EU Risk Management Plan for Palonosetron

Active substance(s) (INN or common name):	Palonosetron (as hydrochloride) intravenous and oral
Pharmaco-therapeutic group (ATC Code):	Antiemetics and antinauseants, serotonin ($5HT_3$) antagonists (ATC Code A04AA55)
Name of Marketing Authorisation Holder or Applicant:	Helsinn Birex Pharmaceuticals Ltd.
Number of medicinal products to which this RMP refers:	2
Product(s) concerned (brand name(s)):	Aloxi 250 micrograms solution for injection Aloxi 500 micrograms soft capsules

Details of the currently approved RMP:

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Approved with procedure: EMEA/H/C/563/IB/053

Date of approval (opinion date): 02 March 2022

EU-QPPV name: David Power

EU-QPPV signature [redacted]

RMP version to be assessed as part of this application:

RMP Version number: 7.1

Data lock point for this RMP: 24 July 2021

Date of final sign off: 02 March 2022

Rationale for submitting an updated RMP: The EU Risk Management Plan (RMP) Version 6, dated 23 July 2014, was updated to create the current version 7.1, with DLP 24 July 2021. This version has been compiled in accordance with the format and content of the EMA guideline on GVP Module V Rev. 2 effective on 31 March 2017. In agreement with GVP Module V Rev.2, safety concerns have been reviewed. Key relevant changes made in Version 7.1 are listed below and in Annex 8.

- Section I. – *Product Overview*: Aloxi 250 micrograms solution for injection and Aloxi 500 micrograms soft capsules are reported in the same Products Overview.
- Part II Module SI *Epidemiology of the indication and target population* has been updated including pre-chemotherapy recommendations by emetogenic potential of chemotherapy agents.
- Part II Module SIII *Clinical trial exposure* has been updated to include the most recent clinical trials results.
- Part II Module SV *Post-authorisation experience* has been updated with the most recent data from last PSUR up to 24 July 2021.
- Part II Module SVII Identified and potential risks has been reviewed in line with the current guidance and definitions on important identified and potential risks and missing information.
- Section SVII.2 *New safety concerns* has been reviewed in line with the current guidance and definitions on important identified and potential risks and missing information.

Other RMP versions under evaluation: Not applicable.

This document integrates and provides an update of the safety information of Palonosetron as EU RMP version 6 endorsed by CHMP at the time of type II variation for the extension of the therapeutic indication for the IV formulation to paediatric patients 1 month of age and older.

Table Modules.1 – Overview of the RMP Parts and Modules in the current RMP

Part	Module/annex	Module version and procedure number where the module was last approved	Module version for the proposed update
Part II Safety Specification	SI Epidemiology of the indication and target population(s)	V 6.0 EMEA/H/C/563/II/038	V 7.1
	SII Non-clinical part of the safety specification	V 6.0 EMEA/H/C/563/II/038	V 7.1
	SIII Clinical trial exposure	V 6.0 EMEA/H/C/563/II/038	V 7.1
	SIV	V 6.0	V 7.1

Part	Module/annex	Module version and procedure number where the module was last approved	Module version for the proposed update
	Populations not studied in clinical trials	EMEA/H/C/563/II/038	
	SV Post-authorisation experience	V 6.0 EMEA/H/C/563/II/038	V 7.1
	SVI Additional EU requirements for the safety specification	V 6.0 EMEA/H/C/563/II/038	V 7.1
	SVII Identified and potential risks	V 6.0 EMEA/H/C/563/II/038	V 7.1
	SVIII Summary of the safety concerns	V 6.0 EMEA/H/C/563/II/038	V 7.1
Part III Pharmacovigilance Plan		V 6.0 EMEA/H/C/563/II/038	V 7.1
Part IV Plan for post-authorisation efficacy studies		V 6.0 EMEA/H/C/563/II/038	V 7.1
Part V Risk Minimisation Measures		V 6.0 EMEA/H/C/563/II/038	V 7.1
Part VI Summary of RMP		V 6.0 EMEA/H/C/563/II/038	V 7.1
Part VII Annexes	ANNEX 2 Tabulated summary of on-going and completed pharmacoepidemiological study programme.	V 6.0 EMEA/H/C/563/II/038	V 7.1
	ANNEX 3 Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan	V 6.0 EMEA/H/C/563/II/038	V 7.1
	ANNEX 4 Specific adverse event follow-up forms	V 6.0 EMEA/H/C/563/II/038	V 7.1
	ANNEX 5 Protocols for proposed and on-going studies in Part IV	V 6.0 EMEA/H/C/563/II/038	V 7.1
	ANNEX 6 Details of proposed additional risk minimisation activities	V 6.0 EMEA/H/C/563/II/038	V 7.1
	ANNEX 7 List of references	V 6.0 EMEA/H/C/563/II/038	V 7.1
	ANNEX 8 Summary of changes to the risk management plan over time	V 6.0 EMEA/H/C/563/II/038	V 7.1

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Part I: Product Overview

Active substance(s) (INN or common name)	Palonosetron (as hydrochloride)
Pharmacotherapeutic group(s) (ATC Code)	Antiemetics and antinauseants, serotonin (5HT3) antagonists (ATC Code A04AA55)
Marketing Authorisation <Holder> <Applicant>	Helsinn Birex Pharmaceuticals Ltd.
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Aloxi 250 micrograms solution for injection Aloxi 500 micrograms soft capsules
Procedure type (centrally or nationally authorised)	Centralised procedure
Brief description of the product including:	Chemical class: Palonosetron is a potent and highly selective serotonin subtype 3 (5-HT_3) receptor antagonist with a strong binding affinity for this receptor. 5-HT_3 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.
	Summary of mode of action: Antineoplastic agents may cause emesis through effects at several receptor sites. The development of acute emesis is known to depend on 5-HT_3 receptor, which has been demonstrated to selectively participate in the emetic response. Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.
	Important information about its composition: Palonosetron is a white to off-white crystalline powder, which is freely soluble in water. The crystalline form I is produced by the commercial synthesis process, while form II have demonstrated that in aqueous medium it readily converts into polymorph form I, which is freely soluble in water. Excipients include mannitol, disodium edetate, sodium citrate, citric acid monohydrate, sodium hydroxide and hydrochloric acid (both for pH adjustment) and water for injections. Capsule content: mono/diglycerides of caprylic/capric acid, polyglycerol oleate, glycerol, purified water, butylhydroxyanisole. Capsule shell: gelatin, sorbitol (E420), glycerol, titanium dioxide (E171). Printing Ink: Iron oxide black (E172), polyvinyl acetate phthalate, macrogol 400.
Hyperlink to the Product Information:	**Current Product Information Annexes**
Indication(s) in the EEA	Proposed: Not applicable.
	Current: Aloxi solution for injection is indicated in adults for the: • prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, • prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Aloxi for injection is indicated in paediatric patients 1 month of age and older for the: • prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

	Aloxi soft capsules is indicated for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.
Dosage in the EEA	Aloxi IV in adults: 250 micrograms palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Aloxi should be injected over 30 seconds. The efficacy of Aloxi 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. Paediatric population: 20 micrograms (the maximum total dose should not exceed 1,500 micrograms) palonosetron administered as a single 15-minute intravenous infusion beginning approximately 30 minutes before the start of chemotherapy. The safety and efficacy of Aloxi in children aged less than 1 month have not been established. No data are available.
	Oral Aloxi in adults: 500 micrograms palonosetron administered orally approximately one hour before the start of chemotherapy. Paediatric population: the safety and efficacy of Aloxi in children have not been established. Currently available data are described in section 5.1 and section 5.2 of the SmPC, but no recommendation on posology can be made.
Pharmaceutical form(s) and strengths	Aloxi solution for injection (clear, colourless solution): each ml of solution contains 50 micrograms palonosetron (as hydrochloride). Each vial of 5 ml of solution contains 250 micrograms palonosetron (as hydrochloride).
	Oral Aloxi: each soft capsule contains 500 micrograms palonosetron (as hydrochloride). Soft capsule: light beige, opaque, oval, soft gelatine capsules, imprinted with black logo "AlO", filled with a clear yellowish solution.
Is/will the product be subject to additional monitoring in the EU?	No additional monitoring in the EU.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication:

Aloxi solution for injection is indicated in adults for the:

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

Aloxi for injection is indicated in paediatric patients 1 month of age and older for the:

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

Aloxi soft capsules is indicated for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.

Incidence: The incidence of acute and delayed chemotherapy-induced nausea and vomiting (CINV) was investigated in highly and moderately emetogenic chemotherapy treatment regimens. In a study on 298 patients recruited from 14 oncology practices in six countries (Grunberg SM et al. 2004), 67 patients received highly emetogenic chemotherapy (HEC) and 231 patients received moderately emetogenic chemotherapy (MEC). Greater than 90% of the patients classified as receiving HEC were given cisplatin, whereas 70% of the patients receiving MEC were given regimens containing cyclophosphamide, doxorubicin, and/or epirubicin. Most of the patients (83%) received combination chemotherapy. Overall, more than 35% of patients experienced acute nausea, and 13% experienced acute emesis. In patients receiving HEC, 60% experienced delayed nausea, and 50% experienced delayed emesis. In patients receiving MEC, 52% experienced delayed nausea, and 28% experienced delayed emesis. Delayed nausea and emesis were observed in 60% and 50% of HEC patients, respectively, and in 52% and 28% of MEC patients, respectively. Delayed emesis and nausea appeared without the onset of acute symptoms in 38% and 33% of HEC patients, respectively, and in 19% and 21% of MEC patients, respectively. As many as 60% of patients who receive cancer chemotherapy experience some degree of nausea and vomiting (Bender CM et al. 2002). CINV was found to be a substantial problem for patients receiving MEC in ten community oncology clinics. Thirty-six percent of patients developed acute CINV, and 59% developed delayed CINV (Cohen L et al. 2007). The emetogenicity of chemotherapy also significantly influences incidence and duration of the symptoms (Grunberg SM et al. 2004). In the absence of appropriate prophylaxis delayed emesis develops in approximately 90% of patients treated with cisplatin, a cytotoxin with the highest emetic potential (Hesketh PJ et al. 2008).

Prevalence: A study sought to determine the prevalence of acute and delayed CINV across ten community oncology settings. During cycle 1, only 33% of patients had neither acute nor delayed CINV. Of the 36% patients who developed acute CINV, 8% developed acute CINV only. Of the 59% who

developed delayed CINV, 53% reported delayed only and 47% reported acute and delayed CINV. A similar pattern was seen at cycles 2 and 3 (Cohen L et al. 2007). A study conducted in 4 oncology centers in Canada examined the proportion of CINV in patients receiving highly emetogenic chemotherapy regimens. Of 266 patients, 26% reported nausea or vomiting on day 1 and 44% reported nausea and vomiting from day 2 to 5 after chemotherapy (Lachaine J et al. 2005).

Pediatric patients

CINV has been estimated to occur in up to 70% of the paediatric population undergoing chemotherapy (Dupuis LL et al, 2017). Delayed CINV can be present in up to 80% of patients and is more prevalent in patients with uncontrolled acute CINV. The occurrence of CINV in children is influenced by psychological and behavioural characteristics, such as parent and child state, trait anxiety scores and child behaviour problems, although these features have not been well defined as specific CINV predictors (Ruggiero A et al 2018).

Demographics of the population in the authorised indication and risk factors for the disease:

Demographic data on the population of cancer patients that could receive treatment with palonosetron for the prevention CINV are available from published observational studies evaluating the incidence and impact of CINV, mostly among patients receiving highly or moderately emetogenic chemotherapy. Although these studies apply specific inclusion criteria (e.g., aged 18 years or older, good functional performance status, and treatment with specific chemotherapy), they provide useful information on the main demographics for the palonosetron targeted population. In many studies, females represented the largest group of patients, ranging from 60% to 70% of the entire study population, with the mean and median age around 55 years (Hilarius DL et al. 2012; Molassiotis A et al.2008; Haiderali A et al. 2011).

In population-based cancer registries, most patients who are diagnosed with cancers for which relevant treatment guidelines recommend highly or moderately emetogenic chemotherapy are adults, the great majority of whom are older than 55 years of age. The target population may be more predominantly female than the general population because two of the cancers most closely associated with CINV (breast and ovarian cancer) occur primarily or exclusively in females. In addition, palonosetron may be indicated more often in female patients due to their higher risk of CINV than males.

The demographic profile of the target population most closely resembles the demographics of those with the types of cancer most frequently associated with CINV, as described below.

- Breast cancer: Although only female breast cancer is reported by GLOBOCAN, about 1% of breast cancer occurs in males (Boyle P et al. 2008; Bloechl-Daum B et al. 2006) In the EU, nearly half of new diagnoses are among females aged 65 years or older, and more than 80% of new diagnoses are among females aged 50 years or older. In the US, 43% of the new diagnoses are among females aged 65 year or older, and 77% are among females aged 50 years or older.
- Colorectal cancer: In the EU in 2008, 182,614 cases were diagnosed among males and 151,478 were diagnosed among females. A total of 58% of new diagnoses were among individuals aged 70 years and older. Very few cases occurred among those aged younger than 50 years, comprising only 5% of the total. In the US in 2008, 153,881 cases of colorectal cancer were diagnosed: 74,610 among females and 79,271 among males. A total of 53% of

new diagnoses were among those aged 70 years or older and only 9% were in individuals aged younger than 50 years.

- Lung cancer: In the EU in 2008, there were 206,874 (71%) cases diagnosed among males and 82,532 (29%) among females. Nearly half (47%) of all new diagnoses in the EU were among individuals aged 70 years or older, and 51% of new diagnoses were among those aged 45 to 69 years. In the US in 2008, 215,021 cases of lung cancer were diagnosed: 100,330 (47%) among females and 114,691 (53.3%) among males. A total of 52% of new diagnoses were among those aged 70 years or older and only 6% were in individuals aged younger than 50 years.
- Ovarian cancer: Ovarian cancer occurs exclusively in females. In the EU in 2008, slightly more than half of the 44,728 females diagnosed with ovarian cancer were aged 65 years or older. In the US, 48% of the 21,652 females diagnosed in 2008 were aged 65 years or older.
- Non-Hodgkin lymphoma: In the EU in 2008, there were 38,707 (52%) cases diagnosed among males and 35,455 (48%) among females. Nearly half (47%) of all new diagnoses in the EU were among individuals aged 70 years or older, and 43% of new diagnoses were among those aged 45 to 69 years. In the US in 2008, 66,126 incident cases of NHL were diagnosed: 30,673 (46%) among females and 35,453 (54%) among males. A total of 45% of new diagnoses were among those aged 70 years or older and only 8% were in individuals aged younger than 40 years.

Pediatric patients

The heterogeneity of pediatric cancer is substantial and even the most common pediatric cancer (i.e. acute lymphoblastic leukemia) is characterized by biological and clinical diversity (Kupfer GM, 2013).

Leukemias are the most common type of childhood cancer and acute lymphoblastic leukemia (ALL) is the most frequent neoplasm in children. Although ALL incidence peaks in the first 5 years of life, it represents an even greater number of leukemia cases in older children because the number of acute myelogenous leukemia (AML) cases further decline. Overall, ALL is more common in whites, boys, and in the developed world. Approximately 18% of childhood leukemia cases involve AML. This ratio of ALL-to-AML remains constant throughout childhood, except for a predilection for AML in the neonatal period. Chronic leukemias account for less than 5% of all pediatric leukemias. Chronic myelogenous leukemia (CML) is the most common type and corresponds to the adult type of CML marked by the Philadelphia chromosome.

Tumors of the CNS constitute the other major type of childhood cancer. Roughly 20% of childhood cancers involve brain tumors. Patients with CNS tumors remain an underreported segment of the pediatric population with cancer because only one half is referred to specialty centers. Morbidity is clearly the greatest problem in patients with brain tumors because many of these tumors are in locations that are difficult to treat. Most pediatric brain tumors occur in the first decade of life. Brain tumors are heterogeneous, which makes their overall classification difficult. The most common brain tumor in children is medulloblastoma, which accounts for 10-20% of childhood brain tumors and 40% of tumors in the posterior fossa. Most brain tumors, chiefly medulloblastomas and glial tumors, involve the posterior fossa after the first 2 years of life. Neuroblastoma is the most

common non-CNS solid tumor. Both long-term survival and short-term treatment remain challenges in the care of patients with neuroblastoma.

Rates of Hodgkin disease, which accounts for 5% of childhood cancers, peak in children younger than 14 years. Non-Hodgkin lymphomas make up a large, heterogeneous category of childhood cancers which are responsible for 6% of all pediatric cancers. NHL is a disease of young children and is more prevalent than Hodgkin lymphoma in the first decade of life; it has an overall predilection for boys.

Wilms tumor is the most common renal tumor overall, comprising approximately 5-6% of childhood cancers; however, in infancy, related tumors such as mesonephric nephroma are more common. The patient's age affects the prognosis, in those patients who present in infancy have the best outcomes.

Retinoblastoma is a relatively rare but classic solid tumor with an overall incidence of around 2%. Hereditary retinoblastoma occurs early, often at birth and 80% before age 2 years and is most likely to be bilateral.

Rhabdomyosarcoma, which comprises roughly 3% of childhood cancers, is another solid tumor with an incidence that peaks in children younger than 6 years and again in early adolescence.

Osteosarcoma is a bone tumor associated with the rapid bone growth characteristic of the adolescent growth spurt. Although more common overall, it is less common than Ewing sarcoma in the first decade of life. Osteosarcoma is most common in patients who are taller than their peers and is diagnosed at an early age in more girls than boys.

Ewing sarcoma represents a group of tumors that includes peripheral primitive neuroectodermal tumors and primary bony tumors. An interesting feature of Ewing sarcoma is its extreme rarity among black racial groups and significant occurrence in white racial groups. Although the greatest incidence is observed in the second decade of life, Ewing sarcoma occurs more throughout the age spectrum than does osteosarcoma.

The most important risk factors for the onset of CINV include young age (< 50 years of age), female gender, light, or no alcohol use (<1.5 oz/day), higher chemotherapy doses and emetogenicity of the chemotherapeutics. Other risk factors include history of motion sickness, vomiting associated with pregnancy, history of prior chemotherapy and CINV (Hesketh PJ et al. 2010). Of all the known predictive factors, the intrinsic emetogenicity of a given chemotherapeutic agent is the predominant factor and should serve as the primary consideration during the selection of appropriate antiemetic treatment. It has been shown that more than one-third of patients with just one risk factor experienced emesis, despite the treatment with a 5 HT3 antagonist and a corticosteroid alone (Navari RM 2003).

