EU Risk Management Plan for Akynzeo

Active substance(s) (INN or common name):	Fosnetupitant and palonosetron (Fixed combination) intravenous Netupitant and palonosetron (Fixed combination) oral
Pharmaco-therapeutic group (ATC Code):	Antiemetics and antinauseants, serotonin ($5HT_3$) and neurokinin-1 (NK_1) receptor antagonists (ATC Code A04AA55)
Name of Marketing Authorisation Holder or Applicant:	Helsinn Birex Pharmaceuticals Ltd.
Number of medicinal products to which this RMP refers:	4
Product(s) concerned (brand name(s)):	Akynzeo 235 mg/0.25 mg concentrate for solution for infusion Akynzeo 235 mg/0.25 mg powder for concentrate for solution for infusion Akynzeo 300 mg/0.5 mg hard capsules Akynzeo 300 mg/0.5 mg oral suspension

Details of the currently approved RMP:

Approved with procedure: EMA/X/0000258060

RMP version to be assessed as part of this application:

RMP Version number: 4.0

Data lock point for this RMP: 10 October 2024

Date of final sign off: 09 December 2025

Rationale for submitting an updated RMP: This RMP is being submitted as part of the line-extension application for a new pharmaceutical form of Akynzeo, i.e., Akynzeo 300 mg/0.5 mg oral suspension. In this new pharmaceutical form, the strength of the two active ingredients is the same of the approved hard capsule formulation, as well as the route of administration and the therapeutic indication.

Other RMP versions under evaluation: Not applicable.

This version has been compiled in accordance with the format and content of the EMA guidance on the format of the RMP in EU (Rev. 2.0.1) dated 31 October 2018 and GVP Module V Rev.2.

This document provides available information on the proposed new pharmaceutical form of Akynzeo oral suspension; furthermore, it integrates and provides an update of the safety information of the EU RMP version 3.0, endorsed by CHMP on 17 September 2021 and approved by the EC on 15 November 2021, as part of the line-extension application for a concentrate solution for infusion pharmaceutical form.

All formulations contain palonosetron. The neurokinin receptor antagonist (RA) of the IV formulations is fosnetupitant which is rapidly converted to netupitant when infused in the bloodstream, while netupitant is the active ingredient of the oral fixed combination.

Table Modules.1 – Overview of the RMP Parts and Modules in the current RMP (V 3.0, EMEA/H/C/003728/X/0031)

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 3.0	4.0
	SII Non-clinical part of the safety specification	V 3.0	4.0
	SIII Clinical trial exposure	V 3.0	4.0
	SIV Populations not studied in clinical trials	V 3.0	4.0
	SV Post-authorisation experience	V 3.0	4.0

Part	Module/annex	Module version and procedure number where the module was last approved	Module version for the proposed update
	SVI Additional EU requirements for the safety specification	V 3.0	N.A.
	SVII Identified and potential risks	V 3.0	N.A.
	SVIII Summary of the safety concerns	V 3.0	N.A.
Part III Pharmacovigilance Plan		V 3.0	N.A.
Part IV Plan for post-authorisation efficacy studies		V 3.0	N.A.
Part V Risk Minimisation Measures		V 3.0	N.A.
Part VI Summary of RMP		V 3.0	4.0
Part VII Annexes	ANNEX 2 Tabulated summary of on-going and completed pharmacoepidemiological study programme.	V 3.0	N.A.
	ANNEX 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	V 3.0	N.A.
	ANNEX 4 Specific adverse event follow-up forms	V 3.0	N.A.
	ANNEX 5 Protocols for proposed and on-going studies in Part IV	V 3.0	N.A.

Part	Module/annex	Module version and procedure number where the module was last approved	Module version for the proposed update
	ANNEX 6 Details of proposed additional risk minimisation activities	V 3.0	N.A.
	ANNEX 7 List of references	V 3.0	4.0
	ANNEX 8 Summary of changes to the risk management plan over time	V 3.0	4.0

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Table of content

Part I: Product(s) Overview

Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Fosnetupitant and palonosetron (Fixed combination) intravenous Netupitant and palonosetron (Fixed combination) oral
Pharmacotherapeutic **group(s) (ATC Code)**	Antiemetics and antinauseants, serotonin ($5HT_3$) and neurokinin-1 (NK_1) receptor antagonists (ATC Code A04AA55)
Marketing Authorisation **<Holder> <Applicant>**	Helsinn Birex Pharmaceuticals Ltd.
Medicinal products to which **this RMP refers**	Akynzeo 235 mg/0.25 concentrate for solution for infusion Akynzeo 235 mg/0.25 powder for concentrate for solution for infusion Akynzeo 300 mg / 0.5 mg hard capsules Akynzeo 300 mg/0.5 mg oral suspension
Invented name(s) in the European Economic Area (EEA)	Akynzeo
Procedure type (centrally or nationally authorised)	Centralised procedure
Brief description of the product including:	Chemical class: Akynzeo intravenous fixed combination medicinal product contains two active substances – palonosetron a 5-HT_3 (serotonin) receptor antagonist (RA), and fosnetupitant, rapidly converted to netupitant when infused in the bloodstream. Netupitant belongs to the class of neurokinin 1 (NK_1) RAs. Akynzeo oral fixed combination medicinal product contains two active substances – palonosetron and netupitant. Both agents have a strong binding affinity for their own receptor and little or no affinity for other receptors.
	Summary of mode of action: Antineoplastic agents may cause emesis through effects at a number of 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. Substance P (neurotransmitter which belongs to tachykinin family) contributes mostly to the pathophysiology of delayed emesis and exerts its biological effects *via* interaction with the NK_1 receptors. Netupitant is a selective NK_1 RA which blocks these receptors located in the central nervous system and in the gastrointestinal tract wall.
	Important information about its composition: The combined treatment with palonosetron and netupitant has a robust pharmacological rationale because the two compounds have different and complementary mechanisms of action. They inhibit different receptors, both of which are involved in the development of chemotherapy-induced nausea and emesis, which explains the expected additive synergistic effect.
Hyperlink to the Product Information:	Proposed Labelling.

Indication(s) in the EEA	Proposed: Akynzeo oral suspension is indicated in adults for the: Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy. Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.
	Current: Akynzeo hard capsules, Akynzeo powder for concentrate for solution for infusion and, Akynzeo concentrate for solution for infusion are indicated in adults for the: Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy. Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.
Dosage in the EEA	Proposed: Akynzeo oral suspension: One 300 mg/0.5 mg sachet should be administered approximately one hour prior to the start of each chemotherapy cycle.
	Current: Akynzeo IV in adults: One vial of Akynzeo for injection; reconstituted in 50 ml of 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, should be administered as 30-minute infusion starting approximately 30 minutes prior to the start of chemotherapy. Akynzeo hard capsules in adults: One Akynzeo 300 mg/0.5mg capsule should be administered approximately one hour prior to the start of each chemotherapy cycle.
Pharmaceutical form(s) and strengths	Proposed: Akynzeo 300 mg/0.5 mg oral suspension White to off white homogeneous suspension
	Current: Akynzeo 235 mg fosnetupitant/0.25 mg palonosetron concentrate for solution for infusion. Clear, colorless to slightly yellow solution in a single-dose vial for dilution. Akynzeo 235 mg fosnetupitant/0.25 mg palonosetron powder for concentrate for solution for infusion. White to off-white lyophilized powder in a single-dose vial for reconstitution.
	Akynzeo 300 mg netupitant/0.5 mg palonosetron Capsule, hard. Hard, opaque, gelatine capsule with white body and caramel cap with "HE1" printed on the body. Excipient(s) with known effect: each capsule contains 7 mg of sorbitol and 20 mg of sucrose.

Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

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

Indication(s)

Both IV and oral Akynzeo are indicated for the:

- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.
- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Natural history of the indicated condition including mortality and morbidity:

Chemotherapy-induced nausea and vomiting (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).

Of all the known predictive factors, the intrinsic emetogenicity of a given chemotherapeutic agent is the predominant factor allowing predicts 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. On the basis of 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.

The emetic potential in the absence of antiemetic prophylaxis of the chemotherapeutic agent administered is classified as high (the emetic risk is ≥90%), moderate (emetic risk 30-90%), low (emetic risk 10-30%) and minimal (emetic risk <10%). Chemotherapy cycles, including cisplatin, have been associated with a high risk of development of CINV in patients. International and national antiemetic guidelines have developed antiemetic prophylaxis recommendations for each emetic risk level.

Table 1 summarises the emetogenic potential of chemotherapy agents (intravenous and oral) in adults (2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting (Herrstedt J et al. 2024).

Table 1 Relative emetogenic potential of chemotherapy in adults – Intravenous and Oral

Emetogenic potential of single intravenous antineoplastic agents			
High (emetic risk ≥90%)	**Moderate (emetic risk 30–90%)**	**Low (emetic risk 10–30%)**	**Minimal (emetic risk <10%)**
Anthracycline/ Cyclophosphamide combination	Alemtuzumab	Aflibercept	Asparaginase (calaspargasepegol)
Carmustine	Arsenic trioxide	Amivantamab	Atezolizumab
Cisplatin	Azacitidine	Axicabtagene-ciloleucel	Avelumab
Cyclophosphamide 1,500 mg/m^2	Bendamustine	Belinostat	Belantamab-mafodotin
Dacarbazine	Busulfan	Blinatumomab	Bevacizumab
Chlormethine (mechlorethamine)	Carboplatin	Bortezomib	Bleomycin
Streptozocin	Clofarabine	Brentuximab-vedotin	Cemiplimab
	Cyclophosphamide < 1,500 mg/m²	Cabazitaxel	Cladribine (2-chlorodeoxyadenosine)
	Cytarabine > 1,000 mg/m²	Carfilzomib	Daratumumab
	Cytarabine/daunorubicin liposomal	Catumaxomab	Dostarlimab
	Daunorubicin	Cetuximab	Durvalumab
	Dinutuximab beta	Copanlisib	Emapalumab
	Doxorubicin	Cytarabine 1000 mg/m^2	Fludarabine
	Epirubicin	Decitabine	Ipilimumab
	Idarubicin	Docetaxel	Nivolumab
	Ifosfamide	Doxorubicinpeg-liposomal	Obinutuzumab
	Irinotecan	Elotuzumab	Ofatumumab
	Irinotecan peg-liposomal	Enfortumab-vedotin	Pembrolizumab
	Lurbinectedin	Eribulin	Polatuzumab-vedotin
	Naxitamab	Etoposide	Pralatrexate
	Oxaliplatin	5-Fluorouracil	Ramucirumab
	Romidepsin	Gemcitabine	Rituximab
	Sacituzumab-govitecan	Gemtuzumab-ozogamicin	Trastuzumab
	Temozolomide	Inotuzumab-ozogamicin	Tremelimumab
	Thiotepa	Isatuximab	Vinblastine
	Trabectedin	Ixabepilone	Vincristine
	Trastuzumab-deruxtecan	Loncastuximab-tesirine	Vinorelbine
		Margetuximab	
		Melphalan-flufenamide	
		Methotrexate	
		Mirvetuximab-soravtansine	
		Mitomycin	
		Mitoxantrone	
		Moxetumomab-pasudotox	
		Necitumumab	
		Nelarabine	
		Paclitaxel	
		Paclitaxel nab-albumin	
		Panitumumab	
		Pemetrexed	

Emetogenic potential of single intravenous antineoplastic agents			
High (emetic risk ≥90%)	**Moderate (emetic risk 30–90%)**	**Low (emetic risk 10–30%)**	**Minimal (emetic risk <10%)**
		Pertuzumab Tafasitamab Tagraxofusp Teclistamab Temsirolimus Tisagenlecleucel Tisotumab-vedotin Topotecan Trastuzumab emtansine Vinflunine	

Emetogenic potential of single oral antineoplastic agents			
High/ Moderate		**Low/ Minimal**	
Abemaciclib	Lenvatinib	Acalabrutinib	Methotrexate
Adagrasib	Lenvatinib	Afatinib	Neratinib
Avapritinib	Midostaurin	Alectinib	Nilotinib
Bosutinib	Mobocertinib	Alpelisib	Nintedanib
Cabozantinib	Mobocertinib	Apalutamide	Olutasidenib
Ceritinib	Olaparib	Asciminib	Osimertinib
Crizotinib	Procarbazine	Axitinib	Palbociclib
Cyclophosphamide	Ribociclib	Bexarotene	Panobinostat
Enasidenib	Ribociclib	Brigatinib	Pazopanib
Fedratinib	Selinexor	Capecitabine	Pemigatinib
Hexamethylmelamine (altretamine)	Temozolomide	Capmatinib	Pexidartinib
Imatinib	Vinorelbine	Chlorambucil	Pomalidomide
		Cobimetinib	Ponatinib
		Dabrafenib	Pralsetinib
		Dacomitinib	Regorafenib
		Darolutamide	Relugolix
		Dasatinib	Ripretinib
		Duvelisib	Ruxolitinib
		Encorafenib	Selpercatinib
		Entrectinib	Sonidegib
		Erdafitinib	Sorafenib
		Erlotinib	Sotorasib
		Estramustine	Sunitinib
		Etoposide	Talazoparib
		Everolimus	Tazemetostat
		Fludarabine	Tegafureuracil
		Futibatinib	Tepotinib
		Gefitinib	Thalidomide
		Gilteritinib	Tioguanin(6-thioguanine)
		Glasdegib	Tivozanib
		Hydroxyurea	Topotecan
		Ibrutinib	Trametinib
		Idelalisib	Trifluridineetipiracil
		Infigratinib	Tucatinib
		Ivosidenib	Umbralisib
		Ixazomib	Vandetanib
		Lapatinib	Vemurafenib
		Larotrectinib	Venetoclax
		Lenalidomide	Vismodegib
		Lorlatinib	Vorinostat
		Melphalan (L-phenylalanine mustard)	Zanubrutinib

The majority of 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).

Detailed epidemiology (i.e., incidence, prevalence and mortality) of the prevention of acute or delayed CINV in the target population is provided in Table 2 below.

