- Female gender.
- Younger age.

Emetic classifications: The American Society of Clinical Oncology has developed a rating system for chemotherapeutic agents and their respective risk of acute and delayed emesis.

High risk: Emesis that has been documented to occur in more than 90% of patients:

- Cisplatin (Platinol).
- Mechlorethamine (Mustargen).
- Streptozotocin (Zanosar).
- Cyclophosphamide (Cytoxan), 1,500 mg/m2 or more.
- Carmustine (BiCNU).
- Dacarbazine (DTIC-Dome).
- Dactinomycin.

Moderate risk: Emesis that has been documented to occur in 30% to 90% of patients:

- Carboplatin (Paraplatin).

- Cyclophosphamide (Cytoxan), less than 1,500 mg/m2.
- Daunorubicin (DaunoXome).
- Doxorubicin (Adriamycin).
- Epirubicin (Pharmorubicin).
- Idarubicin (Idamycin).
- Oxaliplatin (Eloxatin).
- Cytarabine (Cytosar), more than 1 g/m2.
- Ifosfamide (Ifex).
- Irinotecan (Camptosar).

Low risk: Emesis that has been documented to occur in 10% to 30% of patients:

- Mitoxantrone (Novantrone).
- Paclitaxel (Taxol).
- Docetaxel (Taxotere).
- Mitomycin (Mutamycin).
- Topotecan (Hycamtin).
- Gemcitabine (Gemzar).
- Etoposide (Vepesid).
- Pemetrexed (Alimta).
- Methotrexate (Rheumatrex).
- Cytarabine (Cytosar), less than 1,000 mg/m2.
- Fluorouracil (Efudex).
- Bortezomib (Velcade).
- Cetuximab (Erbitux).
- Trastuzumab (Herceptin).

Minimal risk: Emesis that has been documented to occur in fewer than 10% of patients:

- Vinorelbine (Navelbine).
- Bevacizumab (Avastin).
- Rituximab (Rituxan).
- Bleomycin (Blenoxane).
- Vinblastine (Velban).
- Vincristine (Oncovin).
- Busulphan (Myleran).
- Fludarabine (Fludara).
- 2-Chlorodeoxyadenosine (Leustatin).

In addition to emetogenic potential, the dose and schedule used are also extremely important factors. For example, a drug with a low emetogenic potential given in high doses may cause a dramatic increase in the potential to induce N&V. Standard doses of cytarabine rarely produce N&V, but these are often seen with high doses of this drug. Another factor to consider is the use of drug combinations. Because most patients receive combination chemotherapy, the emetogenic potential of all of the drugs combined and individual drug doses needs to be considered.

Delayed N&V

Delayed (or late) N&V occurs more than 24 hours after chemotherapy administration. Delayed N&V is associated with cisplatin, cyclophosphamide, and other drugs (e.g., doxorubicin and ifosfamide) given at high doses or given on 2 or more consecutive days.

Etiologies:

Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis.

Risk factors:

All predicative characteristics for acute emesis are considered risk factors for delayed emesis.

VI.2.2 Summary of treatment benefits

Efficacy of single-dose (0.25 mg, 0.75 mg) palonosetron I.V. injection in preventing acute and delayed nausea and vomiting induced by moderately or highly emetogenic chemotherapy was studied in three Phase 3 trials.

In these 3-arm double blind studies, efficacy was based on demonstrating non-inferiority of a single dose of palonosetron I.V. compared to ondansetron I.V. or dolasetron I.V. Non-inferiority criteria were met if the lower boundary of the two-sided 97.5% confidence interval for the difference in the complete response rate of palonosetron minus ondansetron or dolasetron was above -15% (non-inferiority margin 15%).

The primary endpoint was Complete Response (no emetic episode and no rescue medication) during the first 24 hours (acute phase) after chemotherapy. Secondary endpoints included complete Response at further time periods (24-120 hours, delayed phase) and Complete Control (complete response and no more than mild nausea).