Pediatric patients

Data on risk factors for the onset of CINV in childhood are limited. In a secondary analysis of a trial evaluating the efficacy of acupressure in antiemetic prophylaxis regimens for children receiving highly emetogenic chemotherapy acute-phase CINV was associated with non-white racial groups. In addition, delayed-phase CINV was associated with poor acute-phase CINV control, non-CNS cancer, and administration of cisplatin (Dupuis LL et al. 2019)

Main existing treatment options: According to the Multinational Association of Supportive Care in Cancer (MASCC) and the American Society of Clinical Oncology (ASCO) guidelines for CINV management, (Hesketh PJ et al. 2017, Roila F et al. 2016), the 5-hydroxytryptamine receptor antagonists (5-HT_3 RAs) are the most effective antiemetics used for the prophylaxis of acute CINV. All 5-HT_3 RAs have been rarely associated to cardiac events such as prolongation of the QT interval (Tricco et al 2015). In addition, as a consequence of excess serotoninergic activity the occurrence of Serotonin Syndrome has been associated with 5-HT_3 RAs particularly when used in combination with other serotonergic drugs (Rojas Fernandez 2014). Other categories of drugs with the highest therapeutic index for the management of CINV are the neurokinin-1 receptor (NK1R) antagonists, and glucocorticoids (especially dexamethasone). In addition, more recent data have demonstrated substantial antiemetic activity for the antipsychotic medication olanzapine when used in combination with other antiemetics (De Remer DL et al. 2016). These agents are used alone and in specific combinations, depending on the emetogenicity of the specific chemotherapy regimen being administered and its tendency to produce not only acute but also delayed emesis.

In general, most of the regimens that are associated with delayed emesis are those that are highly emetogenic, although there are some moderately emetogenic agents that also fit into this category. Administration of metoclopramide as antiemetic agent should be reserved for special circumstances, including known intolerance to 5-HT_3 RAs or to steroids. The combination of weak antiemetic effects with potential beneficial side effects (sedation, euphoria) also makes cannabinoids a useful adjunct to the antiemetic therapy in selected patients (Jordan K et al. 2007).

Pediatric patients

A systematic review of 34 studies which examined a range of different antiemetics, used at different doses and comparators, suggests that 5-HT_3 RAs with dexamethasone are effective in patients who are to receive highly emetogenic chemotherapy although the risk-benefit profile of additional steroid remains uncertain. (Phillips RS et al. 2016). Current CINV guidelines in pediatric patients include 5-HT_3 RAs in the antiemetic prophylaxis of children receiving highly and moderately emetogenic chemotherapy.

Natural history of the indicated condition in the untreated population, including mortality and morbidity: CINV remains a major adverse effect of cancer chemotherapy that may seriously impair patients' quality of life, causes nutrition and metabolic disturbances, and interferes with the patients' motivation to follow recommended treatment regimens. CINV can be classified as acute, if occurring within the first 24 hours after the start of chemotherapy; delayed, if CINV occurs more than 24 hours after chemotherapy administration and lasts for several days; anticipatory, if it occurs prior to chemotherapy administration; breakthrough occurring despite the preventive therapy, and refractory occurring during subsequent cycles when antiemetic agents have failed in earlier cycles (Hawkins R et al. 2009).

The emetogenic potential of a given chemotherapeutic agent is the most relevant factor allowing to predict the development of CINV (Hesket PJ 2008). Another critical factor that led to the rational evolution of treatment for CINV was the recognition of a distinct emetic clinical syndrome. Most important in this regard was the concept of acute as compared with delayed emesis, first identified with use of the agent cisplatin. In the absence of effective antiemetic prophylaxis, virtually all patients receiving cisplatin will have nausea and vomiting 1 to 2 hours after receiving

chemotherapy. At approximately 18 to 24 hours, the emesis typically subsides, only to recur and reach a second peak at approximately 48 to 72 hours after receipt of the agent (Grunberg SM et al. 2004). Based on the cisplatin model, emesis occurring within the first 24 hours has been defined as acute, and emesis occurring more than 24 hours later as delayed.

Most published observational studies that have evaluated the incidence and/or impact of CINV among adult patients in the United States (US) and/or in the European Union (EU) focused on patients receiving agents known to be associated with a high or moderate emetogenic potential and included a broad spectrum of cancer types. In these studies, breast cancer, gastrointestinal cancers, lung cancer, ovarian cancer, and lymphomas were the cancer types most frequently associated with the development of the CINV (Hilarius DL et al. 2012; Molassiotis A et al.2008; Haiderali A et al. 2011; Ihbe-Heffinger A et al. 2004). Cessation of chemotherapy due to CINV may allow the disease to progress, resulting in significant increases in morbidity and mortality (Lindley CM et al. 1989). CINV can result in significant weight loss, electrolyte and acid-base imbalances, dehydration, renal toxicity, aspiration pneumonia, and esophageal damage. These effects are particularly debilitating to patients with cancer (Bender CM et al. 2002).

Important co-morbidities: A large population-based study used data from the Eindhoven Cancer Registry to assess the prognostic role of increasing age and comorbidity for 13 major cancer types among cancer patients aged 50 years or older who were newly diagnosed between 1995 and 2002 in the southern Netherlands (Janssen-Heijnen ML et al. 2005). Comorbidities were defined as life-shortening diseases that were present at the time of cancer diagnosis. Hypertension was the concomitant comorbidity with the highest prevalence (26%), followed by heart disease (23%), previous cancers (20%), congestive obstructive pulmonary disease (COPD) (17%) and diabetes mellitus (16%). Men were found to have a higher prevalence of cardiovascular diseases than women, and this disease was highest for patients with cancer of the digestive tract, lung, and kidney and those with NHL. In a meta-analysis, pooled mean prevalence of depression was found to be 8–24% in cancer patients in non-palliative-care settings during or after treatment (Krebber AMH et al. 2014).

Part II: Module SII - Non-clinical part of the safety specification

Palonosetron is a well-known active substance, authorised in the EU countries by the European Commission since 2005 as a medicinal product under the brand name ALOXI® (EU/1/04/306/001-002-003). As such, non-clinical profile of palonosetron is well established.

The non-clinical development programme of palonosetron was designed to characterize the toxicity, general safety pharmacology and pharmacodynamics drug interactions of palonosetron. The non-clinical studies were conducted in various in vitro and in vivo experimental models.

The non-clinical programme included acute, sub-chronic (1 month and 3 month) and chronic (6 month and 9 month) toxicity studies, carcinogenicity (mice and rats) and reproduction toxicity studies as well as in vitro and in vivo mutagenicity studies. Toxicity studies in juvenile rats and dogs, vein irritation studies, blood compatibility studies, phototoxicity and photoallergenicity studies have also been carried out.

Since palonosetron is co-administered with cancer chemotherapeutic agents, assessment of potential interactions was undertaken. Palonosetron was investigated for possible interaction with five chemotherapeutic agents (cisplatin, cyclophosphamide, mitomycin C, doxorubicin and cytarabin) in various murine tumour models. An in vitro study was carried out to investigate the cytochrome P450 (CYP) mediated metabolism of palonosetron, its interaction with human CYP isoforms, and the possible induction of CYP. Key safety findings which originated from all performed non-clinical studies within the non-clinical development programme of palonosetron (IV/OS) are presented in Table 1.

Table 1 Key safety findings from non-clinical studies

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
Single and repeat-dose toxicity In dogs, oral palonosetron for 2 weeks, 1 month or 3 months at doses of 20 mg/kg/day (once or twice a day) evidenced clinical signs (e.g., convulsions), one dead animal, and a possible but equivocal effect on QTc interval duration (without clinical sequel). At 20 mg/kg/day, marked clinical signs were observed, including multiple episodes of clonic and/or tonic convulsions and blood chemistry changes. (PALO-02-13). Convulsions occurred in all the acute toxicity studies (intravenous and oral formulations) at least with the highest dose used. In chronic toxicity studies (26 weeks) in rats (PALO-99-08), and 9 months in dogs (PALO-99-10), convulsions were observed with the highest dose (14 mg/kg/day and 10 mg/kg/day, respectively).	Results of single and repeat-dose toxicity studies showed that palonosetron-related convulsive events occurred only at very high doses, which by far exceed the dose-equivalent in adult humans either for intravenous or oral administration of the drug. The described effects were considered of potential relevance to humans. For further information on convulsive events, see also the underneath section "General safety pharmacology".
Reproductive toxicity & developmental toxicity No treatment-related teratogenic effects were seen. Maternal toxicity was the limiting factor in the embryo-foetal studies. Palonosetron did not affect pre- or postnatal development, except at high oral doses, unrepresentative of the clinical situation. Although oral treatment of rats (one-month repeat-dose toxicity study) was associated with degeneration of the seminiferous epithelium, this was not observed in intravenous fertility studies, leading to the conclusion that this toxic effect might be due to a metabolite. Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats. However, in the female rat oral study there was a small but statistically significant reduction in the number of females treated at 60 mg/kg/day that mated, with a consequent reduction in the number of pregnancies.	Results of the reproductive and developmental studies enabled reasonable assumption of palonosetron safety administration in humans. In humans two quantifiable metabolites in urine (M4 and M9) were observed, 100-fold less active than palonosetron. Therefore, it seems that the toxic effects in rats might be not relevant to humans. However, no clinical evidence is available on the effect of palonosetron on human fertility.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Genotoxicity Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis test or the mouse micronucleus test. It was, however, positive for clastogenic effects in the CHO chromosomal aberration test.	According to the results obtained and to the International Conference on Harmonisation (ICH) guideline on genotoxicity (CHMP/ICH/141/95), palonosetron was considered as non-genotoxic.
Carcinogenicity and mutagenicity High doses applied daily for two years caused an increased rate of liver tumours, endocrine neoplasms (in thyroid, pituitary, pancreas, adrenal medulla) and skin tumours in rats but not in mice. The underlying mechanisms are not fully understood. Except for a small increase in hepatocellular adenomas in female rats, the increase in the incidences of tumours in palonosetron carcinogenicity studies were predominantly those of the endocrine system for which the rat is known to be particularly susceptible.	Described effects on liver were unlikely to be of relevance to human, clinical human exposure being a short-term administration. The area under the curve (AUC) achieved in performed studies were much higher than the exposure achievable in man in single dose administration, and therefore the potential risk to humans was not considered relevant.
General safety pharmacology Non-clinical studies indicate that palonosetron, only at very high concentrations, may block ion channels involved in ventricular de- and re-polarisation and prolong action potential duration. *In vitro* studies confirmed the expected effects of palonosetron on delayed rectifier potassium current (I_{Kr}) and fast sodium current (I_{Na}) and action potentials, known as class effects of 5-HT_3 RAs, but at very high concentrations. *In vivo* studies using several species showed effects on cardiac conduction, but no 'Torsade de pointes' were observed, despite doses of up to 1 mg/kg, which is 300-fold higher than the therapeutic dose in humans. Results from safety pharmacology studies with palonosetron suggested little concern for effects on respiratory, gastrointestinal, renal, central, and autonomic system functions at therapeutic doses. Although convulsions, ataxia, subdued behaviour, and occasional changes in gait were reported in many of the toxicity studies, in general these occurred only at fatal or near fatal dosages and probably reflect extreme physiological conditions.	The changes observed in the *in vitro* studies to assess the cardiovascular safety of palonosetron were consistent with the known effects of 5-HT_3 RAs, all of which inhibit both I_{Kr} and I_{Na} currents (Kuryshev YA et al. 2000). The changes occurred at very large, supra therapeutic doses or concentration greater than those anticipated in clinical practice, therefore it was considered unlikely that palonosetron at the proposed therapeutic dose would have any effect on these channels in humans. Based on the preclinical data, the possibility that palonosetron can have a role in the onset of seizures during its clinical use is negligible, however due to the clinical relevance of the reactions, and since an association between palonosetron and convulsive events in human beings cannot be surely ruled out, the event was a potential risk for palonosetron.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mechanism of drug interactions Since palonosetron is co-administered with chemotherapeutic agents, potential for interactions between palonosetron and five chemotherapeutic agents (cisplatin, cyclophosphamide, mytomycin C, doxorubicin and cytarabin) was assessed in various murine tumour models. There was no effect of palonosetron on the antitumor activity of these chemotherapeutic agents. CYP2D6 is the major CYP isoenzyme involved in the metabolism of palonosetron. *In vitro* experimental tests showed that palonosetron is a competitive inhibitor of CYP1A2, CYP2D6 and CYP3A.	Since the in vivo concentration of palonosetron is much lower than concentrations studied with a set of human liver microsomal samples, the inhibition potential of palonosetron is not expected to have clinical implications. A study in healthy subjects aimed to evaluate the potential for interaction between intravenous palonosetron and metoclopramide (CYP2D6 inhibitor) was conducted. Study results did not show significant pharmacokinetic (PK) interaction. Results of the population PK analysis in the Phase III CINV trials indicated no significant effect of co-medications that are CYP2D6 inducers (dexamethasone and rifampicin) and inhibitors including amiodarone, celecoxib, chlorpromazine, cimetidine, doxorubicin, fluoxetine, haloperidol, paroxetine, quinidine, ranitidine, ritonavir, sertraline, terbinafine on palonosetron clearance.

Overall, non-clinical data currently available lead to the conclusion that no additional non-clinical data are needed. Summary of the well-known safety concerns of palonosetron are provided in Table 2 below.

Table 2 Summary of safety concerns from non-clinical data

Safety concern
Important identified risk (confirmed by clinical data) None
Important potential risk (confirmed by clinical data) QT/QTc interval prolongation Convulsive events
Missing information None

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

The clinical development programme of palonosetron included several studies also aimed to evaluate the PK of palonosetron, following IV and oral administration in healthy subjects and in patients. For palonosetron IV formulation (fixed dose of 0.25 mg and 0.75 mg) for the prevention of acute and delayed nausea and vomiting associated with moderately and highly emetogenic chemotherapy it was performed more than ten years ago and comprised three pivotal randomized active controlled trials (PALO 99-03, -04, -05). All the studies that contributed to defining the pharmacological profile of palonosetron were single-dose studies since palonosetron is intended for single-dose administration in commercial use. The clinical program also included an open uncontrolled trial that assessed the safety

of the highest dose of the drug (i.e., 0.75 mg) intravenously in cancer patients receiving multiple chemotherapy cycles (PALO-99-06) and a Phase 1 single dose open label, randomized, cross-over study in male and female Chinese healthy volunteers to evaluate the pharmacokinetic of oral palonosetron (0.25, 0.50, 0.75 mg) in 18 subjects (PALO-14-21). A total of two Phase 2 studies were conducted with palonosetron IV doses ranging from 0.3 µg/kg up to 90 µg/kg (Studies 2330, 2120). One of the two studies was early discontinued due to poor enrolment (Study 2120). Conversion of the weight-based doses used in the Phase 2 studies to fixed doses was calculated to select the doses to be tested in the Phase 3 trials.

The clinical development program of the oral formulation included one randomized active controlled Phase 3 study (PALO 03-13) and was intended to investigate the efficacy of three doses of palonosetron (0.25 mg, 0.50 mg, and 0.75 mg) for the prevention of moderately emetogenic chemotherapy. Likewise, the IV formulation, an open uncontrolled repeated cycles study with the highest oral dose of 0.75 mg was also conducted (PALO-03-14). In addition, a Phase 2 study utilized the IV formulation administered as oral solution (Study 2332). Furthermore, oral palonosetron was the active comparator in clinical studies run with netupitant in patients receiving repeated cycles of anthracycline based chemotherapy (NETU 08-18) or highly emetogenic chemotherapy (NETU 07-07). More recently the post-operative nausea and vomiting (PONV) indication was pursued in the US.

The overall clinical development programme included two Phase 3 randomized placebo controlled clinical trials (PALO-04-06, PALO-04-07) that were conducted to assess the efficacy of three palonosetron IV doses (0.025 mg, 0.050 mg, and 0.075 mg) and two Phase 2 studies (Study 2500 and Study 2502). This study utilized weight-based doses of palonosetron administered intravenously. The weight-based doses were then converted to fixed doses (approximate 4 dose groups). In all studies only a single dose of palonosetron prior to cancer chemotherapy course or anaesthesia was given intravenously or orally. Repeated exposures according to the number of chemotherapy cycles administered are available for the open label uncontrolled trials with IV or oral palonosetron. In addition, a randomized, double-blind, multicenter, parallel group, stratified, Phase 3 study to evaluate the efficacy and the safety of single IV 0.075 mg Palonosetron versus Placebo to prevent postoperative nausea and vomiting following elective abdominal or gynecological laparoscopic surgery (PALO-16-57) was performed. This PONV IV double-blind study in adult cancer patients has involved 208 patients treated with palonosetron and 201 patients with placebo.

The clinical efficacy of palonosetron in CINV was mainly investigated in the cancer population scheduled to receive highly or moderately emetogenic chemotherapy. The tested dose of 0.25 mg corresponds to the dose available on the European and American market, whereas the 0.75 mg is the approved dose in Japan. In cancer patients palonosetron was administered prophylactically as a single intravenous or oral dose prior to each chemotherapy cycle. With regards to study population, pivotal clinical trials allowed the inclusion of in- or out- patients, naïve or not naïve to chemotherapy. Either subjects of both gender and with a Karnofsky performance status equal to or more than 50% were eligible for these studies, meaning that only disabled patients or unable to care for self or with a disease progressing rapidly were not included. With reference to age, overall, more cancer patients aged 18 to 64 years (approximately 70%) were exposed to intravenous palonosetron compared to those aged 65 years (about 30%); and many patients were females (breast cancer). A similar pattern of age and gender distribution was also observed for oral palonosetron exposure. As for race, most palonosetron-treated patients were Caucasian (ranging from 66–72%), followed by Hispanic, ranging from 24.3% to 31%, and Black, 3% or less.

A double-blind randomized study was carried out to determine the optimal dosage of palonosetron in Japanese cancer patients receiving highly emetogenic chemotherapy. A total of 555 patients received palonosetron 0.75 mg IV dose, whereas 559 patients were given IV granisetron prior to chemotherapy.

The available data on Japanese patients appears to reflect as much as possible the standard population usually treated with antiemetic prophylaxis.

The clinical development of palonosetron was also run in China, where a clinical study (PALO-14-01) in 318 cancer patients was performed to compare the intravenous (palonosetron ZhiRuo® 0.25 mg) versus the oral formulation (palonosetron Aloxi® 0.50 mg) prior to moderately emetogenic chemotherapy.

The data collected in this population substantially reflects the data obtained in the same setting of patient of different racial origin. To complement the exposure in Asiatic population safety data originating from the Korean post marketing surveillance study in CINV and PONV sponsored by licence partner CJ CheilJedang Corp were collected in 20.415 patients for PONV and 7.755 for CINV, respectively.

As part of the late stage of the clinical development program of palonosetron, clinical studies have been conducted in special populations, including patients with renal impairment, apart from subjects with end stage renal disease undergoing haemodialysis, and patients with hepatic impairment. Moreover, a study in healthy volunteers who were poor or extensive metabolizers of CYP2D6 was carried out. In all studies a single intravenous dose of 0.75 mg was given. In addition to the patients belonging to special populations that have been studied as per above table, patients with hepatic, cardiovascular or renal failure might have been enrolled at the discretion of the investigator in the Phase 3 clinical development programme.