Table 2 Epidemiology of the disease

Indication	**Prevention of acute / delayed chemotherapy-induced nausea and vomiting (CINV)**
Target population	To estimate the population of cancer patients that could receive treatment with the fixed combination for the prevention of CINV, we have focused on the cancer types known to be most frequently associated with CINV. These include breast cancer, colorectal cancer, lung cancer, ovarian cancer, and lymphomas. Some of the selected tumour types are among the most frequent cancers. However, it is acknowledged that the population of patients who might receive the fixed combination is much broader and comprises a wider range of cancer types. Overall, the incidence of cancer types associated with CINV increases with age and is higher in older age groups. According to the NCI's Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review, 1975-2022, in the US approximately 60% of all cancer cases occurred among patients aged 65 years or older and 78% among patients aged 55 years or older, while the median age of patients at cancer diagnosis was 67 years according to the most recent statistical data from SEER Program. This means that half of cancer cases occur in people below this age and half in people above this age. A similar pattern is seen for many common cancer types. For example, the median age at diagnosis is 63 years for breast cancer, 66 years for colorectal cancer, 71 years for lung cancer, and 68 years for prostate cancer. According to the USA Centers for Disease Control and Prevention (CDC), the incidence rate of breast cancer in the United States is approximately 129.8 new cases per 100,000 women annually, making it one of the most prevalent cancers among women in the country. Prostate cancer has an incidence rate of about 112 new cases per 100,000 men each year, highlighting its significant impact on the male population. Colorectal cancer affects approximately 38.4 new individuals per 100,000 people annually, indicating its considerable presence among both men and women. Lung cancer, with an incidence rate of around 47.8 new cases per 100,000 men and women per year, remains a major health concern. These rates are age-adjusted and based on data collected from 2018 to 2022 according to the US SEER Program results. In Europe, based on data from GLOBOCAN 2022 (Elmadani M et al 2025), breast cancer is the most commonly occurring cancer, with approximately 130 new cases per 100,000 people annually. Colorectal cancer follows closely, with around 125 new cases per 100,000 people each year, underscoring its significant prevalence. Lung cancer, with about 118 new cases per 100,000 people annually, continues to be a widespread issue. Prostate cancer, affecting roughly 117 new cases per 100,000 people per year, is also notably common among men. Additionally, bladder cancer has an incidence rate of approximately 50 new cases per 100,000 people annually, highlighting its notable presence in the European population.
Incidence of target indication	The incidence of acute and delayed CINV was investigated in highly and moderately emetogenic chemotherapy treatment regimens. Patients were recruited from 14 oncology practices in six countries. Of the 298 eligible patients,

Indication	**Prevention of acute / delayed chemotherapy-induced nausea and vomiting (CINV)**
	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. A majority 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% HEC patients, respectively, and in 19% and 21% MEC patients, respectively (Grunberg SM et al. 2004). 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). The emetogenicity of chemotherapy was again confirmed to be relevant; 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 of target indication	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 incidence 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).
Mortality of target indication	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 comorbidities in target population	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 recent 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).

Indication	**Prevention of acute / delayed chemotherapy-induced nausea and vomiting (CINV)**
Risk factors for the disease	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-HT_3 antagonist and a corticosteroid alone (Navari RM 2003).

Indication	**Prevention of acute / delayed chemotherapy-induced nausea and vomiting (CINV)**
Demographic profile of target population	Demographic data on the population of cancer patients that could receive treatment with the fixed combination for the prevention CINV are available from published observational studies evaluating the incidence and impact of CINV, mostly among patients receiving high- or moderate-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 targeted population of the fixed combination. In the majority of 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) occur primarily or exclusively in females. In addition, the fixed combination 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, in 2021, according to the most recent data available from the CDC, there were 272,454 new breast cancer cases reported in females. Approximately 43% of these new diagnoses were among females aged 65 years or older, and 77% were among females aged 50 years or older. ● Colorectal cancer: According to the World Cancer Research Fund (WCRF) and the European Cancer Information System (ECIS), the age-standardized incidence rate (ASR) for colorectal cancer in Europe is approximately 62.4 per 100,000 among males and around 43.6 per 100,000 among females. The majority of newly diagnosed cases continue to be among older individuals, with a significant proportion occurring in those aged 70 years and older. Cases among individuals younger than 50 years remain relatively low, at around 9%. ● Lung cancer: According to the ECIS, in the EU in 2022, there were approximately 312,000 new cases of lung cancer diagnosed. About 60% of these cases were among males, and 40% among females. Nearly half (47%) of all new diagnoses were among individuals aged 70 years or older, and 48% were among those aged 45 to 69 years. Cases among individuals younger than 50 years remain relatively low, at around 5%. In the US in 2022, 236,740 cases of lung cancer were diagnosed: 108,520 (46%) among females and 128,220 (54%) among males. A total of 53% of new diagnoses were among those aged 70 years or older, and 7% were in individuals aged younger than 50 years (L Siegel R et al, 2022). ● Ovarian cancer: Ovarian cancer occurs exclusively in females. In the EU in 2022, according to the ECIS, slightly more than half of the 44,000 females diagnosed with ovarian cancer were aged 65 years or older. In the US, according to the SEER Program results, about 48% of the 19,880 females diagnosed in 2022 were aged 65 years or older. ● Non-Hodgkin lymphoma: In the EU in 2022, according to the ECIS, there were approximately 54,000 cases diagnosed among males and 46,000 among females. Nearly half (47%) of all new diagnoses in the EU were among individuals aged 70 years or older. In the US in 2022, there were an estimated 80,350

Indication	**Prevention of acute / delayed chemotherapy-induced nausea and vomiting (CINV)**
	incident cases of NHL: 35,210 (44%) among females and 45,140 (56%) 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 (Sedeta E et al, 2022).
Main treatment options	The three categories of drugs with the highest therapeutic index for the management of CINV are the type three 5-hydroxytryptamine (5-HT_3) receptor antagonists, 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) makes also cannabinoids a useful adjunct to the modern antiemetic therapy in selected patients (Jordan K et al. 2007). Pre-chemotherapy recommendations by emetogenic potential of chemotherapy agent are summarised below.

For adult patients receiving HEC, all guidelines recommend providing prophylaxis, including combinations of an NK1 receptor antagonist (RA), olanzapine, a 5-HT3 RA and a corticosteroid (primarily dexamethasone). For adult patients receiving MEC, all guidelines recommend a 5-HT3 RA with dexamethasone. The addition of an NK1 RA is recommended for patients receiving specific MEC (MASCC/ESMO) and for selected patients with CINV risk factors (NCCN and MASCC/ESMO) (Hesketh 2020; Herrstedt 2024; NCCN 2024).

Prevention Of Acute And Delayed Nausea And Vomiting Induced By Highly Emetogenic Chemotherapy (HEC)

Here are the recommendations for high emetic risk Chemotherapy (ChT) according to 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting (Herrstedt J. et al. 2024).

Prevention of acute nausea and vomiting following non-anthracycline (AC) ChT of high emetic risk:

- A four-drug regimen including single doses of a 5-HT3-RA, dexamethasone, an NK1-RA (aprepitant, fosaprepitant, netupitant, fosnetupitant or rolapitant) and olanzapine given before ChT is recommended [I, A].
    - Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.

Prevention of delayed nausea and vomiting following non-AC ChT of high emetic risk:

- In patients receiving non-AC high emetic risk ChT treated with a combination of a 5-HT3-RA, DEX, an NK1-RA and olanzapine to prevent acute nausea and vomiting, dexamethasoneeolanzapine on days 2-4 is suggested to prevent delayed nausea and vomiting.

- A few studies have investigated a 1-day dexamethasone regimen as an option in cisplatin with one study demonstrating comparable efficacy between a 1-day and multi-day dexamethasone schedules.
- If aprepitant 125 mg is used on day 1, then aprepitant 80 mg x 1 should be administered on days 2 and 3.

Prevention of acute nausea and vomiting following AC based ChT of high emetic risk:

- In women treated with AC-based ChT, a four-drug regimen including single doses of a 5-HT3-RA, dexamethasone, an NK1-RA (aprepitant, fosaprepitant, netupitant, fosnetupitant or rolapitant) and olanzapine given before ChT is recommended [I, A].
  - This recommendation is based on extensive data in women treated with adjuvant AC for breast cancer.
  - Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.

Prevention of delayed nausea and vomiting following AC-based ChT of high emetic risk:

- In women treated with a combination of a 5-HT3-RA, dexamethasone, an NK1-RA and olanzapine to prevent acute nausea and vomiting, olanzapine on days 2-4 is suggested to prevent delayed nausea and vomiting.
  - This recommendation is based on extensive data in women treated with adjuvant AC for breast cancer.
  - If aprepitant 125 mg is used on day 1, then aprepitant 80 mg x 1 should be administered on days 2 and 3.

Dose and schedule of olanzapine in the prevention of acute and delayed nausea and vomiting following ChT of high emetic risk:

- The best investigated dose is 10 mg. 5 mg is superior to placebo, but it is unknown if it is as effective as 10 mg, because no robust studies have compared the 5 mg and 10 mg doses. The only schedule investigated is once daily for 4 days (see sub-bullet about sedation) [II, B].
  - If sedation is a concern, a starting daily dose of 5 mg and/or administration at bedtime is an option.

Prevention Of Acute And Delayed Nausea And Vomiting Induced By Moderately Emetogenic Chemotherapy (MEC)

Here are the recommendations for Moderate Emetic risk Chemotherapy (MEC) according to 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. (Herrstedt J. et al. 2024).

Prevention of acute nausea and vomiting following carboplatin-based MEC:

- A three-drug regimen including single doses of a 5-HT3-RA, dexamethasone and an NK1-RA (aprepitant, fosaprepitant, fosnetupitant, netupitant or rolapitant), given before ChT is recommended for patients receiving carboplatin AUC >5.

- Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination.
- agent NEPA.

- There are no data justifying the use of an NK1-RA for carboplatin AUC <5 [I, A].

Prevention of delayed nausea and vomiting following carboplatin-based MEC:

- No steroid (or other antiemetic) should be routinely administered after day 1 carboplatin administration [II, B].
  - If aprepitant 125 mg is used on day 1, then aprepitant 80 mg x 1 should be administered on days 2 and 3.
  - One day of steroids has demonstrated non-inferiority compared with 3 days of steroids.

Prevention of acute nausea and vomiting following oxaliplatin-based MEC:

- A two-drug regimen, including single doses of a 5-HT3-RA and DEX, given before ChT, is recommended for patients receiving oxaliplatin.
  - Palonosetron is the preferred 5-HT3-RA in this population.
- The addition of an NK1-RA (aprepitant, fosaprepitant, netupitant, fosnetupitant or rolapitant) is suggested for oxaliplatin ChT-induced nausea and vomiting (CINV) prophylaxis in women aged >50 years old [III, B].
  - Netupitant/fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.
- There is no evidence that an NK1-RA should be routinely used first line in women >50 years old [III, B].

Prevention of delayed nausea and vomiting following oxaliplatin-based MEC:

- No steroid (or other antiemetic) should be routinely administered after day 1 oxaliplatin administration [II, B].
  - If aprepitant 125 mg is used on day 1, then aprepitant 80 mg x 1 should be administered on days 2 and 3.
  - One day of steroids has demonstrated non-inferioritycompared with 3 days of steroids.

Prevention of acute nausea and vomiting following other MEC (non-carboplatin, non-oxaliplatin):

- A two-drug regimen including single doses of a 5-HT3-RA and DEX, given before ChT, is recommended for patients receiving other MEC [II, C].
  - The emetic potential of sacituzumabegovitecan and trastuzumabederuxtecan appears to be at the high end of the moderate category, most closely resembling that of carboplatin AUC >5. While prospective studies are needed, it is suggested to prevent emesis as for carboplatin AUC >5.

Prevention of delayed nausea and vomiting following other MEC (non-carboplatin, non-oxaliplatin):

- No steroid (or other antiemetic) should be routinely administered after day 1 MEC administration [II, B].

- One day of steroids has demonstrated non-inferiority compared with 3 days of steroids.

Olanzapine in ChT of moderate emetic risk prevention

- No evidence exists for the use of olanzapine as first-line prophylaxis

Important co-morbidities

Comorbidities are traditionally viewed as prevalent conditions that commonly co-exist or co-occur among the targeted population of interest. In the following section a list, although not exhaustive of the most common comorbidities in patients diagnosed with the cancer types in which CINV is known to develop more frequently, is displayed.

Because the burden of cancers is greater among older patients, and advancing age is associated with increased vulnerability to other age-related health problems, most published studies have focused on the assessment of comorbidities among older patient populations (Janssen-Heijnen ML et al. 2005; Gross CP et al. 2007; Janssen L et al. 2011).

Table 3 List of the most common comorbidities in the target population

Cardiac diseases	Heart disease (e.g. congestive heart failure, atrial fibrillation, coronary artery disease) Hypertension
Respiratory disease	COPD
Metabolic disorders	Diabetes mellitus, decreased appetite
Neoplasm	Multiple primary cancers
Mood disorders	Depressive disorders, anxiety, insomnia
Diseases due to the citotoxic effects of chemotherapy	Infections of bacterial, viral, fungal origin localized at different organs or apparatus, e.g. mucositis, lung infections, urinary infections

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

Fosnetupitant is the netupitant prodrug (a phospho-netupitant derivative) which has been developed to improve the solubility of netupitant and obtain a viable IV formulation. Preclinical studies demonstrate that fosnetupitant is rapidly converted to netupitant in vivo following IV administration.

In preclinical species administered with fosnetupitant chloride hydrochloride, plasma exposure to netupitant and to the three main circulating metabolites, M1, M2 and M3, are comparable with the exposures measured after direct IV or oral administration of equivalent netupitant doses.

The in vivo effect of fosnetupitant and netupitant was evaluated in the scratching, biting, and licking responses elicited by Substance P (SP) injected in mice. The two compounds at 10 and 1 but not at 0.1 mg/kg were able to significantly counteract the nociceptive behavior induce by SP in a similar and dose dependent manner. The two compounds exhibited a similar efficacy and potency in this test. Moreover, under the present experimental condition the pharmacological effects of fosnetupitant can be entirely interpreted as due to its conversion to netupitant. Therefore, the effects of fosnetupitant are mainly attributable to netupitant.