Moderately Emetogenic Chemotherapy

Two Phase 3, double-blind trials involving 1132 patients compared single-dose palonosetron I.V. with either single-dose I.V. ondansetron (Study 1) or I.V. dolasetron (Study 2) given 30 minutes prior to moderately emetogenic chemotherapy including carboplatin, cisplatin $\leqslant$ 50 mg/m^2 , cyclophosphamide < 1500 mg/m^2, doxorubicin > 25 mg/m^2, epirubicin, irinotecan, or

methotrexate. Concomitant corticosteroids were not administered prophylactically in Study 1 and were only used by 4-6% of patients in Study 2. The majority of patients in these studies were women (77%), Caucasian (65%, Hispanic: 31%) and naïve to previous chemotherapy (54%).

The mean age was 55 years (18-97 years).

The two pivotal Phase 3 studies demonstrated non-inferiority of a single I.V. dose of palonosetron 0.25 mg in the prevention of acute nausea and vomiting associated with initial course of moderately emetogenic chemotherapy, vs. I.V. ondansetron 32 mg or I.V. dolasetron 100 mg. In addition, the difference in efficacy in Study 1 was statistically significant in favour of palonosetron (p=0.006) but was not statistically significant in Study 2.

Highly Emetogenic Chemotherapy A Phase 3, double-blind trial involving 667 patients compared single dose palonosetron I.V. with single-dose I.V. ondansetron given 30 minutes prior to highly emetogenic chemotherapy including cisplatin $\geqslant$ 60 mg/m², cyclophosphamide, or dacarbazine. Dexamethasone, or in the event of a shortage, methylprednisolone, was co-administered prophylactically before chemotherapy in 67% of patients. Of the 667 patients, 51% were women, 60% Caucasian (Hispanic: 36%), and 59% naïve to previous chemotherapy. The mean age was 52 years (18-86 years).

A single I.V. dose of palonosetron 0.25 mg was shown to be non-inferior to I.V. ondansetron 32 mg in preventing acute nausea and vomiting following highly emetogenic chemotherapy.

VI.2.3 Unknown relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Risk	**What is known**	**Preventability**
Severe constipation	Patients should talk to their doctor or pharmacist before using Ferant: • If they have acute bowel obstruction or a history of repeated constipation. • If you have an imbalance of certain minerals in your blood such as potassium and magnesium which has not been treated.	These risks can be prevented by respecting the product information.
Severe hypersensitivity reactions	Do not use Ferant: - If you are allergic to palonosetron or any of the other ingredients of this medicine	These risks can be prevented by respecting the product information.

Risk	What is known
QT/QTc prolongation	Patients should talk to their doctor or pharmacist before using Ferant: • If they have a personal or family history of alterations in heart rhythm (QT prolongation).
Convulsive events	Prescription only medicine
Serotonin syndrome	Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines, including: • SSRIs (selective serotonin reuptake inhibitors) used to treat depression and/or anxiety including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram • SNRIs (serotonin noradrenaline reuptake inhibitors) used to treat depression and/or anxiety including venlafaxine, duloxetine. • 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.

Risk	What is known
Effect in pregnancy	If you are pregnant or think you might be, your doctor will not administer Ferant to you unless it is clearly necessary. It is not known whether Ferant will cause any harmful effects when used during pregnancy. Ask your doctor or pharmacist for advice before using any medicine if you are pregnant or think you might be. Prescription only medicine
Effect in lactating women	It is not known if Ferant is found in breast milk. Ask your doctor or pharmacist for advice before using Ferant if you are breast-feeding. Prescription only medicine
Effect on fertility	If you are pregnant or think you might be, your doctor will not administer Ferant to you unless it is clearly necessary. It is not known whether Ferant will cause any harmful effects when used during pregnancy. Ask your doctor or pharmacist for advice before using any medicine if you are pregnant or think you might be. Prescription only medicine

Effect in children aged less than 1 month (potential off-label use for CINV prevention)	No data are available for children aged less than 1 month. Prescription only medicine
Effects in patients with end stage renal disease undergoing haemodialysis	No data are available for patients with end stage renal disease undergoing haemodialysis. Prescription only medicine

Summary of risk minimisation activities by safety concern

Routine risk minimization measures are considered enough to cover all risks. All safety concerns presented in the section above are known for palonosetron and other similar medicinal products and they are described in the proposed product information. These risks can be prevented or their severity can be limited by following the instructions in the summary of product characteristics and package leaflet.

Planned post-authorisation development plan

None.

Summary of changes to the risk management plan over time

Not applicable.