Since 2003, some clinical trials in CINV have been carried out with the approved IV dose of 0.25 mg. Adult patients with specific type of cancer scheduled to receive moderately or highly emetogenic chemotherapy represented the target population.

In the framework of a clinical program intended to investigate the efficacy and safety of a fixed dose combination of an intravenous formulation of Akynzeo (netupitant-palonosetron), a clinical study (PALO-15-17) testing two different ways of palonosetron infusion (30 sec vs 30 minutes) has been conducted in adult patients undergoing one cycle of cisplatin-based chemotherapy. A total of 440 patients were randomized and treated.

Paediatric population was also investigated: two studies were conducted both in CINV (PALO-99-07, PALO-10-20) and PONV (PALO-07-29, PALO-10-14). The tested dose of 20 mcg/kg up to a maximum dose of 1.50 mg prior to multiple repeated courses of chemotherapy proved to be effective and safe in cancer patients aged one month and older.

In study PALO-99-07 palonosetron doses of 3 mcg/kg up to a maximum total dose of 0.25 mg and 10 mcg/kg up to a maximum total dose of 0.75 mg were assessed in 72 cancer patients receiving highly or moderately emetogenic chemotherapy. Study PALO-10-20 was conducted in a total of 330 paediatric CINV patients exposed to palonosetron (10 mcg/kg up to a maximum of 0.75 mg or 20 mcg/kg up to a maximum dose of 1.50 mg) prior to multiple repeated courses of chemotherapy. The active comparator was ondansetron given at 0.15 mg/kg, up to a maximum total dose of 32 mg.

Two studies were also conducted in PONV in pediatric population: study PALO-07-29 investigated the efficacy and safety of two doses of IV palonosetron (1 and 3 mcg/kg up to a maximum total dose of 0.075 mg and 0.25 mg, respectively) in a total of 150 subjects, while study PALO-10-14 assessed the safety and efficacy of IV palonosetron (1 µg/kg, up to a maximum dose of 0.075 mg) compared to ondansetron.

A palonosetron non-Helsinn sponsored clinical study in children presented the results of a trial run in Turkey in 286 children aged 3-13 years inclusive undergoing dental rehabilitation under general

anesthesia. Three doses of palonosetron were tested (0.0025, 0.0050 or0.0075 mg) and all doses were well tolerated (Bicer C et al. 2011).

SIII.2 Clinical Trial exposure

Cumulative exposure to palonosetron in clinical trials has been calculated starting from the product Development International Birth Date (DIBD, 02 June 1992), considering the number of patients treated in the Helsinn completed trials belonging to the palonosetron development program. Since the start of palonosetron development, a **total of 8,215 patients** were exposed, of which **6,006 for CINV** prevention and **2,209 for PONV** prevention (Table 3). Exposure data are provided in following tables below.

Patient exposure data are sorted by indication, and by dose and route of administration (

Table 4), by gender and age group (Table 5, Table 6, Table 7), and by racial or ethnic origin (Table 8, Table 9). The total number of patients exposed to palonosetron does not exactly match in the underneath tables as patients enrolled in the pivotal CINV trials evaluating two doses of palonosetron (0.25 mg and 0.75 mg) versus an active comparator could participate in the open-label, uncontrolled study with the IV formulation (0.75 mg). Patients who received the dose of 0.25 mg were considered as new patients exposed to the palonosetron dose of 0.75 mg; patients who received in the pivotal trials the active comparators (ondansetron, dolasetron) were considered as new patients exposed to palonosetron 0.75 mg. Exposure to palonosetron in special populations is provided in Table 10 below. Exposure data of paediatric patients that were included in the paediatric clinical trials are sorted by study, indication and dose (Table 11) and by age group and gender (Table 12). Overall, a total of 883 paediatric patients exposed to different doses of IV palonosetron were enrolled in 4 Helsinn-sponsored trials (PALO-10-20, PALO-99-07, PALO-10-14 and PALO-07-29).

Table 3 Exposure by indication (totals)

Total population	
	Persons
CINV prevention	6,006
PONV prevention	2,209
TOTAL	**8,215**

Table 4 Exposure by dose, route of administration and age group (by indication)

CINV prevention			
Dose of exposure	**Palonosetron**		**Total**
	IV n (%)	**Oral n (%)**	**N (%)**
Adult population			
<0.25 mg	32 (1.0)	32 (1.4)	64 (1.1)
0.25 mg	2,271 (68.5)	202 (8.8)	2,473 (44.1)
0.50 mg	0 (0.0)	1,566 (68.4)	1,566 (27.9)
0.75 mg	1,232 (37.2)	422 (18.4)	1,654 (29.5)
>0.75 mg	77 (2.3)	69 (3.0)	146 (2.6)
Sub-total	3,313	2,291	5,604
Paediatric population			
3 µg/kg	35 (8.7)	0 (0.0)	35 (8.7)
10 µg/kg	204 (50.7)	0 (0.0)	204 (50.7)
20 µg/kg	163 (40.5)	0 (0.0)	163 (40.5)
Sub-total	402	0	402
TOTAL	**3,715**	**2,291**	**6,006**

PONV prevention			
Dose of exposure	**Palonosetron**		**Total**
	IV n (%)	**Oral n (%)**	**N (%)**
Adult population			
<0.025 mg	47 (3.3)	0 (0.0)	47 (2.7)
0.025 mg	374 (26.0)	37 (12.9)	411 (23.8)
0.050 mg	307 (21.3)	0 (0.0)	307 (17.8)
0.075 mg	575 (39.9)	64 (22.2)	639 (37.0)
>0.075 mg	137 (9.5)	187 (64.9)	324 (18.8)
Sub-total	1,440	288	1,728
Paediatric population			
1 µg/kg	405 (84.2)	0 (0.0)	405 (84.2)
3 µg/kg	76 (15.8)	0 (0.0)	76 (15.8)
Sub-total	481	0	481
TOTAL	**1,921**	**288**	**2,209**

Table 5 Exposure by gender (totals)

Total population	
CINV prevention	
Gender	**Persons**
Male	2,293
Female	3,713
Sub-Total	**6,006**
PONV prevention	
Gender	**Persons**
Male	342
Female	1,867
Sub-Total	**2,209**
TOTAL	**8,215**

Table 6 Exposure by age group (by indication)

CINV prevention	
Age group	**Persons**
	n (%)
Adult population	
16 years*	1 (0.0)
>18 <65 years	4,289 (76.5)
65 < 75 years	1,069 (19.1)
75 < 85 years	236 (4.2)
≥85 years	9 (0.2)
Sub-total	**5,604**
Paediatric population	
0 < 2 years	42 (10.4)
2 < 6 years	117 (29.1)
6 < 12 years	113 (28.1)
12 < 18 years	130 (32.3)
Sub-Total	**402**
PONV prevention	
Age group	**Persons**
	n (%)
Adult population	
>18 < 65 years	1,647 (95.3)
65 < 75 years	69 (4.0)
75 < 85 years	10 (0.6)
≥85 years	2 (0.1)
Sub-total	**1,728**
Paediatric population	
0 < 2 years	29 (6.0)
2 < 6 years	158 (32.8)
6 < 12 years	179 (37.2)
12 < 18 years	115 (23.9)
Sub-Total	**481**

*One patient belonging to paediatric age group was enrolled in a study including adult subjects with testicular cancer on treatment with highly emetogenic chemotherapy

Table 7 Exposure by age group and gender (totals)

Total population		
Age group	**Male n (%)**	**Female n (%)**
0 < 2 years	39(1.5)	32 (0.6)
2 < 6 years	154 (5.8)	121 (2.3)
6 < 12 years	170 (6.5)	122 (2.3)
12 < 18 years	139 (5.3)	107 (1.9)
≥18 < 65 years	1,492 (56.6)	4,444 (79.6)
65 < 75 years	519 (19.7)	619 (11.1)
75 < 85 years	116 (4.4)	130 (2.3)
≥85 years	6 (0.2)	5 (0.1)
TOTAL	**2,635**	**5,580**

Table 8 Exposure by ethnic or racial origin (by indication)

Ethnic/racial origin	**CINV prevention**	**PONV prevention**
	n (%)	**n (%)**
Caucasian	4,470 (74.4)	1,639 (74.2)
Black / African American	99 (1.6)	213(9.6)
Hispanic	838 (14.0)	121 (5.5)
Asian	546 (9.1)	225 (10.2)
Other	53 (0.9)	11 (0.5)
Sub-total	**6,006**	**2,209**

Table 9 Exposure by ethnic or racial origin (totals)

Total population	
Ethnic/racial origin	**Persons**
Caucasian	6,109
Black / African American	312
Hispanic	959
Asian	771
Other	64
TOTAL	**8,215**

Table 10 Exposure by special populations (totals)

Special population	**Persons**
Renal impairment*	16
Mild/Moderate	9
Severe	7
Hepatic impairment*	24
Mild	8
Moderate	8
Severe	8
Paediatric population	883
CINV prophylaxis	402
PONV prophylaxis	481
Poor metabolizers of CYP2D6*	3
Extensive metabolizers of CYP2D6*	3
Total	**929**

** Subjects exposed to palonosetron 0.75 mg dose.*

Table 11 Exposure in paediatric patients by indication, study, and dose of exposure (totals)

Indication	**Study**	**Palonosetron**				**Ondansetron**
		1 µg/kg	**3 µg/kg**	**10 µg/kg**	**20 µg/kg**	
PONV	PALO-07-29	74	76	0	0	0
	PALO-10-14	331	0	0	0	330
Sub-total		**405**	**76**	**0**	**0**	**330**
CINV	PALO-99-07	0	35	37	0	0
	PALO-10-20	0	0	167*	163	164
Sub-total		**0**	**35**	**204**	**163**	**164**
Total		**405**	**111**	**204**	**163**	**494**

**One additional patient received palonosetron instead of ondansetron by error on cycle 4*

Table 12 Exposure in paediatric patients by age group, and gender (totals)

	Dose	**Palonosetron**			
		1 µg/kg n (%)	**3 µg/kg n (%)**	**10 µg/kg n (%)**	**20 µg/kg n (%)**
Age group	<2 years	25 (6.2)	10 (9.0)	21 (10.3)	15 (9.2)
	2 < 6 years	141 (34.8)	21 (18.9)	60 (29.4)	53 (32.5)
	6 < 12 years	146 (36.0)	43 (38.7)	58 (28.4)	45 (27.6)
	12 < 18 years	93 (23.0)	37 (33.3)	65 (31.9)	50 (30.7)
	Sub-total	**405**	**111**	**204**	**163**
	TOTAL	**883**			
Gender	Male	245 (60.5)	69 (62.2)	112 (54.9)	75 (46.0)
	Female	160 (39.5)	42 (37.8)	92 (45.1)	88 (54.0)
	Sub-total	**405**	**111**	**204**	**163**
	TOTAL	**883**			

In conclusion, no changes to the number of subjects exposed during clinical trials to palonosetron between the DLP of the last PSUSA (PSUSA/00002268/201907; 24/07/2019) and the current RMP v7.0 DLP (24/07/2021) occurred.

Part II: Module SIV - Populations not studied in clinical trials

Pregnant females

There has been no data in females of childbearing potential, in line with the inclusion/exclusion criteria of the clinical study protocols. Women of childbearing potential were required to be using reliable contraceptive measures and to have a negative pregnancy test result at the pre-treatment visit to qualify for enrolment into Phase II-III studies with palonosetron. Because the non-clinical reproduction studies are not always predictive of human responses, palonosetron is not recommended for use during pregnancy, unless its administration is considered essential by the physician as described in the current Summary of Product Characteristics (SmPC). Palonosetron has not been administered to patients undergoing labour and delivery, so the potential effects on mother or child are unknown.

In conclusion, safety in human pregnancy has not been established for palonosetron, and animal reproduction studies do not always predict human responses.

Pediatric population

As far as the paediatric population is concerned, a paediatric plan sponsored by Helsinn was completed and pediatric use in CINV patients aged one month and older was granted by the regulatory authorities in the USA and EU. Overall, a total of 883 paediatric patients exposed to different doses of IV palonosetron were enrolled in 4 trials in the CINV (PALO-99-07, PALO-10-20) and PONV setting (PALO-07-29, PALO-10-14).

In the PONV studies most patients were aged 6 to <12 years (36.5%) or 2 to <6 years (34.6%), while 6.5% were less than 2 years of age. Although enrolment of neonates aged 0 to 28 days was permitted, the youngest patient treated was aged 30 days. The higher proportion of patients in the age groups 6 to <12 years and 2 to <6 years is attributable to the type of elective surgical procedures performed for localized or mild systemic diseases. Although the total number of patients (n=53) aged less than 2 years was limited, safety results of PONV studies were consistent with the established safety profile of palonosetron and did not indicate safety risk for paediatric patients undergoing elective surgery. As expected in this setting of surgical patients, the most common adverse events were reported in the Injury, poisoning and procedural complication SOC.

In the CINV studies the enrolment in age groups 2 to <6 years, 6 to < 12 years, and 12 to < 18 years was approximately 30% of the total in each age group for palonosetron treated patients. Although the study protocols allowed enrolment of youngest patients, few subjects were recruited and no full term newborns treated with the study medication. The palonosetron safety profile observed in the CINV studies was as expected based on the treatment-emergent adverse events (TEAEs) frequently reported in the context of cancer patients receiving treatment with cytotoxic chemotherapy, with the most common TEAEs in the SOCs *'Blood and lymphatic disorders', 'Gastrointestinal disorders', and 'General disorders and administration site conditions'*. No clinically relevant differences regarding the type and frequencies of TEAEs was observed in each group of patients stratified by age as well as no increased incidence of TEAEs was seen with the higher dose of 20 mcg/kg palonosetron dose compared to the lower dose levels of 3 mcg/kg and 10 mcg/kg in patients exposed up to 4 chemotherapy cycles.

No data related to palonosetron are available for cancer patients aged less than 1 month.

Elderly

Approximately 23% of subjects aged ≥ 65 years participated in the clinical development programme of the IV formulation and 30% in the pivotal oral formulation studies for the CINV prevention. Overall, no clinically significant age effect on the incidence of AEs was noted in the pivotal Phase 2/3 trials. At the SOC level, gastrointestinal, infection, investigational, psychiatric, and metabolic AEs were more

common among subjects ≥ 65 years at all doses and formulations. Gastrointestinal AEs which were generally more frequent in the older population included constipation, nausea, flatulence, and stomatitis. It is known that the prevalence of constipation rises with age, most dramatically in patients ≥ 65 years of age or older. In addition, constipation appears to be influenced by decreased caloric intake and lessened daily physical activity in the elderly.

For the IV palonosetron development programme, cardiac AEs were also more common among older subjects, but the overall incidence was low. Concomitant diseases or increased risk for complications associated with chemotherapy described in elderly may also contribute to the occurrence of AEs including haematological toxicities. Nervous system AEs were less frequently observed compared to younger subjects. Overall, these findings support the observation that there were no apparent palonosetron dose-related effects associated with increasing age of patients using palonosetron.

Even though the number of observed AEs was higher in the elderly (patients over 65 years of age), it can be assumed that there is no significant unknown safety concern associated with palonosetron administration to elderly subjects compared to young healthy subjects. Furthermore, a population PK/PD model designed to identify the factors that may influence the disposition of palonosetron in a target population of adult cancer patients receiving chemotherapy was conducted (PALO-99-33). Since cancer patients may have different underlying diseases requiring different concomitant medications in addition to chemotherapeutic agents, the experimental study examined demographic variables, including age, co-medications, renal, hepatic, and cardiac impairment for their possible effects on the PK of palonosetron. Elderly patients (aged 65 years and older) made up 19% of the studied population.

Several factors were found to affect palonosetron volume of distribution, although all the covariates combined explained only 12% of the inter-individual variability observed. Since the overall incidence of AEs did not seem to be influenced by age, gender, and race, it is assumed that the differences observed in volume of distribution do not have an impact on the occurrence of AEs.

In conclusion, all these results indicate that no dose adjustments or restriction in use are required for palonosetron administration to elderly patients.

Hepatic impairment

As approximately 50% of palonosetron is metabolized in the liver, hepatic insufficiency could be associated with a significant reduction in the total body clearance and prolongation of the elimination half-life of palonosetron. To estimate the effect of different degrees of hepatic impairment on the PK of palonosetron, study PALO-99-51 was conducted in 24 symptomatic patients assigned to one of the three groups of 8 patients each, with the severity of hepatic impairment scored according to the Child Pugh classification. Plasma and urine PK data showed that hepatic impairment does not significantly affect total body clearance of palonosetron. Study results demonstrated that from a PK perspective, no dose reduction is required in patients with hepatic impairment.

Even though the patients with hepatic insufficiency could have been enrolled at the discretion of investigator in the Phase 3 clinical development programme for both IV and oral palonosetron formulations, an analysis of general AEs was not undertaken because of the relatively small subset of patients suffering from hepatic impairment. However, PK results indicate that no implications for palonosetron use, or dose adjustments are considered necessary in population with hepatic impairment or insufficiency.

Renal impairment

PK data received in healthy volunteers indicate that approximately 40% of palonosetron is eliminated unchanged in the urine, while 50% is metabolized. Renal insufficiency could be associated with a reduction in the total body clearance and prolongation of the elimination half-life of palonosetron.

A study (PALO-99-35) was carried out to estimate the potential effects of chronic renal impairment on the PK of palonosetron and its primary metabolite M9. The study enrolled 25 subjects who were administered with 0.75 mg palonosetron as a single IV bolus. Nine subjects suffered from mild-to-moderate renal impairment (creatinine clearance [CLcr] 30–80 ml/min) and seven subjects suffered from severe renal impairment (CLcr 10–19 ml/min). Additional nine subjects were healthy volunteers serving as a control group. As a result, severe renal impairment appeared to be associated with an increase in the palonosetron terminal elimination half-life, probably due to a reduction in renal clearance. However, the total body clearance in these patients was found to be like healthy subjects.

The results of this study demonstrated that from a PK perspective, dosage adjustment is not necessary in patients with any degree of renal impairment. No data are available on patients with end stage renal disease undergoing haemodialysis. Therefore, the implications or potential consequences of palonosetron administration cannot be predicted.

Race

Analysis of data obtained from the population PK analysis conducted in cancer patients treated with palonosetron showed that results of palonosetron PK parameters were similar in subjects of Caucasian and Hispanic origin.