The non-clinical development programme of the intravenous and oral fixed combination was designed based on the US Food and Drug Administration (FDA) guidance "Nonclinical Safety Evaluation of Drug or Biologic Combinations" and specific FDA requests. Afterward the programme was endorsed by a Scientific Advice with the European Medicines Agency (EMA). Non-clinical studies were conducted to characterise the pharmacology, pharmacokinetics and toxicology of the fixed combination in accordance with the Guideline on the Non-Clinical Development of Fixed Dose Combination Medicinal Products (EMEA/CHMP/SWP/258498/2005).

The non-clinical development programme of the fixed combination included a variety of studies conducted with fosnetupitant or netupitant as monotherapy and with the IV and oral fixed combination.

Based on the referred guidance, the general safety pharmacology studies of the fixed combination on central nervous system (CNS), gastrointestinal (GI) tract, respiratory tract and renal/urinary system were performed only with fosnetupitant and netupitant as monotherapy.

The effects on cardiovascular system were investigated in *in-vitro* and *in-vivo* studies with fosnetupitant or the combination. The effects on cardiovascular system were also investigated for netupitant using a broader approach.

The Development programme included *in vitro* and *in vivo* studies performed with netupitant, its metabolites (desmethyl derivative M1, N-oxide derivative M2 and hydroxymethyl derivative M3) and with the fixed combination. Absorption, Distribution, Metabolism, Excretion (ADME) studies were performed with netupitant only.

Toxicology studies included repeat-dose studies performed with fosnetupitant and the intravenous fixed combination.

Toxicology studies included single dose studies performed with netupitant only, repeat-dose studies performed with netupitant and the oral fixed combination, and chronic toxicity studies (6-month in rats and 9-month in dogs) conducted solely with netupitant.

In vitro and *in vivo* genotoxicity and reproductive toxicity studies were conducted with fosnetupitant and netupitant as monotherapy.

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.

Key safety findings which originated from all performed non-clinical studies within the non-clinical development programme of palonosetron and the fixed combination are provided separately in Table 4, sorted by palonosetron, fosnetupitant, netupitant and the intravenous and oral fixed combination.

Table 4 Key safety findings from non-clinical studies

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
PALONOSETRON (IV/OS)	
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 and 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. With the exception of 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.[47] *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.	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.
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.[4]	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 considered to be a potential risk for palonosetron.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mechanism of drug interactions	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.
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.	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.

Key Safety findings (from non-clinical studies)	Relevance to human usage
FOSNETUPITANT	

Repeat-dose toxicity The toxicity of fosnetupitant was investigated following IV administration to Wistar Hannover rats. The animals were treated with 0, 13.16, 39.47 and 78.94 mg/kg/day of fosnetupitant (corresponding to 10, 30 and 60 mg/kg/day of netupitant) for a total of 14 days. Fosnetupitant only at the dose of 78.94 mg/kg/day produced a slight decrease in body weight, a slight increase in liver weight and some local injection site changes (PNET-11-06). Fosnetupitant in a subsequent 2 week IV toxicity study in rats followed by a 2 week recovery period (PNET-11-21) at 0, 3.95, 13.16 and 39.47 mg/kg/day (equivalent to 3, 10 and 30 mg/kg/day of netupitant) for 14 days followed by 14 days of recovery showed slight toxic effects mainly in the liver in the high-dose group. These effects were completely reversible after a 2-week recovery period. No treatment related lesions were noted at the site of injection. The toxicity of fosnetupitant was investigated in Wistar Hannover rats after daily intravenous administration of escalating doses of 3.95, 13.16 and 39.47 mg/kg/day (equivalent to 3, 10 and 30 mg/kg/day of netupitant) for 4 weeks followed by a 2 weeks recovery period. Dose and treatment-related changes in the liver of both sexes treated with the high-dose and with the mid-dose group (only males) were observed. These changes consisted mainly of dose-related centrilobular hypertrophy and correlated with a trend of increased liver weight (up to +23% in females) in both sexes treated with the high dose and in the males treated with the mid-dose. However, no significant differences were observed in liver weights after the 2-week recovery period. In a preliminary IV toxicity study in dogs (PNET-11-07) the maximum tolerated dose (MTD) was established at 39.47 mg/kg/day due to effects on body weight and food consumption. The repeated IV administration of fosnetupitant for 14 consecutive days at the dose of 26.31 mg/kg/day (equivalent to 20 mg/kg/day of Netupitant) induced a slight reduction in body weight in both sexes, associated with decreased food intake. At post mortem observation, some control and treated animals showed red to dark color area in the subcutis of the injection sites. The toxicity of fosnetupitant after daily IV administration to Beagle dogs for 2 consecutive weeks (PNET-11-22) was investigated including a 2-week recovery period. Fosnetupitant dosages were 0, 1.32, 3.95 and 13.16 mg/kg/day (equivalent to 1, 3 and 10 mg/kg/day of	Even though fosnetupitant was well tolerated when administered intravenously to the ears vein of rabbits and the local tolerance was satisfactory in the 4-week toxicity studies in rats and dogs, local tolerability was to be carefully monitored in the safety trial with the IV fixed combination to establish its local tolerability in cancer patients and healthy volunteers. The frequency of TEAEs potentially referred to local tolerability was small: in the IV NEPA fixed combination group, 1 out of 203 patients experienced injection site extravasation; and in the Oral NEPA fixed combination group (N=201), where a placebo infusion was performed, 1 patient experienced infusion site extravasation and 1 patient experienced 2 episodes of injection site reaction. For events suggesting a thrombophlebitis or phlebitis the overall frequencies were small and very similar between the two treatments groups. Body weight as well as food intake were not affected by treatment in healthy volunteers. The satisfactory local tolerability observed in Phase 1 studies in healthy subjects with fosnetupitant alone along with the results of the safety study in patients reassure on the local tolerability; this is not predicted to be a safety concern for the IV fixed combination.

Key Safety findings (from non-clinical studies)	Relevance to human usage
netupitant). Decrease in body weight was observed in males of the high-dose group. Female animals, including controls, showed a slight decrease in body weight during the study. During the recovery phase, body weight of both sexes was comparable with the control data. Furthermore, slight decrease in food consumption was observed in males treated with the mid- and high dose starting from the first week of treatment. No treatment-related changes in food consumption were observed in females groups. Electrocardiographic tracings recorded during the study did not show any abnormality linked to treatment. **Reproductive toxicity and developmental toxicity** Fosnetupitant had no relevant effects on fertility. Studies conducted in order to assess the potential for embryofoetal developmental toxicity were carried out in both rats and rabbits. In rat studies one foetus with malformation (hindlimb malrotated) and one dead foetus were observed in the high dose group (39.47 mg/kg). At skeletal examination of foetuses, no ossification of pubis was detected in 6 foetuses of the high dose group distributed in 3 different litters. No malformations were detected in the foetuses of the control, low and mid dose groups. The no observed adverse effect level (NOAEL) was 13.16 mg/kg/day. In rabbit studies increase in intrauterine deaths (early/late resorption and dead foetuses) was recorded in treated groups with statistically significance in the mid- and high dose groups. The NOAEL was 3.13 mg/kg/day. In pre- and post-natal development study in rats with fosnetupitant in the high dose females of F0 generation receiving 39.47 mg/kg/day reduction in body weight and food consumption was observed. As a consequence lower litter weight and mean pup weight were present in the same group, in association with a slight increase in pup loss and a slight delay in the pre-weaning development tests. No relevant effects in term of body weight were noted in F2 generation. In conclusion, the dosage of 13.16 mg/kg/day is considered the NOAEL for dams and pups of F0 and F1 generations, in terms of development of the conceptus and the offspring. No effects were noted in the reproductive performance of animals of both sexes. **Genotoxicity** Fosnetupitant did not show mutagenic or clastogenic activity in a standard battery of in vitro and in vivo genotoxicity tests.	The potential of a teratogenic effect of fosnetupitant in humans is limited and based on the preclinical findings observed in rabbits and rats. No data are available from clinical studies; therefore the teratogenic effects may constitute a safety concern.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenecity and mutagenicity Carcinogenicity studies are not required for the CINV indication.	
General safety pharmacology Cardiovascular safety pharmacology studies were performed to investigate the effects of fosnetupitant and its metabolites on the cardiovascular system. Cardiovascular effects in dogs were examined in a 2-week study with IV fosnetupitant in Beagle dogs at 1.32, 3.95 and 13.16 mg/kg/day (equivalent to 1, 3 and 10 mg/kg/day of netupitant), followed by 2 weeks of recovery period. All electrocardiographic tracings recorded during the study did not show any abnormality which could be considered treatment-related. The QT interval and QRS complex reached statistical significance in high dose males soon after dosing in Week 2. However, all values remained within the physiological limits and no statistically significant increments in QTc were observed. Slight changes in QT and QRS complex were due to the main netupitant metabolite, M1 which is present in plasma and accumulate also in heart tissue. Plasma exposure of M1 is higher in dog if compared to human.	The potential clinical relevance of these preclinical findings was monitored during the clinical development programme of the IV fixed combination. A centralized ECG reading was applied in the study to investigate any ECG abnormality thru repeated chemotherapy cycles. The study showed no evidence of any increase in QTc duration and no clinically relevant specific outliers. Across all cycles, no patient had a QTcF >500 msec with a baseline value of ≤500 msec. Overall, no relevant differences between IV NEPA fixed combination and Oral NEPA fixed combination were detected with regard to increased QTc pre- and post-dose.
NETUPITANT	
Single and repeat-dose toxicity Following oral administration of single dose to dogs (study 1009567), netupitant produced a slight to moderate body weight loss and/or a lower body weight gain at all dose-levels and reduced food consumption at 300 and 400 mg/kg dose-levels. The no observed adverse effect level (NOAEL) was considered to be 200 mg/kg. Single oral administrations of netupitant were also tested in Wistar rats (study 1009566) at 500, 1000, 1500 and 2000 mg/kg. Microscopic signs of phospholipidosis were noted in several organs/tissues, with associated necrosis in the liver (at 1500 mg/kg and 2000 mg/kg) and in mesenteric lymph nodes (at 2000 mg/kg). The NOAEL was 500 mg/kg. A 4-week study in rats with netupitant at 3, 10 and 30 mg/kg dose-levels (study 1006011) was performed. At 30 mg/kg dose decreased food consumption and body weights, increase in gamma glutamyl transpeptidase (GGT) and sorbitol dehydrogenase (SDH) through recovery period were observed. Additionally, increased liver and adrenal weights, mild findings in lungs, mesenteric lymph nodes and spleen, indicative of phospholipidosis, minimal hypertrophy of periacinar hepatocytes and slight follicular	The potential clinical relevance of these preclinical findings was monitored during the clinical development programme of the oral formulation by collection of blood samples to assess liver function. No clinically relevant laboratory abnormalities were observed in the completed Phase I studies. Review of adverse events (AEs) from the completed Phase III studies showed that overall slightly higher proportion of patients in the oral netupitant/palonosetron combination group had liver transaminases increased (AEs in the Investigations SOC) in comparison to

Key Safety findings (from non-clinical studies)	Relevance to human usage
hypertrophy in the thyroid glands were reported. NOAEL was 10 mg/kg. In a 4-week study in dogs with netupitant at 1, 3, 5, 15 and 50 mg/kg dose-levels (study 1006010), 15 and 50 mg/kg treated groups of animals had adverse effects including clinical signs of QT prolongation, bradycardia, organ weight changes and histopathological findings (some indicative of phospholipidosis). No observed effect level (NOEL) was 3 mg/kg and NOAEL 5 mg/kg. Netupitant administered to rats (study MDS 161/578S) by the oral route daily at 3, 10 and 30 mg/kg/day dose-levels for 13 consecutive weeks or intermittently (5 periods of 7 days of treatment each separated by 2 weeks treatment-free) at 30 mg/kg/day dose-level, produced an increase incidence of hair loss and a lower body weight gain associated with a lower food consumption at 30 mg/kg/day. Histological changes considered to be consistent with a treatment-induced phospholipidosis were seen. As reported in previous studies vacuolization in the liver and as accumulation of foamy macrophages in lungs, mesenteric and mandibular lymph nodes and spleen were observed. The severity and/or incidence of these changes showed a dose-related trend and were more marked in the high dose group treated daily than intermittently. A NOEL was not established in this study. However, the level of histiocytosis in lymph nodes at the low dose level was only slightly above that of the controls and two low dose males had minimal hepatocytic hypertrophy; therefore the NOAEL (no observed adverse effect level) was 3 mg/kg/day. Netupitant was administered by oral route (capsule) in beagle dogs (1009175) at 0, 1, 3 and 10 mg/kg/day dose-levels for 13 consecutive weeks or intermittently (5 periods of 7 days of treatment each separated by 2 weeks treatment-free). The treatment induced reversible histopathological signs of phospholopidosis (vacuolated macrophages) in lymphoid tissue at 10 mg/kg. The NOAEL was considered to be 3 mg/kg. For netupitant, the onset of phospholipidosis in animal studies was dependent upon both the dose and the duration of dosing. Necrosis was only seen after the onset of phospholipidosis and when more generalized and severe phospholipidosis was present. Effects were reversible or partially reversible after the recovery period. In the 4-week and 13-week repeat-dose studies with netupitant, accumulation was noted for netupitant and was more pronounced for metabolite M1, which is considered to play a major role in the induction of phospholipidosis and QT prolongation.	palonosetron group. None of these laboratory abnormalities was assessed as a serious AE. The presence of lamellar inclusion bodies (biomarker for phospholipidosis) was examined by electron microscopy during a single ascending dose trial up to 450 mg netupitant (NP16603) and in apomorphine-challenge study (NP16602). Both studies were conducted in healthy volunteers. Blood samples were collected pre-dose and at 24 hours post-dose for isolation of leukocytes. The reason for choosing this time interval was based on pre-clinical findings in the rat, where phospholipidosis–inducing compounds produce lamellar inclusions at 24 hours post-dosing. No lamellar inclusions were observed in any of the post-dose samples examined. The plasma levels of metabolite M1 in humans are much lower than those seen in rats and dogs. In general, when other drugs induce phospholipidosis in humans, this is observed after medium, long term administration. No signs or symptoms of phosholipidosis has been observed after netupitant administration in humans, including the absence of lamellar bodies after 7 days administration of netupitant 450 mg in the multiple ascending dose study NP16601. Though the results in humans available so far are favourable, the toxicological significance of phospholipidosis is still unclear. Therefore drug-induced phospholipidosis may represent a potential risk. The risk of phospholipidosis (due to netupitant) classified as important potential risk is removed from the list of safety concerns in the RMP 2.7 for the reasons presented below: - Phospholipidosis may be of less concern for compounds that are administered for a short period (i.e., acute therapy) to a few weeks. Indeed, it is more commonly seen after prolonged administration of the offending agent. The fixed combination formulations are to be administered prior to each cycle of chemotherapy, given with an interval between cycles of at least 14 days; therefore the impact of this potential risk in comparison with the effectiveness for prevention of nausea and vomiting is considered insignificant or even null. - Cumulatively, up to the data lock point (10 October 2018) of the RMP 2.7 of Akynzeo, there are no post-marketing case reports of ADRs associated to phospholipidosis. No further evaluation is required for this safety concern as part of the pharmacovigilance plan.