The available information for the Japanese population derived from results of a clinical trial conducted for the purposes of original marketing authorisation application submitted by the marketing authorization holder of palonosetron in Japan. A total of 1,119 patients were treated: 557 in the palonosetron group and 562 in the granisetron group. Two post-authorization safety studies (1023 and 01B3040) were conducted by the marketing authorisation holder (MAH), aimed to detect the occurrence of AEs associated with palonosetron 0.75 mg and evaluating the role of factors potentially affecting the safety profile of palonosetron. The use-results survey 1023 has started in June 2010 with a target sample size of 1,000 patients scheduled to receive their first cycle of HEC. The enrolment was completed with a total of 1,048 patients included. Study 01B3040 was a prospective study including 900 patients undergoing repeated cycles of the same HEC. The enrolment was completed with 832 patients.

Upon endorsement of palonosetron IV formulation in Korea, the health authority requested from the local MAH to perform a post-marketing surveillance in at least 3,000 patients receiving palonosetron IV either for CINV or PONV prevention. The Korean Post-Marketing Surveillance Study in CINV patients assessed the safety and efficacy of IV palonosetron 0.25 mg administration. The number of subjects included in this surveillance was 8,366. The Korean Post-Marketing Surveillance Study in PONV patients was conducted with the objective to evaluate the safety and efficacy of palonosetron 0.075mg administered to patients undergoing surgical procedures. The number of subjects whose surveillance forms were collected was 21,039. Meanwhile, the company became aware of a Phase 3 study (CJ_ALX_301) conducted in Korea and sponsored by the local marketing authorization holder. This study was planned to evaluate the efficacy and safety of palonosetron (0.075mg IV) versus placebo in the treatment of PONV in patients undergoing general anaesthesia. A total of 151 patients were enrolled of which 75 were treated with palonosetron and 76 with placebo. In this study, palonosetron showed a significant higher efficacy in the treatment of PONV at 24- and 72-hours post-surgery compared to placebo. No safety issues or potential signals were detected, with the most frequent (>5%) TEAEs in line with the known safety profile of palonosetron.

In general, the target sample size of each survey is adequate to allow the detection of any potential safety signal or safety concern. The results of these surveys will contribute to a better characterization of palonosetron safety profile in this special subpopulation.

Overall, the pattern of adverse reactions observed in the Asiatic population is consistent with that observed in Caucasian patients; no particular concern emerged from the review of the safety data collected in these studies.

In conclusion, there is no data suggesting that the efficacy and safety of palonosetron would be significantly influenced by the racial or ethnic origin. Overall, different ethnicity does not represent a safety concern; it can be predicted that the safety profile of the combinations in the real-life use in population of different races will be comparable.

Sub-populations with genetic polymorphisms

A study in 3 poor and 3 extensive metabolizers of CYP2D6 was performed with intravenous palonosetron 0.75 mg (study PALO-99-39). Palonosetron plasma concentrations, PK parameters and renal excretion were similar in the two categories analysed. Palonosetron at clinically relevant concentrations (0.75 mg), i.e., three-times higher than the commercially available dose, neither inhibits nor induces CYP2D6 substrates.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria in pivotal studies in the development programme:

Criterion: Hypersensitivity to 5-HT_3 RAs (e.g., ondansetron, dolasetron, tropisetron, ramosetron)

Reason for exclusion: Patients with a history of positive allergy to these active ingredients are at risk of subsequent reactions to these drugs since the agent may act as an antigen and elicit one of several classic immune responses. Difficulties exists to predict if patients with known hypersensitivity to a 5-HT_3 RA would be also hypersensitive or prone to an increased risk of allergic reactions in association with palonosetron. Potential outcomes of severe allergic reaction to palonosetron may be fatal. The frequency of hypersensitivity reactions reported in the post-marketing experience with palonosetron is 'very rare' (<1/10,000).

Is it considered to be included as missing information? No – It is a contraindication

Criterion: History of Torsade de Point or known history of risk factors for Torsade de Point (heart failure, hypokalemia, family history of Long QT Syndrome)

Reason for exclusion: 5-HT_3 RAs may cause QT/QTc interval prolongation or may have effects on cardiac action potential, therefore patients known to bear these abnormalities were to be excluded from the trial.

Is it considered to be included as missing information? No – It is a warning

Criterion: Pregnancy and Lactating females

Reason for exclusion: Palonosetron is not intended for use during pregnancy as the safety has not been established. There is no experience of palonosetron in human pregnancy. Therefore, palonosetron should not be used in pregnant women unless it is considered essential by the physician. In addition, there are no data regarding the excretion of palonosetron in breast milk.

Is it considered to be included as missing information? No. In the prescribing information it is recommended that palonosetron should not be used during pregnancy or breast-feeding.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Since the beginning of the clinical development programme in 1992, the Palonosetron clinical development program included a total of **8,215 subjects** exposed to palonosetron in CINV and PONV completed clinical studies sponsored by Helsinn. Table 13 summarizes the limitations to adverse drug reaction detection.

Table 13 Limitations to adverse drug reaction detection

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Which are rare or uncommon	More than 8,200 subjects were exposed to palonosetron within the clinical development program	ADRs with minimal frequency of 1 in 1,000 may have been detected within the clinical programme (i.e., 'very common' or 'common' ADRs). Detection of rare or uncommon ADRs could have been affected by the population exposed in clinical trials. However, based on the current post-marketing exposure of more than 17 million patients (see section SV.2), it is unlikely there are any rare or very rare ADRs that are left undetected. The implication for target population is therefore negligible.
Due to prolonged exposure	Palonosetron is intended for short-term therapy (single administration prior to each chemotherapy cycle). No data from clinical studies are available to elucidate the potential effects due to prolonged exposure	Detection of ADRs due to prolonged exposure, cumulative effect, or recognition of ADRs with long latency could have been affected by population exposed in clinical trials. Based on the nature of palonosetron therapy, the implication for the target population due to prolonged exposure or cumulative effects of ADRs do not appear to represent a safety concern
Due to cumulative effects	Palonosetron was administered as single dose up to 6 mg to cancer patients within the clinical development programme (study 2330)	
Which have a long latency	No long-term clinical studies or studies with long-term follow-up periods have been conducted with palonosetron	Palonosetron is given once prior to each chemotherapy cycle. Therefore, the potential risk for target population is considered low.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 14 summarizes the list of populations included or not in clinical trial development programs.

Table 14: List of populations included or not in clinical trial development programs

Type of special population (Any included in pre-authorisation clinical development program yes/no)	**Exposure**
Pregnant women	No
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic or renal impairment • Patients with other relevant co-morbidity such as cardiovascular disease • Patients with a disease severity different from inclusion criteria in clinical trials. • Immuno-compromised patients	 See comment underneath* No No No
Population with relevant different ethnic origin	553 Chinese patients (PALO-14-01, PALO-14-21 and PALO 16-57)
Subpopulations carrying known and relevant genetic polymorphisms	3 subjects poor and 3 subjects extensive metabolizers of CYP2D6 (PALO-99-39)

**A total of 24 subjects with hepatic impairment (PALO-99-51) and 16 with renal impairment (PALO-99-35) were exposed to palonosetron 0.75 mg dose study.*

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The estimates on the cumulative patient exposure from the post-marketing experience since the first launch in the USA up to 24 July 2021 are reported in the tables below. The method applied is described in the paragraph below *SV.1.1 Exposure*. Globally, **17,921,986** patients have been treated since first palonosetron launch in September 2003.

Collectively, there is no evidence of any change in the clinical pattern of palonosetron ADRs or of any new qualitative or quantitative safety concern from the post-marketing experience. The available safety data do not change the established favourable palonosetron benefit-risk profile.

SV.1.1 Exposure

Calculation of patient exposure to palonosetron was derived from sales figures which cover the time interval from September 2003 to 24 July 2021.

Typically, 4 to 6 cycles of chemotherapy constitute a course of chemotherapy. For CINV patient exposure has been estimated considering that a patient receives an average of 6 administrations of palonosetron during the entire course of chemotherapy (US data from IntrinsiQ, 2005 and Cancer Monitor, 2006). It is evident that a patient can receive more than one dose of palonosetron when undergoing repeated courses of chemotherapy, the number of doses administered to one patient will differ due to several factors including tumour type and stage, patient's response to chemotherapy as well patient's general conditions.

The approach for calculation of palonosetron exposure in patients with PONV differs. Assuming that a single dose of palonosetron is administered to patients before undergoing surgery, the number of vials sold should correspond to the number of patients treated.

Patient exposure by indication and pharmaceutical form and by geographical region and pharmaceutical form in the cumulative period are presented in Table 15 and Table 16 below.

Table 15 Cumulative number of patients exposed to palonosetron in post-marketing setting, divided by indication and pharmaceutical form

Exposed patients			
CINV		**PONV**	
Solution for injection	Soft gel capsule	Solution for injection	Soft gel capsule
10'821'125	147,738	6,953,123	0

Table 16 Cumulative number of patients exposed to palonosetron in postmarketing setting, divided by geographical region and pharmaceutical form

Number of patients			
Geographical region	**Solution for injection (CINV)**	**Solution for injection (PONV)**	**Soft gel capsules (CINV)**
EU	1,184,776	0	144,862
RoW	149,943	0	255
North America	5,873,419	22,630	2,278
Central-South America	467,076	627,882	0
Asia	2,886,914	6,294,245	343
Oceania	258,997	8,366	0
Total	**10,821,125**	**6,953,123**	**147,738**

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Palonosetron does not pose a risk of misuse for illegal purposes, as psychoactive effects, including sedation, euphoria, perceptual and other cognitive distortions, and mood changes has not been observed following its administration.

Taking into account the fact that palonosetron is subject to medical prescription, the overall risk of misuse as a recreational drug is substantially negligible.

Part II: Module SVII - Identified and potential risks

Palonosetron is a 5-HT_3RA which is available on the US market since 2003 and in the EEA since 2005 for the prevention of chemotherapy-induced nausea and vomiting. The safety profile emerging either from clinical studies in more than 8,200 subjects or from more than 17 million of cancer patients treated worldwide in the frame of post-marketing surveillance activities raised no signals (qualitatively or quantitatively) of unexpected toxicity for palonosetron IV and os formulations.

There were no changes to the already known safety profile of palonosetron considering that post-marketing data since year 2003 largely contributed to characterize its safety profile.

As discussed in Module SVI, no safety concerns can be envisaged from the use of palonosetron as recreational drug considering the sought indication, and the minimization measures implemented to mitigate the risks, including the pack size and the legal status (medicine subject to medical prescription).

The safety concerns (identified risks, potential risks, and missing information) identified at the time of the previous EU-RMP version 6, dated 23 July 2014, will be discussed, and presented in this module.

Severe Constipation

Constipation in cancer patients is defined as a disorder characterized by irregular and infrequent or difficult evacuation of the bowels (National Cancer Institute 2017). Grade 1 refers to 'occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema'; Grade 2 is defined as 'persistent symptoms with regular use of laxatives or enemas; limiting instrumental activities of daily living (ADL)'; Grade 3 as 'obstipation with manual evacuation indicated; limiting self-care ADL'; Grade 4 as 'life-threatening consequences; urgent intervention indicated'; and Grade 5 as 'death'. A search of published data on severe constipation (Grades 3 or greater) was performed.

In the Italian trial of adjuvant treatment cyclophosphamide, methotrexate, and fluorouracil (CMF) (n=53) or docetaxel (n=48), 1.9% of patients with breast cancer on CMF had constipation of Common Toxicity Criteria, Grade 2 and 1.9% had Grade 3 constipation (Nuzzo F. et al. 2008). In the docetaxel arm, 2.1% of patients had constipation, of Grade 2. Neither treatment group had any patients with Grade 4 constipation.

In the United Kingdom (UK), the National Epirubicin Adjuvant Trial (NEAT) randomized women with early-stage breast cancer to one of two anthracycline regimens: CMF, or epirubicin and CMF (ECMF)

(Earl HM et al. 2008). Toxicity data were obtained for 979 patients in the ECMF arm and 973 in the CMF arm and classified into 4 grades by Common Toxicity Criteria. Grade 3 or 4 constipation was reported by 6% of the patients treated with ECMF and 3% of those treated with CMF.

An interim safety analysis was published from a phase 3 trial in Germany, based on data from the first 25 patients (Mahner S. et al. 2012). Women aged 65 years or older with histologically confirmed recurrent ovarian cancer and previous platinum-based cancer therapy were allocated to this trial. Patients were offered the option of treatment with oral or IV treosulfan, an alkylating agent. For all reported events of drug toxicity, the highest-grade occurrence per patient was counted. Grade 3 constipation occurred in 8% of patients.

In a trial of surgical adjuvant chemotherapy in early-stage NSCLC, 482 patients were randomized: 242 patients to vinorelbine plus cisplatin and 240 patients to observation (Winton T. et al. 2005). In the treated arm, 3% of patients had Grade 3 or 4 constipation.

Forty-five patients with previously treated but recurrent ovarian cancer, were treated with celecoxib and IV carboplatin (Legge F. et al. 2011). Treatment-related constipation of Grade 3 occurred in 1 patient (0.4%); no higher grade of constipation was observed.

A large study in the US that assessed the natural history of constipation among 50,641 patients in hospice care (with any diagnosis) found that nurses judged 8.2% to have moderate constipation and 3.8% to have severe constipation (Strassels SA Et al. 2010). Of the 1,935 patients with severe constipation, 99% patients diagnosed with any malignant neoplasm received opioids, 4.9% had severe constipation. In 2,724 patients with colorectal cancer, 3.9% had severe constipation. In 8,553 patients with malignancies of the trachea, bronchus, or lung, 4.7% had severe constipation.

A retrospective cohort study estimated the risk of intestinal obstruction after intraperitoneal (IP) chemotherapy in patients with ovarian, tubal, or peritoneal malignancies (Kehoe SM et al. 2009). All patients had initially been treated with surgery and IV chemotherapy. Obstruction after IP chemotherapy was assessed as malignant, or adhesion related. The 307 patients all had at least 3 months of follow-up and at least one dose of IP chemotherapy. Outcome events were admissions for complaints potentially related to gastrointestinal obstruction, radiologic diagnosis of intestinal obstruction, and medical or surgical treatment of obstruction. Overall, 104 patients (34%) developed symptomatic intestinal obstruction after IP chemotherapy was started. The obstruction was found to be malignant in 88 patients (85%) and mechanical in 12 patients (12%). In the remaining 4 patients (3%) the type of obstruction could not be classified.

In conclusion, constipation is a common undesirable effect of the drugs belonging to the pharmacological class of the 5-HT_3RA including palonosetron; however severe forms of constipation or complications such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in patient's hospitalization have an important impact on patient's health condition and social economic costs related to hospitalization, testing and corrective measures. Even though the contributory role of some confounding factors, such as chemotherapy, opioid use for pain relief cannot be surely ruled out in the cases collected so far, palonosetron by virtue of its pharmacological activity on the 5-HT_3 receptors expressed in the gastro-intestinal tract can be implicated or there is at least a reasonable possibility that the drug may have aggravated a pre-existing condition.

Constipation was common adverse reaction observed in the clinical trials with IV palonosetron, and uncommon adverse reaction in oral formulation trials. In fact, during the clinical development program of palonosetron, 2 subjects experienced severe constipation following a single IV palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 mcg/kg oral dose in a post-operative nausea and vomiting study and one healthy subject received a 0.75 mg I.V. dose in a pharmacokinetic study. A total of 10 cases of severe constipation were cumulatively collected

since palonosetron first launch in 2003. Due to scanty information in five cases and to the presence of confounding factors such as patients' clinical condition or co-administration of drugs known to cause constipation in the other cases no elements to better characterize the risk of severe constipation emerged. Considering the scientific evidence accumulated, severe constipation was considered an **important identified risk** in the approved version 6 of the RMP for palonosetron.

Severe hypersensitivity reactions

Drug-induced hypersensitivity reactions are of major concern and present a burden for national healthcare systems due to their often-severe nature, high rate of hospital admissions and high mortality (Alfirevic A., Pirmohamed M. 2010).

A review article that focused on hypersensitivity reactions to chemotherapy concluded that at least 27% of patients given more than 7 cycles of carboplatin have hypersensitivity reactions to chemotherapy, and half of those are moderate to severe (Castells MC et al. 2008).

Sixty-nine women in Italy were treated with carboplatin for recurrent ovarian cancer, and 15 (21.7%) had hypersensitivity reactions overall. Of the 15 patients, 13 (86.7%) had reactions in the second treatment cycle (Gadducci A. et al. 2008). The reactions were severe respiratory or cardiovascular effects in 7 patients and various milder events (skin rash, flushing, itching, or abdominal pain) in 8 patients. One additional patient had chest pain without any indications of hypersensitivity, but then had a cardiac arrest and could not be resuscitated.

In an Italian study of ovarian cancer, 12 of 86 women (13.9%) treated with paclitaxel reacted with isolated facial flushing (3 patients), dyspnoea and chest tightness (4 patients), or bronchospasm (5 patients); none of these patients reacted to subsequent courses of paclitaxel (Cormio G. et al.1999). In another clinical trial in Italy, women aged 65 to 79 years and diagnosed with breast cancer were randomized to adjuvant treatment CMF (n=53) or docetaxel (n=48) (Nuzzo F. et al. 2008). In the CMF trial arm, 1.9% of patients had allergic reactions assessed as Grade 3 according to the National Cancer Institute Common Toxicity Criteria. In the docetaxel arm, Grade 3 allergic reactions occurred in 2.1% of patients and Grade 1 allergic reactions occurred in 4.2% (National Cancer Institute 2017).

In another US trial in treatment-naïve patients with advanced non–small cell lung cancer (NSCLC), 82 patients were randomized to vinorelbine-gemcitabine and 83 to carboplatin-paclitaxel (Lilenbaum RC et al. 2005). Two patients (2.4%) experienced mild hypersensitivity reactions to paclitaxel despite premedication.

In the UK, a non-randomized, dose-finding study recruited women with International Federation of Gynecology and Obstetrics (FIGO) stage Ic–IV epithelial ovarian cancer (Vasey PA et al. 2001). As first-line therapy, 139 women received carboplatin and docetaxel. Hypersensitivity reactions to docetaxel were observed in 11 patients (8%) and 4 reactions (3%) were classified as severe.

Severe hypersensitivity reactions, including anaphylaxis, anaphylactic/anaphylactoid reactions and shock have been reported to occur very rarely in the post-marketing usage with the intravenous formulation of palonosetron. One case of skin toxic acute reaction, highly suggestive of Steven-Johnson syndrome/TEN has been reported. No cases have been reported with the oral palonosetron.

Outcomes of severe hypersensitivity reaction may be fatal. Patients with known hypersensitivity to palonosetron or any excipients should avoid the palonosetron therapy. When considering 'very rare' frequency of hypersensitivity events associated with palonosetron IV formulation, the impact on individuals is considered low.

Drug hypersensitivity is responsible for significant mortality, morbidity, and socioeconomic costs. Considering the evidence collected so far for palonosetron, the clinical relevance of these severe forms, the population of cancer patients who are more vulnerable compared to healthy subjects and may have an impaired immune system as well the unpredictable circumstances leading to the occurrence of these events; this is considered an **important identified risk** in the approved version 6 of the RMP for palonosetron.

QT/QTC prolongation

QTc prolongation is an electrocardiographic finding; this abnormality can be brief and asymptomatic or may progress to *Torsade de pointes* (also known as polymorphic ventricular tachycardia), which carries a significant increase in risk of sudden cardiac death (Roger VL. et al. 2012). Estimates of the risk of mortality from *Torsade de pointes* that were specific to cancer patients treated with cytotoxic drugs was not identified in literature. Following out-of-hospital cardiac arrest, in-hospital death was reported for 72% of those who had *Torsade de pointes* and 80% of those who had QTc prolongation (Brady WJ. et al. 1999).

Cardiac toxicity in patients with cancer is a recognized risk of various antineoplastic agents and can manifest as heart failure, myocardial ischemia, arrhythmias, hypertension, or thromboembolism (Bovelli D. et al. 2010). Electrophysiological abnormalities associated with cytotoxic therapies may be transient but can also lead to sudden death related to arrhythmias such as *Torsade de pointes* and ventricular fibrillation (Kitagawa K. et al. 2012). Prolonged cardiac repolarization, which is observed as an increased QT interval on an ECG, or an increased corrected QT interval usually calculated using Bazett's or Fridericia's formulae, is associated with an increased risk of *Torsade de pointes* (Yap YG, Camm AJ. 2003). In the absence of past and constant monitoring, it is difficult to determine when QT prolongation was first present; therefore, published information on the incidence of QT or QTc prolongation among patients diagnosed with cancer is not available. In the following sections, we consider published studies providing the estimated prevalence of QT or QTc prolongation among patients diagnosed with cancer (or the average increase in QT or QTc after chemotherapy in this population), and subsequently we focus attention on the subgroup treated with 5 HT3 RAs.

5 HT3 RAs prevent nausea and vomiting by selectively blocking 5 HT3 receptor at the gastrointestinal vagal afferent nerve, the chemical receptor in the brain stem, and the solitary nucleus (Park PG. et al. 2012). Serotonin which is released as a response to administration of chemotherapeutic agents stimulates vagal afferents via 5 HT3 receptors to initiate the vomiting reflex and 5 HT3 RAs inhibit this process. However, the heart has also vagal innervation where may be a potential for cardiac effects of 5 HT3 RAs (Watanabe H. et al. 1995).

A total of 34 women treated for early breast cancer with combined adjuvant 5 fluorouracil (5 FU), epirubicin, and cyclophosphamide had ECGs recorded before and after each administration of the chemotherapy cycle.67 A trend of QTc interval prolongation was seen after each treatment. QTc interval was classified by the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) classification.60 Of the 34 patients, the worst grade of QTc interval prolongation after any chemotherapy cycle was grade 0 in 19 patients (56%), grade 1 (QTc interval, >0.45 to 0.47 second) in 10 patients (29%), and grade 2 (>0.47 to 0.50 second or ≥0.06 second above baseline) in 5 patients (15%). No patient had grade 3 prolongation (>0.50 second). Of the 34 women studied, 5.9% had supraventricular premature contractions in at least one treatment cycle.

In a study of 22 patients with gastrointestinal cancers (91% with colorectal cancer), 5 FU and high dose leucovorin were given, and ECGs were done before and 24 hours after the first cycle and before each subsequent cycle (Oztop I. et al. 2004). Significant increases in maximum QT interval per cycle

and in QT dispersion were recorded as early as 24 hours after administration of chemotherapy; these anomalies continued and were more pronounced in later cycles. For the 22 patients, the mean (standard deviation [SD]) maximum QT interval in milliseconds was 438.65 (22.91) at baseline, and steadily increased to 506.24 (31.05) by the 12th cycle. During this follow-up, echocardiography results showed no change in systolic or diastolic functions, and troponin was below the detectable level in all patients.

Doxorubicin was given up to a cumulative dose of 400 to 500 mg/m2 to 28 adults with NHL.70 The mean (SD) QTc interval increased from 402 (4) milliseconds to 416 (5) milliseconds during follow-up. Also, during doxorubicin therapy, 5 patients (18%) developed QT dispersion of more than 50 milliseconds, and 2 patients (7%) developed late potentials.

In another study of 644 patients with cancer, 477 had colorectal cancer and 22 had breast cancer. The colorectal and breast cancer patients were treated with regimens including 5 FU or oral capecitabine (Kosmas C. et al. 2008). Seventeen of the patients with colorectal cancer (3.8%) and 1 patient with breast cancer (4.5%) had any type of ECG abnormality at the time of 5 FU administration. In the entire study population, which also included 145 patients with head and neck cancer, 4.03% had symptoms and/or ECG abnormalities indicating cardiac toxicity. The patients with head and neck cancer also received regimens with 5 FU. Treatment with continuously infused regimens of 5 FU (with mitomycin, leucovorin, or cisplatin) was much more likely to be associated with ECG anomalies (prevalence of 4% to slightly more than 12%) than was treatment with short-infusion regimens (prevalence of approximately 2%).

A study of patients with cancer but without personal or family history of QT interval prolongation found that 47 (16%) had a prolonged QTc interval.72 The study patients were not considered to be in terminal stages of cancer even though they were receiving palliative care. Sudden, unexpected deaths occurred in 4% of the 47 study patients with, and in 5% of those without, prolonged QTc interval (Walker G. et al. 2003).

Preclinical studies indicated the potential to cause prolongation of the QT interval by palonosetron.

A search was run in Helsinn corporate safety database from year 2003 up to 24 July 2021, using the MedDRA SMQs Torsade de pointes/QT prolongation and Torsade de pointes/shock associated conditions (broad search). All post-marketing cases independently from seriousness and relationship have been considered for the analysis. All serious study cases, independently from relationship were considered as well.

Since its launch on the market in 2003, a very limited number of cases with clinically relevant cardiac events have been reported. Given the few spontaneous cases of QT prolongation (N= 6) collected, the Company concluded that no increased risks of QT interval prolongation in patients receiving palonosetron were found.

In conclusion, preclinical data, and clinical results provided sufficient evidence to consider QT prolongation an **important potential risk**, although the presence of confounding factors such as chemotherapy, pre-existing cardiac disease and comedications cannot be ignored

Convulsive events

The aetiology of convulsive events in cancer patients includes structural brain lesions (e.g., primary brain tumours, brain parenchymal or meningeal metastases, intracerebral haemorrhage, ischaemic cerebral injury, meningoencephalitis, and radiation necrosis) or systemic factors (e.g., hypoglycaemia, hyponatraemia, administration of certain anticancer medications, and toxic or metabolic encephalopathy). The exacerbation of a pre-existing seizure focus is also possible (e.g., patients with

brain metastases experiencing worsening of seizures in the setting of a systemic infection) (Grewal J. et al. 2008).

As a considerable proportion of seizures among adults with cancer arise due to primary brain tumours or intracranial metastases, cancer sites that would be expected to be commonly associated with seizures include brain, lung, breast, and skin (malignant melanoma). Although uncommon, brain metastases are also seen in colorectal cancer. Among patients diagnosed with brain tumours, seizures are recognized as a frequent presenting symptom, occurring in over 38% of those with primary brain neoplasms and 20% of those with cerebral metastases (Lynam LM et al. 2007).

A targeted search was performed on the risk of convulsive events associated with administration of chemotherapy treatments. The few published articles identified focused on the occurrence of seizures. Cytotoxic drug–induced seizures have been reported as a manifestation of drug toxicity following high-dose therapy with busulphan or chlorambucil as part of a myeloablative conditioning regimen prior to bone marrow transplantation or in the presence of renal or hepatic disorders. Neurological toxicity, including the occurrence of seizures, has been also reported in association with the administration of 5 FU, a widely used chemotherapeutic agent for the treatment of colorectal, breast, and head and neck cancers (Singh G. et al. 2007). Although rare, drug-induced encephalopathy and seizures have been documented in association with cisplatin, an agent widely used in the treatment of solid tumours (Steeghs N. et al. 2003). Neurological toxicity, including the occurrence of seizures, has been also reported in association with the administration of 5-FU for the treatment of colorectal, breast, and head and neck cancers (Singh G. et al. 2007).

In pre-clinical studies in mice, rats, and dogs, neurological clinical signs including palonosetron-related convulsive events occurred only at very high supra-therapeutic concentrations, which by far exceed the dose-equivalent in adult humans either for intravenous or oral administration of the drug.

Reports of seizures have been received in temporal association with palonosetron administration either from clinical trials or from post marketing surveillance. Overall, a total of 19 cases with convulsive events have been collected since palonosetron marketing authorization use from 2003. The presence of confounders and/or more likely alternative explanations (brain disorders, medical history, concomitant administration of neurotoxic drugs, pre-existing risk factors, underlying cancer disease) and the incomplete instrumental evaluation (EEG results not provided for many cases) made questionable the causality association of palonosetron with the occurrence of the events.

In conclusion, in a few collected cases, seizure has occurred after the injection of 5 HT3 RAs which were reported as suspected cause of the seizure (Park PG et al. 2012), (Singh NN et al. 2009), (Zambelli A. et al. 2009). The role of 5-HT_3 RAs, including palonosetron, is possible but questionable due to the presence of confounding factors in the very rare, collected events. Convulsive events may cause a severe and life-threatening condition in some patients. However, due to the very low number of cases cumulatively reported in the post-marketing setting this safety concern does not significantly alter the product positive benefit-risk balance. However, convulsive events potentially associated to palonosetron administration represent an **important potential risk** included in the approved version 6 of the RMP for palonosetron.

Serotonin syndrome

Serotonin syndrome (SS) is a potentially life-threatening drug reaction precipitated using serotonergic drugs; it may occur following single or combination therapeutic drug use or inadvertent interactions between drugs. There is an increased risk if antiemetics are administered in combination with other serotoninergic agents.

This identified 5 HT3 RAs class effect was recognised after the intensive monitoring performed by the FDA because of ondansetron overdose in 2011. The FDA performed both medical literature search and the search in FDA Adverse Event Reporting System (FAERS) database to evaluate the risk of developing a serotonin syndrome in association with the use of 5 HT3 RAs. The combined search results and recommendations were published by the FDA on February 2013 (FDA Office of Surveillance and Epidemiology 2013). The review indicated the potential for SS development after the administration of 5 HT3 RA drug class used alone or in the combination with other serotonergic drugs.

The PRAC, in view of available data considered that the potential for serotonin syndrome across the class of 5-HT_3 RAs exists and this represents a possible safety concern. The CHMP concurred with the scientific conclusions made by PRAC to consider this syndrome a labelled effect for the 5-HT_3 RAs as the systemic bioavailability of serotonin may be increased with the use of these antiemetics that may lead to the stimulation of other serotonin receptor subtypes by endogenous serotonin.

Serotonin syndrome is not an idiopathic drug reaction, but it is preventable and a predictable consequence of excess serotonergic activity at central nervous system and peripheral serotonin receptors (Boyer EW. Shannon M. 2005). Multiple serotonin receptors may be involved in producing the symptoms of the syndrome (Turkel SB et al. 2001). The excess serotonin activity produces a spectrum of specific symptoms including cognitive, autonomic, and somatic effects. The occurrence of SS has been considered a potential class effect of the anti-emetics belonging to the class of the 5-HT_3 RAs; therefore, the regulatory authorities recommended update of the labelling to inform about this risk.

Post-marketing cases have been notified following exposure to palonosetron concomitantly with other serotoninergic agents. Three spontaneous cases and one literature case of SS were cumulatively collected since palonosetron first launch in 2003. The 3 spontaneous cases were poorly documented, as several important information on patient's medical history, clinical features of the event and therapeutic measures taken was lacking. The case of literature is the first report of fentanyl- and meperidine-induced SS precipitated by palonosetron in general anesthesia. These cases did not provide useful information to better characterize, for palonosetron, this known class risk that may derive from the use of 5-HT_3 RAs alone or in association with other serotoninergic agents.

In conclusion, SS represents an **important potential risk** for palonosetron under continuous monitoring by the Company.

Potential for harm from overdose

As for any other medicinal drug, the potential for both intentional and accidental overdose exists. Palonosetron shows a wide safety margin, it is not a product with a narrow therapeutic margin (e.g., anticancer cytotoxic drugs).

The IV formulation is administered as a single dose prior to each cycle of chemotherapy under strict medical monitoring; therefore, the risk for overdose in the target population is unlikely to occur.

As for the oral formulation, blisters containing one or five soft capsules, respectively, are available on the market. It cannot be excluded that patients might self administer a dosage higher than the dose recommended; however, the risk of side effects is limited as doses up to 6 mg IV were given during the clinical development phase and no toxic dose response effects were observed with an incidence of adverse events comparable to the other low dose groups tested.

No sign of increased safety issues was observed with both formulations after multiple cycle administration in cancer patients. No cases of overdose have been reported during the clinical development phase of each formulation.

The potential risk for overdose associated to the palonosetron formulations should be very limited since the drug is subject to medical prescription and administered under close monitoring of healthcare professionals.

The incidence of adverse reactions (outcome indicators) can be considered one of the most relevant variables to evaluate the effectiveness of the risk minimization measures even though the proper assessment is often difficult due to the presence of confounding factors. So far, very few cases of overdose have been reported to occur with palonosetron in the post-marketing surveillance; this suggests that the measures in place are adequate to this purpose.

Potential for transmission of infectious agents

Palonosetron hydrochloride and its excipients are not of human or animal origin. There are no novel excipients in the IV and OS formulation and all excipients are tested and compliant with USP/NF and/or Ph.Eur. compendial analytical procedures. The route of administration of the medicinal product is important in determining the risk associated with transmission of an infectious agent, with the oral route generally being at lower risk than for injected medicinal products. Usually, the risk of transmitting an infectious agent by IV route is preventable using strict aseptic techniques. Palonosetron IV injection is a non-preserved unit-of-use aqueous based solution. The product is aseptically filled and terminally sterilized. The terminal sterilization cycle has been fully validated. Likewise, the processes used to sterilize the components have been validated.

In conclusion, palonosetron manufacturing processes are fully GMP compliant. Finished products are tested on every batch for microbial contamination in compliance with the European Pharmacopoeia (EP) and US Pharmacopeial Convention (USP) monographs. Therefore, there is no potential risk for transmission of infectious agents.

Potential for risks from medication error

No reports of medication error have been notified during the clinical development phase with either the IV or the oral formulation. Palonosetron is intended for use as a single IV or oral dose prior to each chemotherapy cycle. Even though the potential of any unintentional error in the prescribing, dispensing, or administration always exists, the risk is considered low and does not represent a safety concern of palonosetron due to the large safety margin of these medicinal products. Nonetheless, medication errors will be monitored as a part of the routine pharmacovigilance activities, i.e., review of individual case safety reports, signal detection activities and generation of periodic safety update reports.

Post-marketing experience will constitute an important source of information on the real-life use of the combination in clinical practice. Medication errors cause many adverse drug reactions with negative patient health outcomes; it is deemed essential the review of each single case to understand the cause(s), the presence or absence of contributing factors and analyze if these errors occur with the same pattern and frequency to evaluate the adoption and implementation of measures to mitigate and prevent such risk and its potential complications. Palonosetron post-marketing safety data has been reviewed to identify any cases notified so far. The Standardized MedDRA query "medication error" (broad) was used to detect and retrieve such cases in ARGUS database since the first launch of palonosetron on the US market up to 24 July 2021. A total of 71 cases were collected. In two cases, the PT overdose was reported, which is not anymore considered Medication Error in MedDRA dictionary version 23.0: these two cases were then excluded from analysis. Of the remaining 69 cases, inappropriate schedule of product administration was the most frequently reported PT, accounting for

25 cases. In most of them the administration of palonosetron for multiple consecutive days for CINV prevention was reported.

Medication error occurred in 8 cases, incorrect route of product administration in 7 cases (subcutaneous in 5 cases, intramuscular and intra-arterial in the remaining two cases), product administration error in 5 cases (erroneously administered in a child in one case, through a port with a not properly placed needle in another case, accidentally infused into a peritoneal port in the third case, administered paravenously in the fourth case and partially administered in the tissues in the fifth case), product administered to patient of inappropriate age/product use issue in 4 cases, (all concerning administration in pediatric patients in Countries where palonosetron is not indicated for pediatric use), incorrect dose/dosage administered in 4 cases (lower than prescribed in two cases, in two consecutive days in one case and at dosage of 0.075 mg for prevention of CINV instead of PONV in the last case; in one case of incorrect dose administered, drug dispensing error was also reported), accidental exposure to product in 3 cases, incorrect product administration duration and accidental overdose in 2 cases. Single cases were reported of product prescribing error, circumstance, or information capable of leading to medication error, expired product administered, extra dose administered, product preparation issue, product use in unapproved indication and wrong product administered.

No AEs were associated to medication error on 51 (including 6 pediatric cases) out of 69 cases. In most of the remaining 15 cases (including one pediatric case), AEs were reported but patients' clinical conditions or concomitant treatments represent an important contributing factor in their occurrence. Considering the overall exposure of more than 17 million patients treated worldwide with palonosetron since its first launch in 2003, the number of administration error cases is very limited.

In conclusion the potential for medication error is considered negligible; as in most of the cases no AEs were reported, medication errors do not seem to represent a safety concern.

Potential for off label use

The indication approved in the EU countries for palonosetron IV formulation is the prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults. This implies that the administration of the drug is intended only for this specific patient setting and the drug prescription is restricted to Healthcare Professionals who daily manage chemotherapy protocols including chemotherapeutic agents with high or moderate emetogenic potential. Moreover, the MAH submitted to EMA in June 2014 an application to claim the CINV indication for pediatric patients older than 1 month. The availability only upon prescription by a physician and the use limited to the hospital environment reduce the risk of a potential off-label use in children aged less than 1 month.

As for the indication of PONV prevention in adults, approval was granted in many countries including the US, Latin America, and Korea. In Europe, the indication of PONV prevention was not pursued for commercial reasons, so it is assumed that PONV might represent an off-label use of palonosetron IV in the EU. A paediatric efficacy claim for the PONV indication was not pursued, therefore the potential of an off-label use in the paediatric surgical setting in EU might occur. However, the risk of an off-label use in adults and children is unlikely to occur, because of the patient setting (surgical patient) that is different from cancer patients; in addition, the treating physician is usually a surgeon or an anaesthesiologist and palonosetron should be administered under the close supervision of health care professionals.