Key Safety findings (from non-clinical studies)	Relevance to human usage
In the 6-month study (NETU-07-21) in rats with oral netupitant up to 10 mg/kg dose, increased absolute and relative liver weights in males and females and periacinar hepatocytes' hypertrophy in the livers of male and female rats were observed at the end of treatment at the highest dose tested. At the end of the recovery period centriacinar hepatocytes vacuolization in the livers of males and female rats was present. In the 9-month study (NETU-07-22) in dogs, at 10 mg/kg dose-level liver weights (absolute and relative) were increased only in males and minimal periacinar hepatocytic hypertrophy was observed in male dogs at the end of treatment. No significant changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were noticed. Liver weights and hepatocytic hypertrophy returned to normal after the 8-week treatment-free period.	
Reproductive toxicity and developmental toxicity Slight maternal toxicity was seen in rats and rabbits at netupitant dose levels of 10 and 30 mg/kg/day. 45, 51 With the exception of slightly reduced fetal body weight in rabbits at 30 mg/kg/day, litter parameters were unaffected. In the rat, marginally higher numbers of fetuses with tarsal hyperflexion and/or pes adductus were seen at 10 and 30 mg/kg/day. In the rabbit, slight dose related increases in the number of fetuses with positional anomalies of the fore and/or hind limbs, fused sternebra and/or supernumerary ribs were recorded at 10 and 30 mg/kg/day. In rabbits four foetuses from one litter in the 30 mg/kg/day group showed anomalies as cleft palate, microphthalmia and aphakia. Abnormalities of the lung were also observed in a pilot dose-ranging study45 in all groups including the controls. The foetal incidence ranged from 10% in control to 27% in the high dose group. A study (100793) with a higher number of animals compared to the pilot experiment in a small number of animals was performed to further investigate the effects of netupitant in rabbits. Anomalies such as cleft palate, microphthalmia and aphakia were not observed. **Genotoxicity** Netupitant did not show mutagenic or clastogenic activity in a standard battery of *in vitro* and *in vivo* genotoxicity tests.	The potential of a teratogenic effect of netupitant in humans is limited and based solely on the preclinical findings observed in rabbits and rats. The incidence of cleft palate in rats occurred at exposures approximately 7-fold greater than exposures seen in humans. No substantial evidences are available in clinical studies; therefore the likelihood of teratogenic effects may represent a safety concern.
Carcinogenicity and mutagenicity Performance of carcinogenicity studies is not required for the CINV indication.	

Key Safety findings (from non-clinical studies)	Relevance to human usage
General safety pharmacology Cardiovascular safety pharmacology studies were performed to investigate the effects of netupitant and its metabolites on the cardiovascular system. The results of these safety studies showed some effects on the cardiovascular system, while other studies were negative. Cardiovascular effects were observed in conscious dogs with netupitant and its main metabolite M1 only after repeated administration at the highest dose-levels (50 mg/kg/day for 14 days for netupitant and 30 mg/kg/day for 14 days for metabolite M1).	A central ECG evaluation was performed during several Phase I studies. In all clinical studies where ECGs were performed, analysis showed no significant QTc prolongations considered to be related to netupitant alone. The effects of netupitant and its metabolites in *in vitro* and *in vivo* studies were observed at concentrations/doses higher than the therapeutic dosages foreseen in clinical studies.
Mechanism of drug interactions In human liver microsomes, netupitant competitively inhibited the CYP3A4 mediated hydroxylation of testosterone and midazolam (apparent K_i of 1.1 and 2.2 µM, respectively). Results pointed to interactions of netupitant with drugs mainly metabolised by CYP3A4 cannot be excluded.	Clinical implications of these findings are expected and their clinical relevance will be evaluated in drug-drug interaction (DDI) clinical studies with the fixed combination. It can be predicted that the plasma concentrations of active ingredients CYP3A4 substrates might increase when co-administered with netupitant. The potential for DDI effects in humans when netupitant is co-administered with CYP3A4 substrates midazolam, erythromycin and dexamethasone has been investigated. Results showed an increase of plasma exposure of these agents.
Significant interaction in humans are not expected in co-administration of netupitant with vincristine (study NETU-06-15) and cyclophosphamide (NETU-09-10), based on performed *in vitro* studies in human liver microsomes, on the contrary to potential interaction with docetaxel (IC_{50} was 3.7 µM when docetaxel was used as a substrate) in *in vitro* study NETU-09-09. For the hydroxylation of diclofenac, catalysed by CYP2C9, the IC_{50} value of netupitant was approximately 20 µM. Other CYP450 isoenzymes (CYP1A2, CYP2C19, CYP2D6) were not inhibited by netupitant (IC_{50} > 100 µM). Netupitant at concentrations up to 20 µM and metabolites concentration up to 2 µM did not induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 activity in human hepatocytes.	The potential for DDI effects in humans when netupitant is co-administered with chemotherapeutic agents (e.g., etoposide, docetaxel cyclophosphamide) has been investigated. Significant DDI effects are not expected in humans when netupitant is co-administered with vincristine and cyclophosphamide. C_{max}/K_i<0.1, indicate a remote *in vivo* DDI. Mild increases in systemic exposure were shown for docetaxel and etoposide when co-administered with netupitant /palonosetron fixed combination. Based on the low plasma concentration of netupitant expected in humans, significant metabolic interactions with CYP2C9 metabolized drugs are considered unlikely. Results of a study in human healthy volunteers showed that the concurrent administration of netupitant with digoxin did not affect the systemic exposure to digoxin, a P-gp substrate, whereas it increases its C_{max} by 9%. It is not excluded that

Key Safety findings (from non-clinical studies)	Relevance to human usage
In vitro studies indicate that netupitant is an inhibitor of BCRP and P-gp transporters.	this effect maybe clinically relevant in cancer patients, mainly those with impaired renal function concomitantly administered drugs that are P-gp substrates. The relevance of a potential DDI effect on BCRP substrates should be considered when administering these agents along with netupitant in the cancer population.
Other toxicity-related information Netupitant does not appear to be irritating or sensitizing and was not antigenic. Netupitant was classed as a non-phototoxic compound in a previous assessment (Ref. MAA of AKYNZEO® hard capsules, Study report 1003840). However, in the subsequent assessment of fosnetupitant the compound was rated as phototoxic, resulting in a PIF of 2.50 and a Mean Photo Effect (MPE) of 0.288. This variation in the results was due to changes in the criteria for the classification introduced in the latest guideline for phototoxicity (OECD guideline 432, April 2004). Hence, a PIF value of 2.50 is indicative of probable phototoxicity (PIF > 2 and < 5), whereas a MPE value of 0.288 is predictive of phototoxicity (MPE > 0.15).	
FOSNETUPITANT/PALONOSETRON IV FIXED COMBINATION	
Repeat-dose toxicity Convulsive episodes were observed in dogs with the combination (fosnetupitant/palonosetron) only at high dose levels in a 4-week dog study after repeated administration. Convulsive episodes stopped after reduction of palonosetron dose. This effect can be related to the high dose of palonosetron 10 mg/kg IV. In a 4-week study in rats with the intravenous combination treatment-related changes were noted in the liver of both sexes treated with the high dose. The changes consisted of centrilobular hypertrophy associated with increased cytoplasmic eosinophilia, being of moderate degree in the males and of mild degree in the females. This change was correlated with trend of increased liver weight observed in both sexes treated with the high dose and a time-related trend was observed for recovery. No phospholipidosis was observed in toxicology studies with fosnetupitant. Phospholipidosis was not observed in lymphatic tissues, lung and liver	Convulsive episodes mainly associated to the palonosetron component constitute clinically relevant findings that will be monitored in the real life use even though the role of confounders cannot be ignored. No substantial evidences are available in clinical studies; therefore the likelihood of the occurrence of these events may represent a safety concern. The risk of convulsive events classified as important potential risk was removed from the list of safety concerns in the RMP 2.7 for the reasons presented below: - Post-marketing adverse drug reactions (ADRs) up to the data lock point (10 October 2018) of the RMP 2.7 of Akynzeo cumulatively include one case of seizure observed concomitantly with other reactions of substance-induced psychotic disorder, abnormal behavior, confusional state, disinhibition, suicide attempt and drug interaction; the case was confounded by several factors, including patient's medical history and an overdosing of dexamethasone. - During the clinical development program of the oral hard capsules formulation there were no related events; one serious event of seizures

Key Safety findings (from non-clinical studies)	Relevance to human usage
or in other organs in a 2-week or 4-week toxicology studies in rats with fosnetupitant administered intravenously up to 39.47 mg/kg/day (equivalent to 30 mg/kg/day of netupitant). Absence of phospholipidosis signs was also noted in a 2-week and 4-week studies in dogs administered up to 13.16 mg/kg/day (10 mg/kg/day of netupitant).	considered not related was due to the documented presence of brain metastases in a breast cancer patient, and one non-serious not related event of convulsion occurred in a female with metastatic breast cancer. - In study NEPA 15-18 one NEPA IV treated lung cancer patient presented a serious not related event, namely an episode of seizure due to the presence of brain metastases. - There are no scientific evidences to suspect the possibility of a causal relationship with the medicinal product as other factors were the key determinants. - Preclinical data show that some effects with the IV combination have been reported in the central nervous system with convulsions seen after repeated treatment which are likely related to the high dose of palonosetron IV. This effect is not of concern given that convulsions were never observed in the clinical studies with the oral and the IV combination. No further evaluation is required for this safety concern as part of the pharmacovigilance plan. Liver function test was to be assessed at pre-defined time points across the safety study to monitor the potential of liver toxicity associated to the intravenous fixed combination formulation. The analysis of the AEs reported during the safety study comparing the IV versus the oral fixed combination showed that the percentage of patients with increased AST or ALT was higher in the oral treatment group compared to the intravenous treatment arm, while related AEs occurred in a similar percentage of patients. None of these laboratory abnormalities was considered a serious related AE.

Key Safety findings (from non-clinical studies)	Relevance to human usage
	Even though the clinical results are reassuring on the safety profile of fosnetupitant at hepatic level, considering the setting of patients candidate to receive the fixed combination in the real world; the clinical and toxicological significance of these findings still deserves in depth assessment to further characterize this safety concern in terms of frequency, symptoms in a real life use, potential risk factors, and consequences; therefore increase of transaminases may represent a potential risk. The risk of liver transaminases increase classified as important potential risk is removed from the list of safety concerns in the RMP 2.7 for the reasons presented below: - Post-marketing ADRs of liver transaminases increased in the SOC Investigations up to the data lock point (10 October 2018) of the RMP 2.7 of Akynzeo cumulatively are 2 serious for ALT increased and 1 for AST increased, respectively. One serious solicited case of aspartate aminotransferase increased and alanine aminotransferase increased pertained to a female patient with ovarian cancer with liver enzymes already increased before the administration of Akynzeo and chemotherapy which worsened upon chemotherapy treatment. The other serious reaction of ALT increased involved a female patient with breast cancer who presented a higher value of ALT (out of normal range) before Akynzeo and chemotherapy administration. No other details were provided including the outcome of the event. - The above considerations indicate that the use of the Akynzeo for emesis control in CINV patients very unlikely increases liver injury risks in patients receiving chemotherapy similarly to other anti-emetics such as aprepitant and a 5-HT3RAs or palonosetron as single agent, which are drugs commonly used in clinical practice for chemotherapy induced nausea and vomiting prevention. - Liver transaminases increase is tabulated as uncommon undesirable effect in section 4.8 of the SmPC. No further evaluation is required for this safety concern as part of the pharmacovigilance plan.

Key Safety findings (from non-clinical studies)	Relevance to human usage
General safety pharmacology QT prolongation was observed in the 4-week toxicology study and in the telemetered study in dogs with the combination after repeated administrations. In the 4-week study, the intravenous administration of the combination of fosnetupitant + palonosetron caused transient and reversible increased heart rate at mid dose (females only) and at high dose (both sexes) levels. These changes were associated with a transient and reversible increase (without dose-related effects) in QTc (QTcF and QTcv) intervals at the high dose level (male and female animals) and at the mid dose (males only).	In animal studies the metabolite M1 is considered to play a major role in QT prolongation. However, it should be considered that in humans the plasma levels of M1 are much lower than in animal species thus the findings obtained in animals are not directly correlated to human cardiotoxicity. Moreover the accumulation of this metabolite and the parent compound netupitant in humans is unlikely due to the fact that in clinical practice the oral or IV combinations are administered once prior to a chemotherapy cycle. Nevertheless the relevance of these data should be considered in relation to the proposed single administration.

Key Safety findings (from non-clinical studies)	Relevance to human usage
NETUPITANT/PALONOSETRON ORAL FIXED COMBINATION	
Repeat-dose toxicity	
In 28-day study in dogs (NETU-06-05), in the 15/7.5 mg/kg and 20-15/15 mg/kg dose-levels groups, transient CNS effects were noted varying in severity from slight tremors to severely cramped posture and severe seizure-like episodes. The onset of these severe signs varied from minutes after dosing to a few hours after dosing. Minimal to mild hepatocyte hypertrophy was noted in some animals at the end of treatment, which correlated with a high liver weight in one animal. Prolonged ST- and QT-intervals (before and after correction) were noted throughout treatment, notably in males, in 20-15/15 mg/kg group. In females a similar pattern was noted, but less pronounced. Arrhythmias were not present. In a 4-week study in rats with the combination of palonosetron and netupitant at doses 10/3, 18/10 and 60/30 mg/kg (NETU-06-03), changes in clinical signs and blood chemistry, reduced body weight and food consumption, and increased liver weight were observed with the dose of 60/30 mg/kg. All groups showed a minimal hepatocytes' hypertrophy (observed also after the recovery period in the two highest dosage groups). Similar findings to netupitant studies NETU-07-18 (13-week dog) and NETU-07-19 (13-week rat) associated with changes in liver weight, hepatocytic hypertrophy and increased liver enzymes (increase of transaminases) were detected in studies with the fixed combination NETU-06-03, NETU-06-05 and in 13-week study NETU-07-19 in rats. It was determined that liver findings may be regarded as secondary to the induction of liver enzymes involved in drug metabolism.	These pre-clinical findings, predictive of a cardiac potential effect prompted to an ICH E14-compliant study in healthy volunteers (NETU-07-20). There is no evidence of significant changes of QT prolongation, with the combination of netupitant and palonosetron in healthy volunteers; however the potential of cardiac effects in patients (QT prolongation) represents a potential risk. The potential of liver transaminases increase for humans is unpredictable in cancer patients who represent the target population because of the concomitant presence of other predisposing risk factors (filiae, comedications, pre-existing impaired liver function).
General safety pharmacology Palonosetron/netupitant combination was administered orally over 15 days to dogs at doses of 10/2, 10/10 and 10/50 mg/kg in study NETU-07-05. After 7 days of treatment, a dose-dependent decrease in atrio-ventricular (AV) conduction and in ventricular depolarization rate associated with a slight prolongation of ventricular repolarization was observed at the doses of 10/10 mg/kg and 10/50 mg/kg. After 14 days of treatment, these effects were increased and were associated with a prolongation of ventricular repolarization at the dose of 10/50 mg/kg. The NOAEL of fixed combination on cardiovascular	The relevance of these data should be considered in relation to the proposed single administration of the combination netupitant/palonosetron to prevent nausea and emesis during chemotherapy. There is no evidence of significant changes of QT prolongation, with the combination, in healthy volunteers (NETU-07-20).

Key Safety findings (from non-clinical studies)	Relevance to human usage
parameters corresponds to 10/2 mg/kg oral administration. A combination of palonosetron and netupitant induced a slight prolongation of action potential duration in an *in vivo* guinea pig study. A combination of palonosetron/netupitant at dose of 3/30 mg/kg did not produce proarrhythmic effects *in vivo* in study NETU-06-26 performed in rabbits.	
Mechanism of drug interactions For the non-clinical DDI data, refer to sections devoted to performed palonosetron and netupitant DDI studies.	In healthy volunteers approximately 2-fold increases in netupitant exposure were observed when CYP3A4 inhibitor ketoconazole was co-administered with the fixed combination(NETU-10-11). Likewise, co-administration of a CYP3A4 inducer (rifampicin) resulted in a 5-6 fold reduction in netupitant exposure (NETU-10-11). The co-administration of netupitant and palonosetron had no significant effect on the exposure to ethinylestradiol and increased systemic exposure to levonorgestrel by about 40% in healthy female subjects enrolled in study NETU-10-08 with combined oral contraceptives. The co-administration of netupitant and palonosetron resulted in an increased exposure of the investigated chemotherapeutic agents (docetaxel, etoposide and cyclophosphamide) metabolized by CYP3A4 in cancer patients enrolled in study NETU-10-09.

Overall, non-clinical data currently available lead to the conclusion that no additional non-clinical data are needed if the fixed combination is going to be used in special populations (e.g. renally and hepatically impaired patients).

Summary of the fixed combination safety concerns provided in Table 5 includes well-known safety concerns of palonosetron, and safety concerns which originated from the performed non-clinical studies with fosnetupitant or netupitant alone and the IV and oral fixed combination (i.e., from the non-clinical development programme of the fixed combination).

Table 5 Summary of safety concerns from non-clinical data for the fixed combination

Safety concern
Important identified risk
None
Important potential risk
QT/QTc interval prolongation
Convulsive events (due to palonosetron)
Liver transaminases increase
Interaction with CYP3A4 inhibitors and inducers (due to netupitant)
Interaction with CYP3A4 substrates (due to netupitant)
Phospholipidosis (due to netupitant)
Interaction with BCRP substrates (due to netupitant)
Interaction with P-gp (due to netupitant)
Effects on fertility
Teratogenic effects
Missing information
None

Part II: Module SIII - Clinical trial exposure

This section was updated based on the latest PSUR (3-year PSUR No.16 with the data lock point on 10 October 2024, submitted to the EMA on 17 December 2024; PSUSA/00010393/202410, EMA reference EMA/PSUR/0000248514) and data regarding the new oral suspension formulation.

New clinical data regarding the new oral suspension formulation of netupitant/ palonosetron combination product are presented. The newly developed oral suspension of netupitant and palonosetron will allow for easier administration to patients who have difficulties or cannot swallow the available capsule form, without the need for intravenous infusion. It can be stored at room temperature, is in a ready-to-use form and it consists of a single administration preventing both acute and delayed phase CINV.

In this section demographic data relevant to patient's exposure to the IV fixed combination formulation are presented separately at the start of the module; followed by analogue data for the oral fixed combination formulation.

SIII.1 Brief overview of development

The IV formulation was developed as a benefit for patients who are not able to tolerate an oral formulation. The intravenous formulation is a combination of fosnetupitant (water soluble phosphorylated pro-drug of netupitant rapidly converted to netupitant in vivo following IV administration) and palonosetron (IV NEPA fixed combination). The IV NEPA fixed combination program was based on a bioequivalence approach and developed as a line extension of the oral fixed combination. In Europe, oral Akynzeo® was approved in May 2015. The Akynzeo® IV, in the form of powder for concentrate for solution for infusion, was authorized in Europe on 16 March 2020 (EU/1/15/1001/003), and the concentrate for solution for infusion, containing the same excipients of the lyophilized powder, was approved in the EU on 12 November 2021 (EU/1/15/1001/004), both as line extensions of Akynzeo hard capsules with the same indications.

The 5-HT_3 and NK_1 RAs are among the drugs of first choice for an optimal antiemetic prophylaxis in cancer patients receiving chemotherapy. Clinical practice guidelines in oncology recommend that patients

receiving HEC or MEC regimens should be treated with a combination of a 5-HT3 RA, NK1 RA and a systemic corticosteroid.

The clinical development programme of the IV fixed combination comprised six Phase I trials (three PK and safety studies in healthy volunteers, PNET-12-23, PNET-13-63 and PNET-22-08, with fosnetupitant administration, one PK and safety study in cancer patients, NEPA-15-19, with fosnetupitant-palonosetron fixed combination administration, one PK and safety study in healthy volunteers, NEPA-19-13, with IV NEPA fixed combination administered as IV bolus versus 30-minute IV infusion, one bioequivalence study in healthy subjects, NEPA-18-39, with IV NEPA fixed combination and oral NEPA), and one Phase 3 safety study with fosnetupitant-palonosetron fixed combination compared to oral fixed combination (NEPA-15-18). In addition, an efficacy trial on the palonosetron component (PALO-15-17) was designed and agreed with the FDA to demonstrate the non-inferiority of a 30-minute infusion compared to the approved (labeled) 30-second IV bolus dose in cancer patients.

The clinical development programme of the oral fixed combination comprises a total of 26 Phase 1 studies including one [^{14}C]-netupitant ADME study, 4 BE studies and 1 study in special population of patients (PK study in patients with liver impairment – NETU-10-10) conducted with the oral formulations (netupitant alone, netupitant/palonosetron extemporaneous combination and the fixed combination) in both healthy and cancer patients. In parallel to the clinical development programme for the sought indication, a single Phase I study was conducted to evaluate the use of netupitant/palonosetron combination in an acute pain model (NETU-09-11). In light of the results of this preliminary experience, no further trials have been planned to evaluate the potential effect of the oral combination in the acute pain.

A Phase 2 dose-ranging efficacy study (NETU 07-07) in cancer patients was conducted with the extemporaneous combination of netupitant and palonosetron orally, administered at escalating doses to patients receiving their first cycle of highly emetogenic chemotherapy.

An additional Phase 2 study (NETU-08-03) with continuous 8-week use of netupitant alone at doses up to 200 mg in patients with overactive bladder was completed. Of these, 62 patients received oral netupitant 50 mg, 61 the dose of 100 mg and 60 patients 200 mg. The results precluded further investigation of netupitant alone in this indication.

The fixed combination was given as single oral dose to cancer patients in Phase 3 clinical studies undergoing multiple cycles of chemotherapy (NETU 08-18 and NETU 10-29).

The oral fixed combination was first administered in a pilot bioequivalence (BE) study NETU-08-12, assessing the BE of the new netupitant/palonosetron fixed combination (300 mg/0.50 mg) versus combination of the single components netupitant 300 mg and palonosetron 0.50 mg after single dose administration in healthy male volunteers. This pilot BE study was followed by the pivotal BE study NETU-09-07 of the fixed combination compared with single components' administration. It was concluded that the treatments are bioequivalent with respect to both netupitant and palonosetron rate and extent of absorption.

Moreover, NEPA-18-39, a Phase 1, crossover bioequivalence study of IV NEPA (235 mg fosnetupitant/0.25 mg palonosetron) and oral NEPA (300 mg netupitant/0.5 mg palonosetron) in male and female healthy Chinese subjects has been conducted.

Seven clinical studies have been conducted with the oral NEPA fixed combination as test treatment (NETU-12-07, NEPA-14-02 and NEPA-14-39) or with the oral NEPA fixed combination given as control treatment (PNET-12-23, NEPA-15-18, NEPA 17-05 and NEPA-18-39). The studies NETU-12-07 and NEPA-14-02 were conducted in the frame of the application for the registration of the oral fixed combination in China. Study NEPA 17-05 assessed the safety and the efficacy of IV fosnetupitant/palonosetron (260 mg/0.25 mg) combination compared to oral NEPA fixed combination for the prevention of chemotherapy

induced nausea and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in 400 women with breast cancer.

A new oral suspension with the same fixed combination of 300 mg netupitant and 0.5 mg palonosetron as the capsule has been developed. A clinical trial NEPA-23-01 has been conducted to demonstrate bioequivalence of the new oral suspension formulation to the approved hard capsule formulation. The trial was conducted according to an open-label, randomised, single centre, two-treatment, four-period, two-sequence replicative design. 74 healthy subjects were enrolled at one study centre to receive a single dose of 300 mg netupitant and 0.5 mg palonosetron during each period. Of the total 202 TEAEs reported, 158 were mild in intensity, and 44 were moderate in intensity and most had resolved at the end of the study. No SAEs or severe TEAEs were reported. Overall, frequency of TEAEs was similar for the two tested treatments and the suspension showed a similar safety profile as the marketed hard capsule.

All performed studies with the oral netupitant, extemporaneous combination or fixed combination during the clinical development program are summarized in Table 6.

Table 6 Clinical studies (oral netupitant, extemporaneous combination, oral fixed combination)

Clinical Study Number	Type of Clinical Study
NP16599 (1012084)	Netupitant on midazolam, erythromycin DDI study
NP16600 (1007929)	Food effect and age effect PK study
NP16601 (1014020)	Multiple ascending dose PK and safety study
NP16602 (1009726)	Apomorphine PD study, single ascending dose
NP16603 (1007847)	Single, ascending dose PK and safety study
BP17408 (1013846)	BA of SDS vs. SE netupitant capsules; food effect of SE capsules
NETU-06-06	Oral netupitant 150 mg and oral palonosetron 0.75 mg DDI study
NETU-06-07	Oral netupitant and oral dexamethasone DDI/PK study
NETU-06-08	PET oral netupitant NK-1 receptor occupancy study
NETU-06-27	Oral netupitant 450 mg and oral palonosetron 0.75 mg DDI PK/safety study
NETU-07-01	Oral netupitant 450 mg and oral digoxin DDI PK/safety study
NETU-07-20	E14 Thorough QT, ECG/safety study
NETU-08-12	Pilot BE of fixed dose netupitant/palonosetron vs. single components
NETU-09-07	Pivotal BE of fixed dose netupitant/palonosetron vs. single components
NETU-09-11	Phase I to assess analgesic effect in an acute pain model
NETU-09-21	Phase I ADME study with radiolabelled netupitant
NETU-10-08	Phase I DDI with oral contraceptives (ethinylestradiol + norgestrel)
NETU-10-09	Phase I DDI with cyclophosphamide, docetaxel and etoposide in cancer patients
NETU-10-10	Phase I PK in patients with hepatic insufficiency
NETU-10-11	Phase I DDI with a CYP3A4 inhibitor (ketoconazole) and inducer (rifampin)
NETU-10-12	Phase I food and age effect study
NETU-11-02	Phase I BE study on 2 fixed combination manufacturers
NETU-11-23	Phase I bioavailability study on 2 different dissolution batches
NEPA-23-01	Phase I BE study of the new oral suspension formulation versus the approved hard capsule formulation
NEPA-18-39	Phase I, crossover BE study of IV NEPA and oral NEPA in male and female healthy Chinese subjects
NEPA-14-02	Phase I single center (in China) PK study

Clinical Study Number	Type of Clinical Study
NEPA-14-39	Phase I, DDI, single center (in Switzerland), crossover study
PNET-12-23	Phase I, single center (in Germany) PK and safety study
NETU-07-07	Phase II study in cancer patients
NETU-08-03	Phase II study in overactive bladder
NETU-08-18	Phase III efficacy study in cancer patients
NETU-10-29	Phase III safety study in cancer patients
NETU-12-07	Phase III efficacy and safety of a single oral NEPA fixed combination in cancer patients compared to an extemporary combination of granisetron and aprepitant
NEPA-15-18	Phase III safety and efficacy of a single dose of IV NEPA fixed combination infused in 30 min, with oral dexamethasone; oral NEPA fixed combination was a control group
NEPA-17-05	Phase IIIb safety and efficacy of IV NEPA fixed combination versus oral NEPA fixed combination

ADME, absorption, distribution, metabolism, excretion; BA, bioavailability; BE, bioequivalence; CYP3A4, cytochrome P450 isoform 3A4; DDI, drug-drug interaction; E14, International Conference on Harmonisation (ICH) E14-compliant; ECG, electrocardiogram; HEC, highly emetogenic chemotherapy; NK-1, neurokinin 1; PD, pharmacodynamics; PET, positron emission tomography; PK, pharmacokinetics; QT, QT interval represents the duration of ventricular depolarization and subsequent repolarisation; SDS, sodium dodecyl sulphate; SE, sucrose ester

SIII.2 Clinical Trial exposure

Exposure in healthy volunteers to IV NEPA fixed combination corresponds to 50 subjects, that are those treated in the completed clinical trials: 8 subjects in NEPA-19-13 (safety and PK study) and 42 subjects in NEPA-18-39 (bioequivalence study). Of those, 31 were males and 19 were females, all in the age category of 18-65 years. In addition, 7 were Caucasian, 42 Asian, and 1 with race classified as other.