ASCO guidelines recommend as optimal treatment for CINV prophylaxis in patients receiving single day dose of low emetogenic potential chemotherapeutic agent a single dose of a 5-HT_3 RA or a single 8 mg

dose of dexamethasone (Hesketh PJ et al 2017). MASCC/ESMO guidelines for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting in advanced cancer patients includes recommendations also for chemotherapy with low or minimal emetogenic potential. For patients receiving low emetic risk agents, treatment with a 5-HT_3RA or dexamethasone (4 to 8 mg) is suggested for prophylaxis. For patients receiving chemotherapy agents with a minimal risk of causing emesis, antiemetic therapy should not be routinely administered to prevent either acute or delayed CINV. Prophylactic antiemetics (dexamethasone 4 to 8 mg, prochlorperazine, or metoclopramide) may be administered to patients who have had emesis with prior low-risk regimens, or on an "as needed" basis (Roila F et al. Ann Oncol. 2016).

Off-label use might occur if the drug is taken for a non-approved indication, i.e., to prevent radiotherapy-induced nausea and vomiting (RINV). Nausea and vomiting caused by radiation therapy are generally less severe, but equally clinically important than those caused by chemotherapy. Among the antiemetic drugs, the 5 HT3 RAs are the most effective and used agents either as prevention or treatment of RINV. The risk for this potential off-label use appears low, as literature data show that the overall incidence rates for nausea and vomiting following radiotherapy range between 7-39 %, with nausea being more frequent in patients receiving radiotherapy to the lower abdomen or pelvis and to the head and neck area. Albeit less probable, palonosetron use cannot be excluded considering the setting of patients to be treated. The above assumption is valid and applicable also to the oral formulation, although its use is currently very limited as oral palonosetron is available on the market only in few EU countries.

The potential for off-label use in RINV and PONV is very small because there are therapeutic alternatives that are approved for use in these indications.

A potential off-label use of the oral formulation could be related to prevention and/or treatment of the so called "hyperemesis gravidarum" a clinical condition associated with (severe) nausea and accompanied by severe vomiting that does not subside. This severe form of morning sickness cannot be prevented and tends to begin somewhat earlier in the pregnancy and last significantly longer. Similarly, to the IV formulation, the potential off-label use represents the treatment of CINV or PONV.

Palonosetron SmPC states that there are no clinical data on exposed pregnancies and no experience with human pregnancy. Information about the lack of findings in animals is provided in Section 5.3 of the current SmPC. As no data concerning palonosetron excretion in breast milk are available, breast-feeding women should discontinue its use. Should cases be reported to the Company that palonosetron has been administered to pregnant or breast-feeding woman, the case will be fully documented and logged into the safety database for active monitoring until childbirth (in cases of foetal in utero exposure) or for the appropriate time for breast-feeding exposure. Any pathological findings detected in the newborn or breast-fed child will be thoroughly analysed with the support of medical experts, and the need for strengthening the warning information within the palonosetron SmPC will be promptly addressed, together with the evaluation of possible additional actions to be carried out to inform the female patients through their general practitioners of the detected risks. Despite there may be more underreporting of cases of off label use than other post-marketing cases, current post-marketing data do not suggest significant off-label use.

Cumulatively, 41 cases including the PT "off label use" have been collected since the 1st launch of palonosetron on the US market up to 24 July 2021. In 17 cases the off-label use was related to pediatric use in absence of this product indication. In 7 cases palonosetron was administered as IV push instead of injected over 30 seconds; in 8 cases palonosetron was administered for treatment of nausea or vomiting, in 2 cases for treatment of vomiting during pregnancy, in one case after induction of anaesthesia, in one case for treatment of headache, in 5 cases for unapproved indication. AEs associated with off-label use were reported in 29 out of 41 cases. The reported AEs were expected for

palonosetron or may be explained considering contributing factors related to clinical conditions or concomitant treatments. The cases of off-label use represent sporadic and non-systematic episodes and do not seem to represent a safety concern.

Risks associated with pharmacokinetic and pharmacodynamics interactions

The potential interactions of palonosetron have been appropriately studied *in vitro*. At high concentrations, palonosetron was a competitive inhibitor of some cytochrome P450 isoforms (CYP2D6, 1A2 and 3A). Since *in vivo* concentrations of palonosetron were much lower, the inhibition potential of palonosetron has no clinical implications. *In vitro*, palonosetron was not shown to be an inducer of the activity of CYP2D6, CYP1A2, or CYP3A4/5. The results of clinical study PALO-99-39 in 3 extensive and 3 poor metabolisers of CYP2D6 demonstrated that palonosetron plasma concentrations and PK parameters were similar between the two categories analysed.

A post-authorisation commitment following the approval of the marketing authorisation for oral Akynzeo (netupitant-palonosetron) was a study to investigate the *in vitro* interaction of palonosetron with the human ABC (efflux) transporters and the human SLC (uptake) transporters. Results indicate that inhibition of MATE1, MATE2-K, OCT1, OCT2 and OAT3 transporters upon palonosetron administration can be excluded and *in vivo* studies with sensitive probe substrates are therefore not required. Palonosetron is not a substrate of BCRP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 transporters but palonosetron is a substrate for the efflux transporter MDR1/P-gp, which could favour the potential interaction of palonosetron with P-gp inhibitors at the renal level. However, palonosetron is characterized by high solubility, high permeability and is highly metabolized and this potential interaction is considered unlikely to be of clinical relevance. Considering the modest palonosetron increase of exposure foreseen (~20% of AUC) after co-administration with a strong P-gp inhibitor and the available palonosetron clinical safety data at the dose of 0.75 mg (three times the IV marketed dose), it is possible to exclude any clinically significant interaction when palonosetron is co-administered with Pgp inhibitors.

Missing information

Effects in children aged less than 1-month

The completion of the pediatric clinical program in CINV and PONV, after which the paediatric indication approval followed in the USA and EEA, showed that the safety profile of palonosetron in pediatric population is consistent with the established information collected during previous clinical experience in adults as well as from safety information collected from the post-marketing. Palonosetron has been approved in cancer pediatric patients aged 1 month and older hence the potential off-label use is limited in countries where the paediatric indication is not authorized and to patients aged less than 1 month. The risk of an off-label use in children is unlikely to occur, considering that palonosetron should be administered under the close supervision of health care professionals. Nevertheless, since no data on palonosetron effect in children aged less than 1 month are available at the time being, palonosetron safety in neonates has not been established yet.

Effects in patients with end-stage renal disease undergoing haemodialysis

The overall risk of cancer is increased in patients with end-stage renal disease (ESRD). A considerable number of these patients could benefit from antineoplastic treatment, but the management of chemotherapy in such population is particularly challenging. Several factors may have an impact,

including the tumor-related and the renal disease-related life expectancy, the impact of chemotherapy on the quality of life and patient characteristics such as age, performance status, frailty, and comorbidities. The lack of knowledge about cytotoxic drug management may lead to an improper use of chemotherapy and may expose patients to the risk of suboptimal treatment or to aggravation of chemotherapy toxicity. (Pedrazzoli P et al. 2017).

PK data received in healthy volunteers indicate that approximately 40% of palonosetron is eliminated unchanged in the urine, while 50% is metabolized. Renal insufficiency could be associated with a reduction in the total body clearance and prolongation of the elimination half-life of palonosetron. A study (PALO-99-35) was carried out to estimate the potential effects of chronic renal impairment on the PK of palonosetron and its primary metabolite M9. The study enrolled 25 subjects who were administered with 0.75 mg palonosetron as a single IV bolus. Nine subjects suffered from mild-to-moderate renal impairment (creatinine clearance [CLcr] 30–80 ml/min) and seven subjects suffered from severe renal impairment (CLcr 10–19 ml/min). Additional nine subjects were healthy volunteers serving as a control group. As a result, severe renal impairment appeared to be associated with an increase in the palonosetron terminal elimination half-life, probably due to a reduction in renal clearance. However, the total body clearance in these patients was found to be like healthy subjects.

The results of this study demonstrated that from a PK perspective, dosage adjustment is not necessary in patients with any degree of renal impairment. In fact, total body clearance in these patients is like healthy subjects. Due to the large volume of distribution and relatively equal contribution of hepatic metabolism and renal elimination of palonosetron, theoretically dialysis is not likely to affect the clearance of palonosetron. However, no data are available on patients with end stage renal disease undergoing haemodialysis, therefore, the implications or potential consequences of palonosetron administration cannot be predicted and the effects in these patients represent a missing information.

Effects on pregnancy and lactation

Pregnant or lactating females were not eligible because of study entry criteria during the clinical development program. Because preclinical results are not always predictive of the effects in humans, palonosetron is not recommended for use during pregnancy, unless its administration is considered essential by the physician as reported in the labelling (e.g. SmPC). It is expected that pregnant females with a diagnosis of breast cancer, or uterine cancer might undergo chemotherapy in the 2nd or 3rd trimester of gestation or beyond the 14th week when it is possible to delay the initiation of chemotherapy, since the risk of severe problems for the fetus appears to be low, pregnancy termination is not needed and there are little effects on the long-term outcome of the child. Palonosetron has not been administered to patients undergoing labour and delivery, so the potential effects on mother or child are unknown.

A total of 14 ICSRs reporting palonosetron administration to pregnant women were collected globally since the product launch in 2003. In all cases, pregnancy was uneventful for the mother. Concerning the newborns, seven babies were delivered at term and in good health condition; in one case labour was voluntarily induced at week 35 with natural delivery of a baby in good health conditions; in one case the newborn had respiratory disorders not related to palonosetron and in another case unlikely related to palonosetron "missed abortion" was reported. For four cases the outcome of pregnancy is missing/not yet received. No cases of administration of palonosetron during breast feeding have been collected. Since there are no data concerning palonosetron excretion in breast milk, breast-feeding should be discontinued during therapy.

At the time being no additional pharmacovigilance activities other than data collection in the Helsinn safety database and case monitoring until childbirth seem to be necessary. The current risk

minimization activities remain adequate. The effects on pregnancy and lactation represent a missing information.

Effects on fertility

Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats (studies AT 6700, AT 6270). However, in the female rat oral study (AT 6756) there was a small but statistically significant reduction in the number of females treated at 60 mg/kg/day that mated, with a consequent reduction in the number of pregnancies.

No evidence is available on the effect(s) of palonosetron on human fertility; furthermore, no clinical data are accessible from clinical studies since the use of reliable contraceptive methods was an inclusion criterion to be fulfilled. No cases reporting effects of palonosetron on fertility were collected.

The lack of safety data in humans precludes any evaluation on the potential impact of this concern, which therefore is considered a missing information.

Risks linked to the disposal of the used product

Not applicable; palonosetron must be disposed according to local requirements.

Risks linked to the administration procedure

Not applicable when administered as directed.

SVII.1 Identification of safety concerns in the initial RMP submission

Table 17 summarizes the safety concerns identified in the approved version (6) of the RMP for palonosetron.

Table 17 safety concerns identified in the RMP#6 for palonosetron.

Important identified risks	Severe constipation Severe hypersensitivity reactions
Important potential risks	QT/QTc interval prolongation Convulsive events Serotonin syndrome
Missing information	Effect in pregnancy and in lactating women Effects on fertility Effect in children aged less than 1 month (potential off-label use for CINV prevention) * Effects in patients with end stage renal disease undergoing haemodialysis

** The safety and efficacy of Aloxi oral formulation in children have not been established. Aloxi oral formulation is indicated in adults only*

SVII.1.1 Risk not considered important for inclusion in the safety specification

Medication errors and off-label use are known palonosetron risks that do not impact the risk-benefit profile of the drug. As discussed in previous Module SVII - Identified and potential risks, no medication errors were reported in in the clinical development program, therefore the real-life use in the post-marketing environment was helpful to identify few cases of medication errors. These post-marketing cases were analysed but no safety concern has been identified. However, the Company is performing an accurate analysis of each individual spontaneous report of medication error as well as any diligent effort to collect any information useful for a root cause analysis to assess if further actions are necessary to mitigate this risk. At present, potential risks from medications errors are not considered for inclusion among the safety specification. Similarly, few cases of off-label use were collected representing sporadic and non-systematic events. Thus, no safety concerns from off-label use of palonosetron have been identified and palonosetron potential risk from off-label use is not considered for inclusion among the safety specification.

SVII.2 New safety concerns and/or reclassification with a submission of an updated RMP

There have not been identified any new safety concerns associated with palonosetron. The list of safety concerns has been reviewed in line with the current guidance and definitions on important identified and potential risks and missing information. Reasons for the updates of the previous EU-RMP version 6, dated 23 July 2014, are provided in this section.

The risk of **severe constipation** previously classified as important identified risk is removed from the list of safety concerns for the reasons presented below:

- ✓ A total of 10 post-marketing ADRs related to severe constipation were cumulatively collected since palonosetron first launched in 2003 up to the data lock point (24 July 2021). Due to scanty information in five cases and to the presence of confounding factors such as patients'

clinical condition or co-administration of drugs known to cause constipation in the other cases no elements to better characterize the risk of severe constipation emerged.

- ✓ Severe constipation is included as special warning in the current version of the SmPC and constipation is tabulated as common undesirable effect in section 4.8 of the SmPC.

The risk of **severe hypersensitivity reactions**, including anaphylaxis, anaphylactic, anaphylactoid reactions and shock previously classified as important identified risk is removed from the list of safety concerns for the reasons presented below:

- ✓ A total of 38 post-marketing ADRs related to severe hypersensitivity reactions (i.e. anaphylactic reaction, anaphylactoid reaction and anaphylactic shock) in which causality for palonosetron was not excluded have been collected since palonosetron first launched in the US market in 2003 up to the data lock point (24 July 2021).
- ✓ Hypersensitivity to the active substance or to any of the excipients are reported as a contraindication in the SmPC, and precaution in patients with known hypersensitivity to peanut or soya are also reported in the relevant section of the SmPC. In section 4.8 of the SmPC it is reported that very rare post marketing cases (<1/10,000) of hypersensitivity reactions occurred with palonosetron solution for injection for intravenous use.
- ✓ Neither additional pharmacovigilance activities nor additional risk minimization measures have been considered necessary by the competent authorities or the company to further characterize or mitigate this safety concern.

The risk of **convulsive events** classified as important potential risk is removed from the list of safety concerns for the reasons presented below:

- ✓ Post-marketing ADRs up to the data lock point (24 July 2021) cumulatively include 19 cases with convulsive events collected since palonosetron marketing authorization use from year 2003. The presence of confounding elements (concomitant administration of neurotoxic drugs, pre-existing risk factors, underlying cancer disease) and the incomplete instrumental evaluation (EEG results not provided for many cases) made questionable the causality association of palonosetron with the occurrence of the events. The possibility that palonosetron can have a role in the onset of seizures during its use is negligible.
- ✓ Preclinical data show that some effects with high dose of palonosetron IV have been reported in the central nervous system with convulsions seen after repeated treatment. This effect is not of concern given that convulsions were never observed in the clinical studies with palonosetron IV or oral formulation.
- ✓ No further evaluation is required for this safety concern as part of the pharmacovigilance plan.

Effects on **pregnancy and lactation** previously classified as missing information is removed from the list of safety concerns for the reasons presented below:

- ✓ The EU SmPC in section 4.6 provides recommendations to not use palonosetron in pregnant women unless it is considered essential by the physician.
- ✓ No clinical data are available for palonosetron on exposed pregnancies. However, in the collected ICSRs reporting palonosetron administration to pregnant women there is no evidence of birth defects.

- ✓ It is recommended that palonosetron should not be used during breast-feeding. As there are no data concerning palonosetron excretion in breast milk, breast-feeding should be discontinued during therapy, as reported in the EU SmPC in section 4.6.
- ✓ The safety concern does not represent a gap in knowledge for the anticipated utilisation in this population.

Signal of birth defects following in-utero exposure to ondansetron and other 5HT3 RAs

The PRAC recommendations on signals adopted at the 8-11 July 2019 PRAC meeting (EMA/PRAC/347675/2019 dated 05 August 2019) reported a signal for ondansetron of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications (Huybrechts KF et al, JAMA 2018; 320(23): 2429-37; Zambelli-Weiner A. et al, Reprod Toxicol 2019; 83:14-20). The assessment of this signal was recommended to MAHs of other 5HT3 RAs, including palonosetron and was performed by Helsinn in the context of Akynzeo (netupitant /palonosetron) PSUR #10 (reference period 11/10/2018 - 10/10/2019), procedure no.: EMEA/H/C/PSUSA/00010393/201910. No literature data on birth defects in association with use of palonosetron during pregnancy have been so far identified and no post-marketing cases of birth defects following in-utero exposure to palonosetron have been collected. Up to Data lock point of this RMP (24 July 2021) a total of 14 ICSRs reporting palonosetron administration to pregnant women were collected globally since the product launch on the US market in 2003. In all cases, pregnancy was uneventful for the mother excluding one case accompained by mild nausea. Concerning the newborns, seven babies were delivered at term and in good health condition; in one case labor was voluntarily induced at week 35 with natural delivery of a baby in good health conditions; in one case the newborn had respiratory disorder considered by the reporter not related to palonosetron and in another case unlikely related to palonosetron "missed abortion" was reported without further details. For four cases the outcome of pregnancy is missing/not yet received. In conclusion, based on currently available information no evidence exists for the signal of birth defects following in-utero exposure to palonosetron.

Effects on **fertility** previously classified as missing information is removed from the list of safety concerns for the reasons presented below:

- ✓ Pre-clinical data, i.e., reproductive studies in animals with palonosetron, do not indicate direct or indirect harmful effects with respect to fertility. Palonosetron was found to have no effect on fertility and reproductive performance of male and female rats. Although oral treatment of rats (one-month repeat-dose toxicity study) was associated with degeneration of the seminiferous epithelium, this was not observed in intravenous fertility studies, leading to the conclusion that this toxic effect might be due to a metabolite.
- ✓ The medicinal product is intended for single application in humans and chemotherapy cycles are usually administered with a 14–21-day interval, therefore such data are of scarce clinical relevance.
- ✓ The long-lasting presence of palonosetron on the market is not indicative of any safety concern in this regard. No cases reporting effects of palonosetron on fertility have been collected.

Effects in patients with **end-stage renal disease undergoing hemodialysis** previously classified as missing information is removed from the list of safety concerns for the reasons presented below:

- ✓ The EU SmPC in section 4.2 - posology and method of administration specifies that no data are available for patients with end stage renal disease undergoing haemodialysis

and in section 5.2 - pharmacokinetics in special populations reports that severe renal impairment reduces renal clearance, however total body clearance in these patients is like healthy subjects and concludes that no dosage adjustment is necessary in patients with renal insufficiency.

- ✓ As reported in the last palonosetron PSUR 26 under section *Effects in patients with end stage renal disease undergoing hemodialysis*, no information was received on this special population in the reporting period, either from post-marketing, clinical trials, or scientific literature.
- ✓ The safety concern does not represent a gap in knowledge for the anticipated utilisation in this population.