In three clinical studies (PNET-12-23, PNET 13-63 and PNET 22-08), exposure in healthy volunteers was performed for fosnetupitant administered as single agent. In the PNET-12-23 and PNTE-13-63 studies, doses of fosnetupitant lower than or equal to 260 mg IV were administered to 169 subjects, while doses more than 260 mg up to 390 mg were given to 37 subjects. Since these studies were conducted with a cross-over design, treated subjects have been counted in all treatments foreseen by the sequence and once in the total sum of number of subjects. Of these 108 were males and 70 females, all in the age group of 18-45 years. The vast majority were Caucasian (N=165); 6 were Black or African American, 4 of Asian origin and 2 reported as "Other".

The PNET-22-08 Phase 1 clinical trial is an open label, single dose, two parts study in male and female healthy subjects aiming to assess the safety and pharmacokinetics of Fosnetupitant 235 mg administered as IV bolus and of derived Netupitant and Netupitant metabolites. In total, 40 subjects received one single IV dose of fosnetupitant 235 mg ready to use solution as a single injection with a varying duration according to the admittance cohort, and 10 subjects received one single IV dose of undiluted IV NEPA fixed combination (IV Akynzeo in 20 mL injectable solution) as one single 30-min IV infusion.

There were three pivotal trials that administered the IV NEPA fixed combination in cancer patients (NEPA-15-18, NEPA-17-05 and NEPA-15-19). A total of 439 cancer patients received IV NEPA fixed combination. Of these, a total of 203 patients were treated in NEPA-15-18 (safety study) and 200 in NEPA-17-05 (safety study), while 36 in NEPA-15-19 (PK study in cancer patients). Overall, the cancer population treated with the NEPA IV formulation (N=439) was predominantly represented by female patients. Most patients were Caucasian and only 4 African Americans treated in the NEPA IV fixed combination group;

most patients belong to the age category 18 - <65 years. Exposure by gender and by gender and age for cancer patients receiving IV NEPA in these studies is provided in Table 7 and Table 8, respectively.

Table 7: NEPA IV Patient exposure stratified by gender

Gender	Nr. of patients
Male	124
Female	315
Total	**439**

Table 8: NEPA IV Patient exposure stratified by gender and age group

Age group (years)	Nr. of patients(n, %)		
	Male	Female	Total
18 - <65 years	73 (58.9)	242 (76.8)	315 (71.8)
65 - <75 years	46 (37.1)	62 (19.7)	108 (24.6)
75 - <85 years	5 (4.0)	11 (3.5)	16 (3.6)
Total sum	**124**	**315**	**439**

Cumulative exposure to the fixed combination formulations in clinical trials has been calculated starting from the product Development International Birth Date (DIBD, 22 September 2008, the approval date of study NETU-08-12) considering the number of patients treated with the fixed combination of netupitant and palonosetron in Helsinn completed trials. Overall, since the start of the clinical development program, a total of 2737 patients (cancer adult patients) were exposed to netupitant and palonosetron (given as oral extemporaneous combination, as oral fixed combination or as intravenous fixed combination) in clinical studies, of these 1850 patients in 5 Phase III studies (NETU-08-18, NETU-10-29, NETU-12-07, NEPA-15-18 and NEPA-17-05) received the oral fixed combination.
With reference to the comparator administered in studies with the oral fixed combination, a total of 725 patients were exposed to palonosetron alone in NETU-08-18 and 136 patients were exposed to palonosetron alone in NETU-07-07. Aprepitant and palonosetron were given to 104 patients in study NETU-10-29 and aprepitant and granisetron were given to 416 patients in study NETU-12-07. In the phase I DDI study (NETU-10-09) 40 patients received both oral fixed combination and palonosetron alone in two periods according to the cross-over study design.

In the phase III study NEPA-15-18, both oral fixed combination and NEPA IV fixed combination were administered.

Overall, 404 patients (203 patients NEPA IV fixed combination and 201 patients oral fixed combination) were treated in this study.

In Table 9 and

Table 10 the number of patients and the overall cancer patient exposure is presented for netupitant/palonosetron and for comparators, respectively.

Table 9 Exposure by Phase I, II and III studies in adult cancer patients – netupitant/palonosetron

Study	Dose (mg)	Number of exposed subjects	Number of exposures*
NETUPITANT/PALONOSETRON (oral)			
NETU-08-18	300 / 0.5	725	2,983
NETU-10-09	300 / 0.5	40	40
NETU-10-29	300 / 0.5	308	1,446
NETU-12-07	300 / 0.5	413	413
NEPA-15-18	300 / 0.5	201	645
NEPA-17-05	300 / 0.5	203[(a)]	660

	Sub-Total	**1,890**	**6,187**
FOSNETUPITANT/PALONOSETRON			
NEPA-15-18 (IV)	235 / 0.25	203	667
NEPA-17-05 (IV)	235 / 0.25	200	641
NEPA-15-19	235 / 0.25	36	36
	Sub-total	**439**	**1344**
NETUPITANT/PALONOSETRON (oral)**			
NETU-07-07	100 / 0.5	135	135
	200 / 0.5	138	138
	300 / 0.5	136	136
	Sub-Total	**409**	**409**
TOTAL		**2,737[(a)]**	**7,940**

**No limit in the number of repeated consecutive cycles for each patient in studies NETU-08-18 and NETU-10-29. In study NEPA-15-18 patients were treated up to 4 repeated consecutive cycles. Therefore multiple exposures to netupitant/palonosetron considered.*

***Extemporaneous combination*

[#] Fosnetupitant 235 mg as free base

(a) A patient received active IV NEPA fixed combination in cycles 1,3,4 and active ORAL NEPA fixed combination in Cycle 2 and therefore it is counted in both treatment groups but only once in the totals.

Table 10 Exposure by Phase I, II and III studies in adult cancer patients – comparators

Study	Dose (mg)	Number of exposed subjects	Number of exposures*
PALO alone			
NETU-08-18	0.5	725	2,987
NETU-10-09	0.5	40	40
NETU-07-07	0.5	136	136
APREPITANT plus ONDANSETRON			
NETU-07-07	125 (Day 1), 80 (Day 2,3) plus 32 IV	134	134
APREPITANT plus PALONOSETRON			
NETU-10-29	125 (Day 1), 80 (Day 2,3) plus 0.5	104	515
APREPITANT plus GRANISETRON			
NETU-12-07	125 (Day 1), 80 (Day 2,3) plus 3	416	416
Sub-Total (aprepitant plus $5HT_3$)		**654**	**1,065**
TOTAL (any comparator)		**1,555**	**4,228**

** No limit in the number of repeated consecutive cycles for each patient in studies NETU-08-18 and NETU-10-29. In study NEPA-15-18 patients were treated up to 4 repeated consecutive cycles. Therefore, multiple exposures to netupitant/palonosetron considered*

Patient exposure per treatment dose group, stratified per age, gender and racial group is presented in Table 11 and Table 12.

Table 11 Exposure by treatment, age, gender in adult cancer patients

Dose (mg)	Age category (Years)	Number of subjects (n, %)		
		Male	**Female**	**Total**
NETUPITANT/PALONOSETRON (oral)				
300 / 0.5	<18	0	0	0
	18 - <65 years	455 (76.6)	1,076 (83.0)	1,531 (81.0)
	65 - <75 years	120 (20.2)	196 (15.1)	316 (16.7)
	75 - <85 years	19 (3.2)	24 (1.9)	43 (2.3)
	Sub-Total	**594**	**1,296**	**1,890**
NETUPITANT/PALONOSETRON (oral)*				
100 / 0.5	<18	0	0	0
	18 - <65 years	64 (83.1)	48 (82.8)	112 (83.0)
	65 - <75 years	11 (14.3)	10 (17.2)	21 (15.6)
	75 - <85 years	2 (2.6)	0 (0.0)	2 (1.5)
	Sub-Total	**77**	**58**	**135**

200 / 0.5	<18	0	0	0
	18 - <65 years	68 (85.0)	50 (86.2)	118 (85.5)
	65 - <75 years	11 (13.8)	7 (12.1)	18 (13.0)
	75 - <85 years	1 (1.3)	1 (1.7)	2 (1.4)
	Sub-Total	**80**	**58**	**138**
300 / 0.5	<18	0	0	0
	18 - <65 years	67 (87.0)	49 (83.1)	116 (85.3)
	65 - <75 years	9 (11.7)	10 (16.9)	19 (14.0)
	75 - <85 years	1 (1.3)	0 (0.0)	1 (0.7)
	Sub-Total	**77**	**59**	**136**
FOSNETUPITANT/PALONOSETRON				
235 / 0.25**	<18	0	0	0
	18 - <65 years	73 (58.9)	242 (76.8)	315 (71.8)
	65 - <75 years	46 (37.1)	62 (19.7)	108 (24.6)
	75 - <85 years	5 (4.0)	11 (3.5)	16 (3.6)
	Sub-total	**124**	**315**	**439**
TOTAL		**952**	**1,785[(a)]**	**2,737[(a)]**

**Extemporaneous combination in study NETU-07-07*
*** Fosnetupitant 235 mg as free base (NEPA 15-18, NEPA-17-05 and NEPA-15-19)*
(a) Patient NEPA-17-05/132001 (F, 63y, White) received active IV NEPA fixed combination in cycles 1,3,4 and active ORAL NEPA fixed combination in Cycle 2 and therefore it is counted in both treatment groups but only once in the totals.

Table 12 Exposure by treatment, ethnic or racial origin, gender, in adult cancer patients

Dose (mg)	**Ethnic/racial origin**	**Number of subjects (n, %)**		
		Male	**Female**	**Total**
NETUPITANT/PALONOSETRON (oral)				
300 / 0.5	White	265 (44.6)	994 (76.7)	1,259 (66.6)
	Black	0 (0.0)	13 (1.0)	13 (0.7)
	Hispanic	0 (0.0)	46 (3.5)	46 (2.4)
	Asian	329 (55.4)	234 (18.1)	563 (29.8)
	Other	0 (0.0)	4 (0.3)	4 (0.2)
	Unknown	0 (0.0)	5 (0.4)	5 (0.3)
	Sub-Total	**594**	**1,296**	**1,890**
NETUPITANT/PALONOSETRON (oral)*				
100 / 0.5	White	77 (100.0)	58 (100.0)	135 (100.0)
	Sub-Total	**77**	**58**	**135**
200 / 0.5	White	79 (98.8)	58(100.0)	137 (99.3)
	Asian	1 (1.3)	0 (0.0)	1 (0.7)
	Sub-Total	**80**	**58**	**138**
300 / 0.5	White	77 (100.0)	59 (100.0)	136 (100.0)
	Sub-Total	**77**	**59**	**136**
FOSNETUPITANT/PALONOSETRON				
235 / 0.25**	White	122 (98.4)	304 (96.5)	426 (97.0)
	Black	2 (1.6)	4 (1.3)	6 (1.4)
	Asian	0 (0.0)	1 (0.3)	1 (0.2)
	American Indian or Alaska Native	0 (0.0)	1 (0.3)	1 (0.2)
	Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.3)	1 (0.2)
	Unknown	0 (0.0)	4 (1.3)	4 (0.9)
	Sub-total	**124**	**315**	**439**
TOTAL		**952**	**1,785[(a)]**	**2,737[(a)]**

**Extemporaneous combination in study NETU-07-07*
*** Fosnetupitant 235 mg as free base (NEPA 15-18, NEPA-17-05 and NEPA-15-19)*

With regards to special population studies, a phase I study (NETU-10-10) in liver impaired subjects has been conducted. In this study a total of 36 subjects have been enrolled and exposed to the oral fixed combination of netupitant and palonosetron: 18 subjects with liver impairment (8 mild, 8 moderate and 2 severe) and 18 matching healthy subjects (Table 13).

Table 13 Exposure by special populations

Treatment	Special population	Number of exposed subjects[a]
NETUPITANT/PALONOSETRON	Hepatic impairment	
	Mild	8
	Moderate	8
	Severe	2
TOTAL		**18**

[a] *Phase I study NETU-10-10*

Table 14 shows the number of healthy subjects administered netupitant and palonosetron fixed combination as one single dose or two single doses (in different periods of a cross-over trial) in each study. Cumulative exposure by age, gender and racial group is provided in *NEPA-18-39 *is a 2x2 cross-over study of NEPA IV and NEPA Oral, with 44 randomized subjects*

Table 15 and Table 16.