The important potential risk of QT/QTc prolongation is to be re-classified as **Torsade de pointes due to QT/QTC prolongation**. The rationale supporting the proposed change of reclassification as Torsade de pointes and removal of QT/QTc prolongation are based on the considerations below summarized concisely:

Reclassification as Torsade de pointes

- ✓ The risk in this case is the clinical outcome of the adverse reaction. Prolonged QT interval can predispose a patient to develop *Torsade de Pointes* which is a life-threatening arrhythmia that can degenerate to ventricular fibrillation and cause patient's sudden cardiac death.
- ✓ There is no threshold of QTc prolongation at which Torsade de Pointes is certain to occur. A QTc greater than 500 milliseconds (ms) has been associated with a twofold to threefold higher risk for Torsade de Pointes, and each 10-ms increase contributes to approximately a 5% to 7% exponential increase in risk. (Li M et al. 2017).

Removal of QT/QTc prolongation

- ✓ Non-clinical and clinical data suggests that palonosetron is lacking any effect on QTc interval or a proarrhythmic potential.
- ✓ 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.
- ✓ Very few spontaneous cases of QT prolongation (N= 6) were collected since year 2003, with no increased risks of QT interval prolongation in patients receiving palonosetron.
- ✓ Two other 5-HT_3 RAs (ondansetron and dolasetron) have been associated with a proarrhythmic effect on QT interval; therefore, QTc prolongation represents a known adverse reaction of the 5-HT_3 RAs to which palonosetron belongs to.
- ✓ Warning and precaution concerning the potential issue of QT prolongation is reported in the EU SmPC of palonosetron, for patients who have or are likely to develop prolongation of the QT interval or for patients taking medicinal products that increase the QT interval.

In conclusion, it would be prudent to consider Torsade de pointes due to QT/QTc prolongation an important potential risk. The SMQ (broad) Torsade de pointes/QT prolongation will be applied to identify such risk.

SVII.3 Details of important identified potential risks and missing information

SVII.3.1. Presentation of important identified and important potential risks

Important identified risks

The two important identified risks of "Severe constipation" and "Severe hypersensitivity" previously reported in the RMP Version 6, dated 23 July 2014 are removed from the list of safety concerns.

Important potential risks

The important potential risk of "QT/QTc prolongation" is to be re-classified as "Torsade de pointes due to QT/QTC prolongation" (Table 18), while "Convulsive events", previously reported in the RMP Version 6, dated 23 July 2014, is removed from the list of safety concerns. "Serotonin Syndrome" (Table 19) is confirmed an important potential risk.

Table 18 Important potential risk - Torsade de pointes due to QT/QTc prolongation

Torsade de pointes due to QT/QTc prolongation	
Potential mechanisms	The exact mechanism is unknown. 5-HT_3 RAs prevent nausea and vomiting by selectively blocking 5-HT_3 receptor at the gastrointestinal vagal afferent nerve, the chemical receptor in the brain stem, and the solitary nucleus (Park PG et al. 2012). Serotonin which is released as a response to administration of chemotherapeutic agents stimulates vagal afferents via 5-HT_3 receptors to initiate the vomiting reflex and 5-HT_3 RAs inhibit this process. However, the heart has also vagal innervation where may be a potential for cardiac effects of 5-HT_3 RAs (Watanabe H. et al. 1995). Preclinical studies indicated the potential to cause prolongation of the QT interval by palonosetron. However, in clinical studies, palonosetron did not induce clinically relevant prolongation of the QT/QTc interval.
Evidence source and strength of evidence	ICSRs, pivotal clinical trials in CINV and PONV prevention. Clinical studies have not showed relevant effects on the prolongation of the QT/QTc interval. Nevertheless, since cancer patients are a vulnerable population receiving potentially cardiotoxic antineoplastic agents, or with medical history remarkable for cardiac disease on treatment with antiarrhythmics, or may carry electrolytes imbalance, it is prudent to consider *Torsade de pointes* due to QT/QTc prolongation an important potential risk.
Characterisation of the risk	QT/QTc prolongation is an electrocardiographic abnormality. This abnormality can be transient and asymptomatic or may progress to ventricular fibrillation and the most severe form of *Torsade de pointes* (also known as polymorphic ventricular tachycardia), which carries a significant increase in risk of sudden cardiac death. Cancer patients may show electrophysiological abnormalities associated with cytotoxic therapies that may be transient but can also lead to sudden death related to arrhythmias such as *Torsade de pointes* and ventricular fibrillation. Cardiac toxicity in patients with cancer is a recognized risk of various antineoplastic agents and can manifest as heart failure, myocardial ischemia, arrhythmias, hypertension, or thromboembolism (Bovelli D. et al. 2010). Cancer patients may show electrophysiological abnormalities associated with cytotoxic therapies that may be transient but can also lead to sudden death related to arrhythmias such as *Torsade de pointes* and ventricular fibrillation (Kitagawa K. et al. 2012). Prolonged cardiac repolarization, which is observed as an increased QT interval on an ECG, or an increased corrected QT interval usually calculated using Bazett's or Fridericia's formulae, is associated with an increased risk of *Torsade de pointes* (Yap YG, Camm AJ. 2003). In the absence of past and constant monitoring, it is difficult to determine when QT prolongation was first present; therefore, published information on the incidence of QT

Torsade de pointes due to QT/QTc prolongation	
	or QTc prolongation among patients diagnosed with cancer is not available. A total of 34 women treated for early breast cancer with combined adjuvant 5 fluorouracil (5 FU), epirubicin, and cyclophosphamide had ECGs recorded before and after each administration of the chemotherapy cycle (Kitagawa K. et al. 2012). Of the 34 patients, the worst grade of QTc interval prolongation after any chemotherapy cycle was Grade 0 in 19 patients (56%), Grade 1 (QTc interval, >0.45 to 0.47 second) in 10 patients (29%), and Grade 2 (>0.47 to 0.50 second or ⩾0.06 second above baseline) in 5 patients (15%). No patient had Grade 3 prolongation (>0.50 second). Of the 34 women studied, 5.9% had supraventricular premature contractions in at least one treatment cycle. In a study of 22 patients with gastrointestinal cancers (91% with colorectal cancer), 5 FU and high dose leucovorin were given, and ECGs were done before and 24 hours after the first cycle and before each subsequent cycle. Significant increases in maximum QT interval per cycle and in QT dispersion were recorded as early as 24 hours after administration of chemotherapy; these anomalies continued and were more pronounced in later cycles. For the 22 patients, the mean (standard deviation [SD]) maximum QT interval in milliseconds was 438.65 (22.91) at baseline, and steadily increased to 506.24 (31.05) by the 12th cycle (Oztop I. et al. 2004). During this follow-up, echocardiography results showed no change in systolic or diastolic functions, and troponin was below the detectable level in all patients. In a study of 644 patients with cancer, 477 had colorectal cancer and 22 had breast cancer. The colorectal and breast cancer patients were treated with regimens including 5 FU or oral capecitabine (Kosmas C. et al. 2008). Seventeen of the patients with colorectal cancer (3.8%) and 1 patient with breast cancer (4.5%) had any type of ECG abnormality at the time of 5 FU administration. In the entire study population, which also included 145 patients with head and neck cancer, 4.03% had symptoms and/or ECG abnormalities indicating cardiac toxicity. The patients with head and neck cancer also received regimens with 5 FU. Treatment with continuously infused regimens of 5 FU (with mitomycin, leucovorin, or cisplatin) was much more likely to be associated with ECG anomalies (prevalence of 4% to slightly more than 12%) than was treatment with short-infusion regimens (prevalence of approximately 2%). A study of patients with cancer but without personal or family history of QT interval prolongation found that 47 (16%) had a prolonged QTc interval. The study patients were not considered to be in terminal stages of cancer even though they were receiving palliative care. Sudden, unexpected deaths occurred in 4% of the 47 study patients with, and in 5% of those without, prolonged QTc interval (Walker G. et al. 2003). Clinical data demonstrate that ECG interval changes are a class effect of the 5-HT_3 RAs. Theoretical concern regarding cardiovascular adverse events with these agents is not supported by clinical experience (Navari RM, Koeller JM 2003). The estimated prevalence of QT or QTc prolongation among patients diagnosed with cancer (or the average increase in QT or QTc after chemotherapy in this population) and treated with 5 HT3 RAs needs to consider the confounding effect of several risk factors including electrolyte imbalance, comorbidities and comedication in addition to chemotherapy. Regular ECG monitoring in cancer patients in clinical trials provides further evidence on the satisfactory cardiac safety of palonosetron, excluding an adverse electrophysiological pharmacological effect on cardiac repolarization due to the anti-emetic treatment. This result denotes a satisfactory cardiac safety profile for IV and oral palonosetron. In the Cardiac Disorders and Investigations SOCs at the data lock point of the last submitted palonosetron PSUR there are no adverse reactions denoting this type of abnormalities or more serious events. Given the few spontaneous cases of QT prolongation (N= 6) collected from year 2003 up to 24 July 2021, there is not an increased risks of QT interval prolongation in patients receiving palonosetron.

Torsade de pointes due to QT/QTc prolongation	
Risk factors and risk groups	Risk factors include drug interaction with concomitant medication such as anthracyclines, cyclophosphamide or antiarrythmic drugs, pre-existing cardiac disease (e.g. cardiac ischaemia, cardiomyopathies, congenital long QT syndrome, rhythm disturbances), hypertension, atherosclerosis, malnutrition or electrolytes abnormalities (including that caused by diuretics and dehydration), or treatment with drugs known to prolong QT interval, hypothyroidism, hypoglycaemia and a wide range of chemotherapy agents. Female sex and older age are also associated with longer QT intervals.
Preventability	Patients at risk to develop QT prolongation, are those concomitantly taking drugs known to increase QT interval, pre-existing cardiac disease or with long QT syndrome. These patients should be monitored closely for any signs of QT/QTc interval prolongation or any other cardiovascular effects of palonosetron. The risk of QT prolongation must be carefully evaluated considering treatment-related toxicities and pharmacologic characteristics of concomitant drugs prolonging QT (e.g., antiemetics, antibiotics, antifungals, antipsychotics).
Impact on the benefit-risk balance of the product	A very limited number of cases with clinically relevant cardiac events have been reported since palonosetron launch on the market in 2003. Considering the clinical trials and the post-marketing experience with palonosetron, and the satisfactory cardiac safety profile emerged from the review of the clinical data, the expected impact of this potential risk is considered very limited. The benefit-risk profile is not affected by this concern.
Public health impact	Fatal cases associated to the use of some 5-HT_3 RAs resulted in the Marketing Authorisation withdrawal or restrictions in use (e.g., dolasetron, ondansetron) but not for palonosetron (FDA drug safety communication 2010 and 2012). Considering that antiemetics are given once prior to each chemotherapy cycle, usually administered with an interval of 14-21 days, it is estimated that the occurrence of such event will be sporadic. However, serious adverse drug reactions related to complications of QT/QTC prolongation following palonosetron exposure will be analyzed to assess the overall impact on public health.

Table 19 Important potential risk - Serotonin syndrome

Serotonin syndrome	
Potential mechanisms	Serotonin syndrome (SS) is not an idiopathic drug reaction; it is a predictable consequence of excess serotonergic activity at central nervous system (CNS) and peripheral serotonin receptors. Serotonin syndrome is the result of overstimulation of 5-HT_{1A} receptors by selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamino oxidase inhibitors and other serotonergic agents. Multiple serotonin receptors may be involved in producing the symptoms of the syndrome (Turkel SB et al. 2001). The serotonin syndrome implies both central and peripheral serotonin dysfunction: blocking one type of serotonin receptor and functionally increasing systemic and CNS levels of serotonin simultaneously, hence presenting excessive serotonin to other receptors. Overall, these factors might increase the risk for serotonin syndrome.
Evidence source and strength of evidence	The occurrence of SS has been considered as a potential class effect of the anti-emetics belonging to the class of the 5-HT_3 RAs. SS is a potentially life-threatening drug reaction that may occur following therapeutic drug use. The excess serotonin activity produces a spectrum of specific symptoms including cognitive, autonomic, and somatic effects, which can be of variable intensity.
Characterisation of the risk	A retrospective analysis of SS registered in the French pharmacovigilance database between 1985 and 2013 was published (Abadie D et al. 2015). Most of the 125 (84.0%) analyzed cases were associated with a recent change in a serotonergic drug (introduction, increasing the dose or overdose). Antidepressants were the most often involved serotonergic drugs, mostly serotonin reuptake inhibitors (SRIs, 42.1%) and to a lesser extent serotonin-noradrenalin reuptake inhibitor (9.1%, mainly

Serotonin syndrome	
	venlafaxine), tricyclic antidepressants (8.6%, mainly clomipramine), and some monoamine oxidase inhibitors (6.2%, mainly moclobemide). Non-psychotropic medications were also involved, generally opioids (14.8%, mainly tramadol). Most of the cases (59.2%) resulted from pharmacodynamic DDIs, most often involving SRIs + opioids (mostly paroxetine + tramadol). However, SS also occurred with a single serotonergic drug in a significant number of cases (40.8%), most often SRIs (mainly fluoxetine) or venlafaxine at usual doses. Lastly, a major pharmacokinetic DDI could have played a role in 1/5 (20.8%) of cases. Milder forms of SS may resolve within a day, the most severe forms may be potentially life-threatening if not immediately recognized and treated. Medical evaluation is crucial to determine the presence of other factors, as co-medications triggering the reaction.
Risk factors and risk groups	Patients on treatment with antidepressant, or with triptanes for migraine or cluster headaches. Patients on therapy with antiparkinson agents, or antidepressants for fibromyalgia or chronic fatigue. Use of illicit drugs (ecstasy, LSD), or herbal and nutritional supplements (St. John's wort, panag ginseng) may increase the risk. Susceptibility to SS may be also conferred by patient's factors, such as the capacity to metabolize certain drugs.
Preventability	Patients after initiating or increasing the dose of a serotonergic agent should be closely monitored. Patients should tell their doctor if they are taking any medicines that can increase the amount of serotonin in the blood, such as medicines used to treat depression and/or anxiety.
Impact on the benefit-risk balance of the product	Further characterization of this potential risk is necessary to evaluate the impact on palonosetron benefit-risk ratio.
Public health impact	The use of multiple drugs is expanding; thus, the SS incidence is probably increasing. So far, it is not possible to estimate the potential public health impact, without further characterization of the relevance of this risk to the palonosetron administration.

SVII.3.2. Presentation of the Missing Information

The missing information of *Effect in pregnancy and in lactating women*, *Effects on fertility* and *Effect in patients with end stage renal disease undergoing haemodialysis* previously reported in the RMP Version 6, dated 23 July 2014 are removed from the list of safety concerns.

Table 20 summarizes the **Effect in children aged less than 1 month** (potential off-label use for CINV prevention) in patients treated with Aloxi IV.

The safety and efficacy of Aloxi oral formulation in children have not been established and its use is indicated for adults only.

Table 20 Missing Information - Effect in children aged less than 1 month

Effects in children aged less than 1 month	
Anticipated risk/consequence of the missing information	Twelve thousand out of 1.2 million new cases of invasive cancers diagnosed annually in the United States involve children. The heterogeneity of pediatric cancer is substantial and even the most common pediatric cancer (i.e., acute lymphoblastic leukemia) is characterized by biological and clinical diversity (Kupfer GM 2013). Nausea and vomiting remain significant problems among paediatric cancer patients. They may have serious consequences for patients' quality of life and their general physical and mental conditions, which can lead to poor adherence with the cancer treatment. The frequency of nausea and vomiting in children is related to the emetogenic risk of the chemotherapeutic agent or combination of drugs being administered. According to the MASCC guidelines all pediatric patients administered moderately or highly emetogenic chemotherapy should receive antiemetic prophylaxis with a combination of a 5-HT_3 RA and dexamethasone (MASCC/ESMO ANTIEMETIC GUIDELINES 2019). Even if the mechanism of neurotransmission is a physiological process that is not expected to vary with ages, in children a distinction between acute and delayed emesis is difficult, due to the chemotherapy regimens frequently administered over several days (Holdsworth MT et al. 2006). Young children undergoing chemotherapy are at greater risk of presenting dehydration and electrolyte imbalance due to emesis, increasing the risk of acute renal failure as an additional complication (Sepulveda-Vildosola et al., 2008) (Dewan et al., 2010). Considering that the proportion of paediatric patients experiencing CINV accounts for approximately 70% in paediatric patients (King CR 1997; Jordan K. 2010), conservatively, one can thus consider that every year approximately 50,000 paediatric patients experience at least one form of CINV in the European Community (considering the current EU population of approximately 500 million, Eurostat 2016). There are important pharmacokinetic differences between children and adults including but not limited to drug metabolism, transporter expression, biliary function, and renal clearance, which result in differences in drug disposition and elimination. The largest deviation from adult pharmacokinetics is observed in the first 12 to 18 months, when organ functions are developing. In older children and adolescents, the pharmacokinetic parameters approach adult values and are thus easier to predict. After the completion of the pediatric clinical program in CINV and PONV, palonosetron has been approved in cancer pediatric patients aged 1 month and older. Palonosetron should be used only before chemotherapy administration and should be administered by a healthcare professional under appropriate medical supervision. Hence the potential off-label use in patients aged less than 1 month is limited. Palonosetron safety in neonates has not been established yet.

Part II: Module SVIII - Summary of the safety concerns

A summary of the safety concerns revised as discussed in previous Module SVII – section SVII.3.1 Details of important identified and potential risks of Part II is provided in Table 21.

Table 21 Summary of safety concerns

Important Identified Risks	None
Important Potential Risks	Torsade de pointes due to QT/QTC prolongation Serotonin Syndrome
Missing information	Effect in children aged less than 1 month (potential off-label use for CINV prevention) *

** The safety and efficacy of Aloxi oral formulation in children have not been established. Aloxi oral formulation is indicated in adults only*

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

Information in this section contains details of pharmacovigilance activities and studies intended to identify and further characterise safety concerns described in previous sections.

III.1 Routine pharmacovigilance activities

At present, taking into consideration the information provided on safety concerns for palonosetron in previous sections, routine pharmacovigilance activities are considered adequate to monitor the safety concerns for both the IV and the oral formulations. Further activities to enhance the current pharmacovigilance practices refer to process improvements in single case and aggregated data processes.

Torsade de pointes due to QT/QTC prolongation represent and serotonin syndrome a potential safety concern requiring special attention and careful monitoring. As part of the routine pharmacovigilance activities, specific adverse reaction follow-up questionnaires for the two safety concerns have been generated to obtain structured information on reported suspected adverse reactions.

Focused follow-up questionnaire of QT/QTc interval prolongation cardiac ADRs

Serious cardiac complication of QT/QTc interval prolongation such as *Torsade de pointes* that can lead to ventricular arrhythmias, cardiac arrest, syncope, sudden death, and sudden cardiac death, represents a potential safety concern requiring special attention and careful monitoring.