Table 14 Exposure by study in Phase I healthy volunteer studies

Treatment	Study	Number of subjects
netupitant/palonosetron	NETU-08-12	8
	NETU-09-07	49
	NETU-10-08	24
	NETU-10-12	36
	NETU-10-11	35
	NETU-09-11	28
	NETU-11-02	88
	NETU-11-23	24
	NEPA-14-02	18
	NEPA-14-39	24
	NEPA-18-39*	44
	NEPA-19-13	8
	NEPA-23-01	74
	PNET-22-08	10
	PNET-12-23	134
TOTAL		**604**

**NEPA-18-39 is a 2x2 cross-over study of NEPA IV and NEPA Oral, with 44 randomized subjects*

Table 15 Exposure by age group and gender in Phase I healthy volunteer studies

Treatment	Age category (Years)	Number of subjects (n, %)*		
		Male	Female	Total
netupitant/palonosetron	<18	0	0	0
	18 - <65 years	394 (98.5)	198 (97.1)	592 (98.0)
	65 - <75 years	6 (1.5)	5 (2.5)	11 (1.8)
	75 - <85 years	0 (0.0)	1 (0.5)	1 (0.2)
Total		**400**	**204**	**604**

**Data from studies: NETU-08-12, NETU-09-07, NETU-10-08, NETU-10-12, NETU-10-11, NETU-09-11, NETU-11-02, NETU-11-23, NEPA-14-02, NEPA-14-39, PNET-12-23, NEPA-18-39, NEPA-23-01, PNET-12-23, PNET-22-08*

Table 16 Exposure by ethnic or racial origin in Phase I healthy volunteer studies

Treatment	Ethnic/racial origin	Number of subjects (n, %)*		
		Male	Female	Total
netupitant/palonosetron	White	335 (83.8)	171 (83.8)	506 (83.8)
	Black	6 (1.5)	3 (1.5)	9 (1.5)
	Hispanic	6 (1.5)	4 (2.0)	10 (1.7)
	Other	6 (1.5)	5 (2.5)	11 (1.8)
	Asian	47 (11.8)	21 (10.3)	68 (11.3)
Total		**400**	**204**	**604**

**Data from studies: NETU-08-12, NETU-09-07, NETU-10-08, NETU-10-12, NETU-10-11, NETU-09-11, NETU-11-02, NETU-11-23, NEPA-14-02, NEPA-14-39, PNET-12-23, NEPA-18-39, NEPA-23-01, PNET-12-23, PNET-22-08*

The total number of females exposed to the fixed combination of netupitant and palonosetron was higher compared to males as phase III study NETU-08-18 mostly involved patients with breast cancer scheduled to receive anthracycline based chemotherapy. The most representative age group was the age category from 18 to 65 years and the population predominantly white. The results are consistent with literature data indicating that females are more prone to chemo-induced emesis: observational studies show that females represent the largest group of patients being treated for CINV, ranging from 60% to 70% of the entire patient population, with the mean and median age around 55 years (Hilarius DL et al. 2012; Molassiotis A et al. 2008).

Likewise, demographic data of study NEPA 17-05 are coherent with those originated from study NETU 08-18. In study NEPA 17-05, the safety population comprised 402 female patients. The mean age was 55.4 years. A slightly larger proportion of patients were in the age class ≥55 years vs <55 years (55.2% vs 44.8%, respectively). Nearly all patients were white (93.3%) and postmenopausal (61.7%). Further information on this study can be found in Part II: Module SV - Post-authorisation experience, section SV.1 Post-authorisation exposure.

Paediatric population

A PK/PD dose finding study in pediatric population was committed by the FDA at the time of oral Akynzeo authorization approval. This study (NEPA 15-31) was planned to enroll 92 pediatric cancer patients aged 0 to < 18 years undergoing treatment with emetogenic chemotherapy, including highly emetogenic chemotherapy.

A single oral dose of netupitant (1.33 mg/kg or 4 mg/kg) was administered concomitantly (in separate liquid formulations) with a single oral dose of 20 µg/kg palonosetron, that is the approved recommended dose to prevent chemotherapy induced nausea and vomiting in children.

A Data Safety Monitoring Board (DSMB) was convened at regular intervals for the evaluation of safety data during the study in order to perform a qualitative safety assessment.

At the beginning of the study, enrollment was open only to patients aged ≥1 year who were randomized to 1 of the 2 netupitant treatment groups and patients aged 6 to <12 months who were treated with the netupitant lower dose (1.33 mg/kg).

As soon as the first 3 patients in the 6 to <12 months age class who were treated with the lower netupitant dose (1.33 mg/kg) completed the study without safety and tolerability concerns, as assessed by the DSMB, the enrollment in the higher netupitant dose group (4 mg/kg) of the same age class (6 to <12 months) was started.

As soon as 6 patients in the 6 to <12 months age class (3 patients for each netupitant dose group) completed the study without safety and tolerability concerns, a decision by the DSMB was made whether a) all remaining patients 6 to <12 months could be randomized to 1 of the 2 netupitant doses and start the assigned treatment, and b) the lower age class 3 to <6 months could start treatment with the lower netupitant dose.

Enrollment of the remaining cohorts occurred in parallel, keeping the original treatment dose escalation scheme: 1) the first 3 patients were treated with the lower netupitant dose, and 2) as soon as the first 3 patients completed the study without safety and tolerability concerns, as assessed by the DSMB, enrollment in the higher netupitant dose group in the same age class was started.

A total of 67 patients were enrolled and 66 were treated with the study drug: 34 (100%) patients in the Lower Netupitant Dose Group and 32 (97.0%) patients in the Higher Netupitant Dose Group.

Forty-four (44) patients (66.7%) received highly emetogenic chemotherapy and 22 (33.3%) moderately emetogenic chemotherapy.

The table below shows the distribution by age group according to each tested dose.

Table 17 Distribution by age group and dose in the pediatric PK/PD study

Treatment	**Age category (Years)**	**Number of subjects (n) by netupitant dose**		
		1.33 mg/Kg or 100 mg	**4 mg/Kg or 300 mg**	**Total**
	1 to < 3 months	1	0	**1**
	3 to < 6 months	3	2	**5**
	6 to < 12 months	4	5*	**9**
	1 to < 2 years	3	5	**8**
	2 to < 5 years	6	6	**12**
	5 to < 12 years	8	8	**16**
	12 to <18 years	9	7	**16**
TOTAL		**34**	**33**	**67**

**1 patient discontinued after randomization to the higher dose group but before receiving the study drug.*

The results obtained from the 66 patients recruited and treated out of the 92 called by the study protocol confirmed a similar efficacy of the 2 doses tested (i.e. 1.33 mg/kg up to a maximum of 100 mg and 4.0 mg/kg up to a maximum of 300 mg) in the delayed CR (primary endpoint) and acute and overall phase CR (secondary endpoints). Additionally, also the safety profile of the 2 doses was comparable.

A population PK analysis was conducted in order to characterize the population PK parameters of parent netupitant, netupitant metabolites M1, M2 and M3, and parent palonosetron.

The ranges of average half-lives were similar between netupitant (74.8 to 201 hours) and its metabolite M2 (85.7 to 175 hours) and appeared to be independent of treatment groups or age classes. Both in the lower and the higher netupitant dose groups, the mean netupitant exposure, $AUC_{0\text{-}inf}$, proved to be similar for the different age classes to that expected in adults after administration of the effective and well-tolerated doses of 100 mg and 300 mg oral netupitant, respectively.

Finally, the exposure increased proportionally with the dose administered and the exposure and PK profile in the paediatric population was quite comparable to the one in adult population.

The PK/PD analysis, based on graphical exploratory data analysis (EDA), indicated that the CR tended to increase with increasing netupitant AUC0-inf in the delayed phase and in the overall phase but not in the acute phase, in line with the mechanism of action of netupitant. Possibly because of data sparseness, this trend did not reach statistical significance and did not allow for a modelling approach.

Palonosetron PK parameters following oral NEPA administration resulted to be similar to those estimated from the population PK study in paediatric patients, following a single 15-minute intravenous infusion of 20 µg/kg palonosetron.

Blood and lymphatic system disorders was the most frequent system organ class (SOC) reported for all age classes, emetogenicity, and chemotherapy schedules. There were no deaths and no TEAEs leading to discontinuation from the study drug in either group. Study-drug-related TEAEs reported were defect conduction intraventricular CTCAE G1 in 1 patient in the lower netupitant dose group, headache, and somnolence in 2 patients in the higher netupitant dose group.

In addition, clinical laboratory assessments, vital signs, and ECGs show that the safety profile of the lower netupitant dose group is similar to that of the higher netupitant dose group.

Overall, the pattern of adverse events was as expected for cancer patients in a setting of cytotoxic chemotherapy and appears to be consistent with the established safety profile in adults for the oral capsules fixed dose formulation.

Considering that the netupitant dose used in the adult population is 300 mg and that other NK1 receptor antagonists are registered in the paediatric population with the same dosage approved for the adults, the dose of 4 mg/kg (2.4 mg/kg for patients aged <3 months) up to a maximum of 300 mg for patients weighing ≥75 kg appears to be appropriate for future paediatric studies with the oral formulation.

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 netupitant and palonosetron.

Safety in human pregnancy has not been established for either palonosetron or netupitant, and animal reproduction studies do not always predict human responses.

Paediatric population

It is expected that in children the IV fixed combination represents a valid and convenient treatment option prior to chemotherapy which is frequently administered by IV route as well as an alternative treatment for those who cannot swallow the capsule; while the oral formulation can be used in children who can swallow the capsule. Indeed, the number of orally administered chemotherapies continues to increase, broadening the range of potential treatment options, and oral chemotherapy used to treat adult cancers may be beneficial in the treatment of paediatric cancers (Bleyer WA et al. 1999; Halfdanarson TR et al. 2010).

Fixed combination medicinal products usually do not represent an appropriate therapeutic choice for children as these types of products do not enable titration of therapeutic doses. Efficient dose titration is usually a key element in the paediatric therapy.

Children generally present the same adverse effects as adults, but they have increased risk with some drugs because of differences in pharmacokinetics or because of drug effects on growth and development.

Netupitant is eliminated by hepatic metabolism (mainly mediated by CYP3A4 in vivo) and thus ontogeny of CYP maturation might have an impact on the dose to be administered to neonates and young infants.

Paediatric results from the dose finding study NEPA 15-31 are considered preliminary and indicate that the dose of netupitant 4.0 mg/kg up to a maximum of 300 mg for patients weighting 75 kg or more could be suitable to be further investigated. More supportive data are warranted to establish the safety and efficacy of the dosage in an adequate sample size.

After approval of the adult IV formulation, discussions were engaged with the EMA and the FDA to prioritise the paediatric development of NEPA IV, based on the following rationale:

- an intravenous formulation of an antiemetic drug is preferred by the paediatric oncologists for a better compliance and ease of use since essentially all paediatric cancer patients receiving chemotherapy have a central venous catheter placed for IV administration purposes;

- an intravenous formulation of an antiemetic drug is an important alternative option for paediatric patients who cannot swallow orally administered medications;

- an intravenous formulation of an antiemetic drug is a more convenient treatment option for oncologists since it can be adjusted to the body weight of the paediatric cancer patient more easily when compared to an oral product.

For these reasons, the actual paediatric clinical program was developed with NEPA IV.

Also, it was considered that paediatric cancer patients are more likely than adults to receive multiday chemotherapy treatment regimens; therefore, Helsinn decided, in agreement with the FDA and EMA, to investigate the safety and efficacy of IV NEPA as single and multiple administration during the single and multiday chemotherapy treatment regimens.

Based on the above, the study NEPA-22-01 titled:

"A multicentre, multinational, pharmacokinetic, safety, and efficacy study with IV NEPA (fosnetupitant/palonosetron) for the prevention of chemotherapy-induced nausea and vomiting in paediatric cancer patients undergoing highly emetogenic chemotherapy (HEC).

A 2-part study with Phase 2, open-label, randomised, single-dose IV NEPA vs fosaprepitant/ondansetron in single-day HEC and repeated dose IV NEPA in multi-day HEC (Part I, single cycle) and with Phase 3, double-blind, randomised, repeated-dose IV NEPA vs fosaprepitant/ondansetron in multi-day HEC (Part II, repeated cycles). "

was designed, with the aim to assess the PK, safety and efficacy of IV NEPA for the prevention of CINV in paediatric cancer patients aged between 0 months (newborns) and <18 years undergoing HEC.

The first patient is planned to be randomized to Part I of the study in June 2025. Part I of the study is a Phase 2, open-label, single-cycle study comparing single-dose IV NEPA vs fosaprepitant/ondansetron for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients undergoing single-day highly emetogenic chemotherapy (HEC) (Cohort 1) and assessing repeated-dose IV NEPA in patients undergoing multi-day HEC (Cohort 2). A total of 95 patients are planned to be enrolled into the 2 cohorts, of which 55 patients will be in Cohort 1 (Single-Day HEC) and 40 patients will be in Cohort 2 (Multi-Day HEC).

Part II of the study is a phase 3 study comparing repeated-dose NEPA vs fosaprepitant/ondansetron for the prevention of CINV in patients undergoing multi-day HEC. A total of 460 patients aged between 6 months and <18 years are planned for enrolment.

A DSMB has been appointed for this study to monitor safety and IV NEPA exposure levels. Specifically, patients will be enrolled following a staggered approach from older to younger patients, and the DSMB will assess the safety data of each completed age group/gathered age group (as appropriate) before authorizing enrolment of the next younger age group/gathered age group.

Elderly

Two studies evaluated the effect of age on PK of the fixed combination. A pilot study (NETU-08-12) evaluated the effect of netupitant after a single component capsule administration and for netupitant and palonosetron after the fixed combination administration. Differences in systemic exposure and the maximum concentration (C_{max}) were minimal in the 6 elderly subjects participating in the pilot study in comparison to non-elderly subjects.