A data collection checklist specifying which information needs to be collected to facilitate the prompt collection of complete or of missing additional pertinent information from the reporting sources of the cases of QT/QTc prolongation has been generated.

Helsinn Drug Safety routinely performs an intensive monitoring of cardiac events related to QT/QTc interval prolongation thanks to a thorough medical assessment on the initial information received and active request for follow-up information, irrespective of the case eligibility for expedited reporting.

Questions to be addressed to the reporter include the request for complete information on the presence of risk factors known to play a role in triggering the event, on therapies taken by the patient (suspect and concomitant drugs), on previous medical history and present medical condition

(signs/symptoms), on concomitant diseases. Availability of instrumental tests results and any documentation that may contribute to better elucidate the event onset is also verified for a comprehensive assessment of the event. Active follow-up is carried out by means of the follow-up questionnaire above described that is utilized on a regular basis by pharmacovigilance personnel involved in case processing as a checklist against which to verify both completeness and pertinence of the initial medical information received with a clinically significant adverse drug reaction report involving the cardiovascular system.

Focused follow-up questionnaire of serotonin syndrome ADRs

Serotonin syndrome is a potentially life-threatening drug reaction that may occur following therapeutic drug use or inadvertent interactions between drugs.

Serotonin syndrome represents a potential safety concern requiring special attention and careful monitoring. A data collection questionnaire in the form of a checklist has been generated to facilitate the timely collection of complete or of missing additional relevant information from the reporting sources of the cases. For a correct assessment of the case a list of questions should be addressed to the reporter. Such a tool will be useful in establishing current capacity for safety monitoring of the adverse reaction and will facilitate the evaluation procedures of any potential case of serotonin syndrome by the pharmacovigilance personnel at Helsinn Drug Safety department.

The forms are provided in Annex 4 of the RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are deemed necessary. The routine pharmacovigilance activities are considered sufficient to address all safety concerns with the aim to get and analyse relevant safety data from post-marketing experience to fully assess the safety of the product.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product, the oral fixed dose combination. No new important risks have been identified for the submitted product, i.e., the IV and oral formulation.

V.1. Routine Risk Minimisation Measures

The description of routine risk minimisation measures by safety concern (i.e., Torsade de pointes due to QT/QTc prolongation, Serotonin syndrome, Effect in children aged less than 1 month) is reported in Table 22 below.

Table 22 Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Torsade de pointes due to QT/QTc prolongation	✓ Routine risk communication: SmPC sections 4.4 and 4.8, PL sections 2 and 4. ✓ Routine risk minimisation activities recommending specific clinical measures to address the risk: advice is given for monitoring of patients with conditions leading to QT prolongation in SmPC section 4.4 and inform patients on the importance of this medical condition in PL section 2 and of possible undesirable effects in PL section 4. ✓ Other routine risk minimisation measures beyond the Product Information: none ✓ Legal status: prescription only medicine
Serotonin syndrome (SS)	✓ Routine risk communication: none. ✓ Routine risk minimisation activities recommending specific clinical measures to address the risk: specific information on the serotonin syndrome when palonosetron is administered with other serotoninergic agents is included in SmPC sections 4.4 and 4.5. Specific information on the SS when palonosetron is administered with other serotoninergic agents and how to make aware patients of the importance of informing healthcare professionals of the use of other medicinal products in PL section 2. ✓ Other routine risk minimisation measures beyond the Product Information: none ✓ Legal status: Prescription only medicine
Effect in children aged less than 1 month *	Routine risk communication: none. Routine risk minimisation activities recommending specific clinical measures to address the risk: the lack of safety and efficacy data in children below 1 month is included in SmPC sections 4.2 and 5.1 in both CINV and PONV settings. Advice is given to female patients concerning fertility and pregnancy in SmPC Section 4.6. Advice to not use the product in children below 1 month is included in PL sections 1, 3 and 4. Other routine risk minimisation measures beyond the Product Information: none Legal status: Prescription only medicine

** The safety and efficacy of Aloxi oral formulation in children have not been established. Aloxi oral formulation is indicated in adults only*

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Rationale for proposing to remove additional risk minimisation measures

Not applicable.

V.3 Summary of risk minimisation measures

Table 23 summarizes the pharmacovigilance activities and risk minimisation activities by safety concern.

Table 23 Summary table of pharmacovigilance and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Torsade de pointes due to QT/QTc prolongation	Routine risk minimisation measures: SmPC Section 4.4 where advice is given for monitoring of patients with conditions leading to QT prolongation; PL section 2 informing patients on the importance of this medical condition and PL section 4 risks of possible undesirable effects. Additional risk minimisation measures: no additional risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up questionnaire form for adverse reaction
Serotonin syndrome	Routine risk minimisation measures: SmPC sections 4.4 and 4.5 where advice is given on the serotonin syndrome when palonosetron is administered with other serotoninergic agents; PL section 2 makeing aware patients of the importance of informing HCP of other medicinal products use. Additional risk minimisation measures: no additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up questionnaire form for adverse reaction
Effect in children aged less than 1 month*	Routine risk minimisation measures: SmPC sections 4.2, 4.6 and 5.1 and PL sections 1, 3 and 4 where advice to not use the product in children below 1 month due to lack of safety and efficacy data is reported. Additional risk minimisation measures: no additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none

** The safety and efficacy of Aloxi oral formulation in children have not been established. Aloxi oral formulation is indicated in adults only*

Part VI: Summary of the risk management plan

A separate RMP Part VI is provided for each product in the RMP. The first summary refers to Aloxi 250 micrograms solution for injection and the second summary to Aloxi 500 micrograms soft capsules.

Summary of risk management plan for Aloxi 250 micrograms solution for injection

This is a summary of the risk management plan (RMP) for **Aloxi 250 micrograms solution for injection**. The RMP details important risks of Aloxi 250 micrograms solution for injection, how these risks can be minimised, and how more information will be obtained about Aloxi 250 micrograms solution for injection risks and uncertainties (missing information).

Aloxi 250 micrograms solution for injection summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Aloxi 250 micrograms solution for injection should be used. This summary of the RMP for Aloxi 250 micrograms solution for injection should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in updates of Aloxi 250 micrograms solution for injection RMP.

I. The medicine and what it is used for

Aloxi 250 micrograms solution for injection is indicated in adults for the:

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

Aloxi 250 micrograms solution for injection is indicated in paediatric patients 1 month of age and older for the:

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

Further information about the evaluation of Aloxi 250 micrograms solution for injection benefits can be found in Aloxi 250 micrograms solution for injection EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Aloxi 250 micrograms solution for injection, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- ✓ Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- ✓ Important advice on the medicine's packaging.

- ✓ The authorised pack size— the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- ✓ The medicine's legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR/PBRER assessment, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of Aloxi 250 micrograms solution for injection is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Aloxi 250 micrograms solution for injection are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks of Aloxi 250 micrograms solution for injection can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Aloxi 250 micrograms solution for injection. Potential risks are concerns for which an association with the use of this medicine is possible based on some preliminary data, but this association has not been fully proven established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	None
Important potential risks	Torsade de pointes due to QT/QTC prolongation Serotonin Syndrome
Missing information	Effect in children aged less than 1 month (potential off-label use for CINV prevention)

II.B Summary of important risks

Important potential risk: Torsade de pointes due to QT/QTC prolongation	
Evidence for linking the risk to the medicine	Clinical studies have not showed relevant effects on the prolongation of the QT/QTc interval. Nevertheless, since cancer patients are a vulnerable population receiving potentially cardiotoxic antineoplastic agents, or with medical history remarkable for cardiac disease on treatment with antiarrhythmics, or may carry electrolytes imbalance, it is prudent to consider Torsade de pointes due to QT/QTc prolongation an important potential risk.

Risk factors and risk groups	Risk factors include drug interaction with concomitant medication such as anthracyclines, cyclophosphamide or antiarrythmic drugs, pre-existing cardiac disease (e.g., cardiac ischaemia, cardiomyopathies, congenital long QT syndrome, rhythm disturbances), hypertension, atherosclerosis, malnutrition or electrolytes abnormalities (including that caused by diuretics and dehydration), or treatment with drugs known to prolong QT interval, hypothyroidism, hypoglycaemia and a wide range of chemotherapy agents. Female sex and older age are also associated with longer QT intervals.
Risk minimisation measures	✓ Routine risk communication: SmPC sections 4.4 and 4.8, PL sections 2 and 4. ✓ Routine risk minimisation activities recommending specific clinical measures to address the risk: advice is given for monitoring of patients with conditions leading to QT prolongation in SmPC section 4.4 and inform patients on the importance of this medical condition in PL section 2 and of possible undesirable effects in PL section 4. ✓ Other routine risk minimisation measures beyond the Product Information: none ✓ Legal status: prescription only medicine.

Important potential risk: Serotonin syndrome	
Evidence for linking the risk to the medicine	The occurrence of Serotonin Syndrome (SS) has been considered as a potential class effect of the anti-emetics belonging to the class of the 5-HT_3 RAs. Serotonin syndrome is a potentially life-threatening drug reaction that may occur following therapeutic drug use. The excess serotonin activity produces a spectrum of specific symptoms including cognitive, autonomic, and somatic effects, which can be of variable intensity.
Risk factors and risk groups	Patients on treatment with antidepressant, or with triptanes for migraine or cluster headaches. Patients on therapy with anti-parkinson agents, or antidepressants for fibromyalgia or chronic fatigue. Use of illicit drugs (ecstasy, LSD), or herbal and nutritional supplements (St. John's wort, panag ginseng) may increase the risk. Susceptibility to serotonin syndrome may be also conferred by patient's factors, such as the capacity to metabolize certain drugs.
Risk minimisation measures	✓ Routine risk communication: none. ✓ Routine risk minimisation activities recommending specific clinical measures to address the risk: specific information on the serotonin syndrome when palonosetron is administered with other serotoninergic agents is included in SmPC sections 4.4 and 4.5. ✓ Specific information on the SS when palonosetron is administered with other serotoninergic agents and how to make aware patients of the importance of informing healthcare

	professionals of the use of other medicinal products in PL section 2. ✓ Other routine risk minimisation measures beyond the Product Information: none ✓ Legal status: Prescription only medicine

Missing information: Effects in children aged less than 1 month	
Risk minimisation measures	✓ Routine risk minimisation measures: ✓ SmPC Sections 4.2, 4.6 and 5.1 ✓ PL sections 1, 3 and 4 where advice to not use the product in children below 1 month due to lack of safety and efficacy data is reported Additional risk minimisation measures: ✓ No additional risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Aloxi 250 micrograms solution for injection.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Aloxi 250 micrograms solution for injection.

Summary of risk management plan for Aloxi 500 micrograms soft capsules

This is a summary of the risk management plan (RMP) for **Aloxi 500 micrograms soft capsules**. The RMP details important risks of Aloxi 500 micrograms soft capsules, how these risks can be minimised, and how more information will be obtained about Aloxi 500 micrograms soft capsules risks and uncertainties (missing information). Aloxi 500 micrograms soft capsules summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Aloxi 500 micrograms soft capsules should be used. This summary of the RMP for Aloxi 500 micrograms soft capsules should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR). Important new concerns or changes to the current ones will be included in updates of Aloxi 500 micrograms soft capsules RMP.

I. The medicine and what it is used for

Aloxi 500 micrograms soft capsules is indicated in adults for the:

- Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults.

Aloxi 500 micrograms soft capsules is indicated in adults only because the safety and efficacy in children have not been established.

Further information about the evaluation of benefits of Aloxi 500 micrograms soft capsulescan be found in Aloxi 500 micrograms soft capsules EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Aloxi 500 micrograms soft capsules together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- ✓ Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- ✓ Important advice on the medicine's packaging.
- ✓ The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- ✓ The medicine's legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR/PBRER assessment, so that immediate action can be taken, as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of Aloxi 500 micrograms soft capsules is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Aloxi 500 micrograms soft capsules are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks of Aloxi 500 micrograms soft capsules can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Aloxi 500 micrograms soft capsules. Potential risks are concerns for which an association with the use of this medicine is possible based on some preliminary data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	None
Important potential risks	Torsade de pointes due to QT/QTC prolongation Serotonin syndrome
Missing information	None

II.B Summary of important risks

Important potential risk: Torsade de pointes due to QT/QTC prolongation	
Evidence for linking the risk to the medicine	Clinical studies have not showed relevant effects on the prolongation of the QT/QTc interval. Nevertheless, since cancer patients are a vulnerable population receiving potentially cardiotoxic antineoplastic agents, or with medical history remarkable for cardiac disease on treatment with antiarrhythmics, or may carry electrolytes imbalance, it is prudent to consider Torsade de pointes due to QT/QTc prolongation an important potential risk.
Risk factors and risk groups	Risk factors include drug interaction with concomitant medication such as anthracyclines, cyclophosphamide or antiarrythmic drugs, pre-existing cardiac disease (e.g., cardiac ischaemia, cardiomyopathies, congenital long QT syndrome, rhythm disturbances), hypertension, atherosclerosis, malnutrition or electrolytes abnormalities (including that caused by diuretics and dehydration), or treatment with drugs known to prolong QT interval, hypothyroidism, hypoglycaemia and a wide range of chemotherapy agents. Female sex and older age are also associated with longer QT intervals.
Risk minimisation measures	✓ Routine risk communication: SmPC sections 4.4 and 4.8, PL sections 2 and 4. ✓ Routine risk minimisation activities recommending specific clinical measures to address the risk: advice is given for monitoring of patients with conditions leading to QT prolongation in SmPC section 4.4 and inform patients on the importance of this medical condition in PL section 2 and of possible undesirable effects in PL section 4. ✓ Other routine risk minimisation measures beyond the Product Information: none ✓ Legal status: prescription only medicine.
Important potential risk: Serotonin syndrome	
Evidence for linking the risk to the medicine	The occurrence of Serotonin Syndrome (SS) has been considered as a potential class effect of the anti-emetics belonging to the class of the 5-HT_3 RAs. SS is a potentially life-threatening drug reaction that may occur

	following therapeutic drug use. The excess serotonin activity produces a spectrum of specific symptoms including cognitive, autonomic, and somatic effects, which can be of variable intensity.
Risk factors and risk groups	Patients on treatment with antidepressant, or with triptanes for migraine or cluster headaches. Patients on therapy with anti-parkinson agents, or antidepressants for fibromyalgia or chronic fatigue. Use of illicit drugs (ecstasy, LSD), or herbal and nutritional supplements (St. John's wort, panag ginseng) may increase the risk. Susceptibility to serotonin syndrome may be also conferred by patient's factors, such as the capacity to metabolize certain drugs.
Risk minimisation measures	✓ Routine risk communication: none. ✓ Routine risk minimisation activities recommending specific clinical measures to address the risk: specific information on the serotonin syndrome when palonosetron is administered with other serotoninergic agents is included in SmPC sections 4.4 and 4.5. ✓ Specific information on the SS when palonosetron is administered with other serotoninergic agents and how to make aware patients of the importance of informing healthcare professionals of the use of other medicinal products in PL section 2. ✓ Other routine risk minimisation measures beyond the Product Information: none ✓ Legal status: Prescription only medicine

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Aloxi 500 micrograms soft capsules.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Aloxi 500 micrograms soft capsules.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not required to be submitted in e-CTD

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

4a) Follow-up form for QT/QTc prolongation

4b) Follow-up form for Serotonin Syndrome

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

4a) Follow-up form for QT/QTc prolongation

Drug:	**PALONOSETRON**
Target AEs:	**QT/QTc interval prolongation, Torsade de Pointes (TdP).**
Other pertinent AEs:	**Ventricular tachycardia, ventricular fibrillation, cardiac arrest, syncope, sudden death / sudden cardiac death**

Verify the presence, or attempt to obtain, the following information for any initial and/or follow-up ICSR of the Target Adverse Events and other pertinent AEs mentioned above.

(A) FOR CONFIRMATION OF DIAGNOSIS

☐ Was the reported event/diagnosis confirmed by a cardiologist or other specialist (e.g. an oncologist)?

☐ If QT/QTc interval prolongation or TdP are reported *verbatim* and ECG information is missing, obtain ECG report to confirm diagnosis (being QT/QTc interval prolongation and TdP electrocardiographic diagnoses).

(B) FOR COMPLETION OF CASE INFORMATION

☐ Check whether any of the following risk factors are mentioned, or obtain information, if missing:

- congenital long QT syndrome mentioned in personal or family medical history
- electrolyte disorders (e.g. hypokalemia, hypomagnesemia, hypocalcemia)
- congestive heart failure
- cardiac hypertrophy
- bradycardia
- diuretic use
- digitalis therapy
- rapid rate of intravenous infusion with a QT-prolonging drug

☐ Check availability of chest radiography, echocardiogram, and/or cardiac enzymes to rule out structural heart disorders (cardiac hypertrophy, CHF) or myocardial ischemia as potential contributor/confounder to the reported *dysrhythmia / sudden death.*

☐ Obtain as much as possible information on concomitant medications.

☐ Obtain as much as possible information on pre-existing clinical conditions, diseases or intercurrent conditions.

4b) Follow-up form for Serotonin Syndrome

Drug:	**PALONOSETRON**
Target AEs:	**Serotonin syndrome**
Other pertinent AEs:	**Patient should have been treated with netupitant/palonosetron alone or concomitantly with a serotonergic agent and have ONE of the following features or group of symptoms:** • **Spontaneous clonus.** • **Inducible clonus with agitation or diaphoresis.** • **Ocular clonus with agitation or diaphoresis.** • **Tremor and hyperreflexia; or** • **Hypertonia, temperature above 100.4°F (38° C), and ocular or inducible clonus.**

Have you attempted to obtain the following information in the initial and/or follow-up report or narrative?

☐ Was the patient administered netupitant/palonosetron concomitantly with any of the following medications?

Antimigraine agents; triptans; antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs], buspirone, tricyclic antidepressants, monoamine oxidase inhibitors [MAOIs]); antipsychotics; anticonvulsants; antiparkinsonian agents; analgesics (e.g., meperidine, tramadol); OTC products (e.g., cough and cold medication containing dextromethorphan); herbal products, dietary supplements, illicit substances, or the antibiotic linezolid.

☐ Was a detailed description of drugs, including dosing, the formulation (e.g. sustained release), any change in dosing and schedule collected?

☐ Was the time of onset of the symptoms reported?

The majority of cases present symptoms within 24 hours and most within 6 hours of a change in dose or initiation of a drug. Very few patients experience symptoms after 24 hours and within 72 hours.

☐ Was a neurological evaluation performed?

Serotonin syndrome is essentially a clinical diagnosis; neurologic manifestations represent the most important clinical features.

<u>Patient's medication history/concomitant conditions are fundamental for an accurate case assessment:</u>

☐ What medication has the patient taken previously?

☐ What adverse drug reactions have been previously experienced?