The second PK study investigating the effect of age on the PK parameters of netupitant and palonosetron after administration of the fixed combination compared 22 healthy adult subjects, aged between 22 and 45 years, with 12 healthy elderly subjects, aged between 66 and 79 years (NETU-10-12). A slightly higher exposure in elderly subjects was observed compared to young adults. However, the increase in exposure to both netupitant and palonosetron is not expected to be clinically relevant. Therefore, no dosage adjustment is required for elderly subjects. All related AEs were in line with the known safety profile of netupitant and palonosetron.

In the safety study NEPA-15-18, a total of 7 IV NEPA treated patients out of 203 (3.4%) were ≥ 75 years of age. The limited number of patients precludes any consideration from a safety perspective.

Only a minority of cancer patients (41/1862, 2.2%) in the multicycle oral Phase III studies were ≥ 75 years of age. From these 41 patients recruited, 19 received the fixed combination, 17 oral palonosetron and 5 aprepitant plus palonosetron. Overall, the number of patients in this subgroup is very limited to allow a meaningful evaluation, however the review of safety data in this subgroup indicates that 36 (87.8%) had any type of TEAEs. No patients with TEAEs were reported in the SOC cardiac disorders for the fixed combination compared to 4 in the palonosetron comparator group and 1 in the aprepitant arm, while as a whole, TEAEs were more common in the blood and lymphatic system disorders (16 patients, 39.0%), in the investigations and nervous system disorders with 10 patients each (24.4%) followed by gastrointestinal disorders and infections and infestations with 8 patients each (19.5%).

To provide an accurate overview of the elderly patients participating to the clinical programme, the data analysis was expanded to comprise patients aged 65 years or older, who are also considered geriatric population as arbitrarily defined in the ICH E7. Phase III studies included more patients with < 65 years (1519/1862, 81.6%) than patients with ≥ 65 year (343/1862, 18.4%). The percentage of patients with at least 1 TEAE during any cycle was comparable in these subgroups of patients overall (89.3%, 1356/1519 patients and 91.5%, 314/343 patients, respectively) and in the netupitant-palonosetron group (89.3%, 749/839 patients vs. 94.8%, 184/194 patients, respectively), with the most commonly reported TEAEs in each of the 2 age subgroups reflecting those in the overall safety population.

At the PT level, the most commonly reported TEAEs in both age groups overall generally reflected those observed in the overall safety population: alopecia (49.6% and 43.1%, respectively), neutropenia (39.3% for patients < 65 years and 40.5% for those ≥ 65 years), leukopenia (21.7% and 27.4%, respectively), asthenia (13.1% and 12.2%, respectively), anaemia (10.6% and 14.6%, respectively), and headache (11.1% and 12.0%, respectively). These events occurred in a slightly higher percentage in the ≥ 65 years group, with the exception of alopecia and asthenia.

As expected, adverse events were most commonly reported in body systems (SOC) that are most often involved with the cytotoxic effects of chemotherapy administration, with the exception of headache, which is a known effect of the antiemetic treatment.

Considering that TEAEs were counted only in the cycle in which they were first reported, the percentage of patients who underwent at least 6 consecutive cycles of treatment who reported TEAEs decreased with each additional cycle of treatment for both age subgroups in the netupitant-palonosetron group, ranging from 68.9% (184/267 patients) at cycle 1 to 31.8% (85/267 patients) at cycle 6 in patients < 65 years of age and from 72.0% (36/50 patients) at cycle 1 to 36.0% (18/50 patients) at cycle 6 in patients ≥ 65 years of age. At each cycle, similar percentages of patients in the 2 age subgroups reported at least 1 TEAE in the netupitant-palonosetron group. Among patients who had at least 6 consecutive cycles of treatment, SAEs were reported in < 2% of patients in either age subgroup, with the exception of cycle 5 in the < 65 years of age, where 6 (2.2%) patients reported SAEs. Overall, it can be assumed that there is no significant unknown safety concern associated with NEPA fixed combination administration to elderly subjects compared to patients with < 65 years.

In 12 healthy subjects aged between 66 and 79 years enrolled in Study NETU-10-12, the exposure to netupitant and palonosetron was marginally increased compared to 22 healthy adults aged between 22 and 45 years. Moreover, a population PK multivariate linear regression analysis showed that age is not a significant covariate for netupitant and palonosetron exposure in cancer patients.

Hepatic impairment

A PK study (NETU-10-10) was conducted to assess the PK of a single dose of the fixed combination in patients with different stages of hepatic impairment classified by Child-Pugh score in comparison to healthy volunteers. In 8 subjects with mild hepatic impairment, exposure to netupitant was slightly higher compared to matching healthy subjects; while in subjects with moderate hepatic impairment exposure to netupitant was significantly higher compared to healthy subjects. Mildly hepatic impaired patients showed a C_{max} of palonosetron slightly higher compared to control with an increase of 14% for C_{max}. However, the increase was not statistically significant. In patients with moderate hepatic impairment, C_{max} of palonosetron was similar to that of matching healthy subjects.

A wide variability of calculated half-lives of netupitant was observed both in moderately impaired subjects and in healthy subjects as well as of the C_{max}/AUC values across all the subject groups for netupitant. The mean exposure values for the healthy subjects matching the moderately impaired are lower than those of the subjects matching the mild impaired subjects, while the exposure mean values for mild and moderate impaired subjects are actually similar. The statistical significance of the moderately impaired group could be largely due to the comparison with the specific matched healthy subjects, and the absolute difference between mild and moderate impaired subjects is small. Therefore, no dose adjustment is needed for mildly or moderately hepatic impaired patients.

The small sample size of severely impaired subjects (n=2) was scarce, a trend toward increased exposure is likely to exist; however, the variability in the data prevented definitive conclusions.

Renal impairment

Renal excretion is a minor route of netupitant elimination. In study NETU-06-27, the mean fraction of an oral dose of netupitant excreted unchanged in urine was very low (less than 1%). Therefore, the risk for accumulation of netupitant in patients with renal impairment is also low. Consistently, study NETU-09-21, the ADME trial, showed that renal excretion was a minor route of elimination (only 3.95% of total radioactivity was recovered in urine). No dedicated study in patients with renal impairment was conducted within this clinical development programme.

On the other hand, approximately 40% of palonosetron is renally secreted unchanged. Mild to moderate renal impairment does not significantly affect palonosetron PK parameters. Severe renal impairment reduces renal clearance. However, total body clearance in these patients is similar to healthy subjects. No studies with palonosetron have been performed in patients with end-stage renal disease requiring dialysis. Due to the large volume of distribution and relatively equal contribution of hepatic metabolism and renal elimination of palonosetron, dialysis is not likely to affect the clearance of palonosetron.

During the oral program, patients with varying degrees of renal impairment were evaluated in the Phase 3 studies for safety using TEAEs, serious TEAEs, and ECGs. No clear difference was observed in the incidence of TEAEs or ECG parameters for patients with normal renal function compared to those of patients with mild and moderate renal impairment in the Phase 3 multicycle studies conducted during the oral program.

Race

In the safety population of the IV NEPA study (NEPA 15-18), 99.3% of patients (401 out of 404) were white, 1 patient (0.2%) was Asian and 2 patients (0.5%) were Black.

In the oral studies conducted, most patients were Asian or White. The percentage of patients with at least 1 TEAE considering all cycles was similar between white and Asian patients in each treatment group, with the most commonly reported TEAEs in these subgroups reflecting those in the overall safety population. Small numbers of patients from the other races participated in the studies.

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.

Analogous results were obtained in a subgroup of cancer patients in the Phase III trial NETU-08-18 undergone PK analysis (NETU-10-02).

In this population PK analysis, none of the covariates including but not limited to race, body mass index (BMI), age, gender, chemotherapy regimen, rescue medication, smoking status, had a significant impact on the disposition of netupitant.

The characterization of the safety profile of the fixed combination in the Asian population derived from two trials run in Asian countries, namely one phase 1 in 18 healthy volunteers and one phase 3 study.

A total of 834 chemotherapy-naïve patients receiving cisplatin-based chemotherapy were enrolled in the phase 3 study; of these 413 treated with netupitant- palonosetron fixed combination and 416 with the active comparator (aprepitant and granisetron). Constipation, known side effects of the 5-HT_3RA, was the most common TEAE observed in both treatment groups at a comparable frequency. As for transaminases the frequency of TEAEs was similar between treatment arms; it was not suggestive of drug induced liver damage being the vast majority of these events assessed as not related by the investigators and likely attributable to the chemotherapeutic effects or to the concomitant use of dexamethasone and other comedications.

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.

There is no data suggesting that the efficacy of the fixed combination 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

No specific studies to evaluate the effects of genetic polymorphism of CYP3A4 on netupitant disposition were conducted.

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-HT3 RAs (e.g., palonosetron, ondansetron, granisetron, dolasetron, tropisetron, ramosetron) or to NK1 receptor antagonists

Reason for exclusion: Patients allergic to a 5-HT_3 RA or to a NK_1 RA can also be allergic to NEPA fixed combination. Patients with a history of positive allergy to these active ingredients are at high risk of subsequent reactions to these drugs since the agent may act as an antigen and elicit one of several classic immune responses.

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

It cannot be predicted if the NEPA fixed combination in patients who are at risk of 'Torsade de pointes' or suffer from any type of arrhythmias further increases the risk. An ICH E14-compliant study with netupitant and palonosetron showed no clinically relevant effects on heart rate, cardiac morphology and cardiac repolarization. The data available so far do not theoretically support this hypothesis. Caution is needed for the concomitant use of the fixed combination with medicinal products that increase the QT interval or in patients who have or are likely to develop prolongation of QT interval. Electrolyte abnormalities (hypokalaemia, hypomagnesemia) should be corrected prior to dosing.

Criterion: Patients scheduled to receive any strong or moderate inhibitor of CYP3A4 or its intake within 1 week prior to Day 1

and

Criterion: Patients scheduled to receive any of the following CYP3A4 substrates: terfenadine, cisapride, astemizole, pimozide.

Reason for exclusion: Netupitant is a substrate of CYP3A4 and demonstrated the ability to competitively inhibit CYP3A4. Non-clinical data indicate drug interaction potential with other CYP3A4 substrates. Netupitant in humans is metabolized by CYP3A4. The potential interactions were not known at the time of the oral clinical development plan with inhibitors/inducers of this CYP450 isoenzyme.

A drug-drug interaction program was conducted in parallel to the oral clinical development plan to evaluate the metabolic/mechanistic pathways and to investigate agents routinely co-administered with antiemetics. Metabolism of netupitant is hepatic and mainly mediated by CYP3A4 isoform.

Co-administration of netupitant with CYP3A4 inhibitors (e.g., ketoconazole) results in the accumulation of netupitant, on the contrary, co-administration of CYP3A4 inducers (e.g., rifampicin) with the fixed combination results in the reduction in netupitant exposure. Netupitant and its metabolites M1, M2, M3 competitively inhibits CYP3A4 and in vitro and in vivo studies results indicate drug interaction potential with CYP3A4 substrates.

Is it considered to be included as missing information? No – In the prescribing information details on the outcomes of the drug-drug interactions studies are described.

Criterion: Lactating females

Reason for exclusion: There are no data regarding the excretion of palonosetron or netupitant in breast milk.

Is it considered to be included as missing information? No. In the prescribing information it is recommended that oral Akynzeo should not be used during breast-feeding. Breast-feeding should be discontinued during treatment with Akynzeo and for 1 month after the last dose.

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

The NEPA IV clinical development programme comprised a total of 439 cancer patients treated over multiple chemotherapy cycles; such limited number of patients does not allow accurately evaluating the incidence of adverse drug reactions (ADRs); data from the oral combination provides information on the very common or common ADRs observed.

Table 18 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	Approximately 3,000 subjects were exposed to netupitant alone, in combination with palonosetron or to the fixed combination within the fixed combination clinical development programme, including healthy volunteers.	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. The potential implications for the target population are unknown. Post-marketing surveillance activities and spontaneous reporting of individual case reports will help to identify the uncommon and rare ADRs.
Due to prolonged exposure	Subjects in Phase I studies received netupitant (alone or in a combination with palonosetron) daily for 7 days. Subjects included in Phase II overactive bladder study received up to 200 mg netupitant alone for 8 weeks.	The fixed combination is intended to be administered once prior to each cycle of chemotherapy for the prevention of CINV. Therefore, the implication for the target population due to prolonged exposure does not represent a safety concern. Although patients may receive multiple cycle of chemotherapy preceded by antiemetic treatment, the potential for cumulative effects of the fixed combination is considered negligible due to the time elapsing from one cycle to the subsequent one.
Due to cumulative effects	In Phase I studies, netupitant was administered orally alone or in combination with palonosetron (extemporaneous or fixed combination) at a daily dose for 7 days (up to 450 mg daily for 7 days).	
Which have a long latency	No long-term clinical studies or studies with long-term follow-up periods have been conducted with the fixed combination.	The fixed combination 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 19: List of populations included or not in clinical trial development programmes

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 impairment • Patients with 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 No
Population with relevant different ethnic origin	No
Subpopulations carrying known and relevant genetic polymorphisms	No
Other	No

*A total of 18 subjects with hepatic impairment participated in a phase 1 study.

In the phase III clinical trials with the fixed combination formulations cancer patients were to be enrolled, including also subjects with metastatic neoplasms. Since liver is the predominant site of metastatic lesions, a specific criterion for patients' eligibility was to be fulfilled as detailed underneath.

Metabolic status adequate for receiving chemotherapy was defined as:

- Bilirubin ≤1.5 x upper limit of normal (ULN)
- Liver enzymes:
  - i. Without known liver metastases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN
  - ii. With known liver metastases, AST and ALT ≤5.0 x ULN

Part II: Module SV - Post-authorisation experience

Postmarketing data are available for the oral NEPA formulation marketed in the USA in 2014 and in EU in 2015.

Marketing authorization approval of the NEPA IV formulation has been granted by the FDA in April 2018 (powder formulation) and May 2020 (solution), and in March 2020 in EU and Australia (powder formulation).

SV.1 Post-authorisation exposure

The launch of the IV combination on the US market took place at the beginning of May 2018, while in EU it was launched in June 2020. Since its launch approximately [redacted] cancer patients received the antiemetic treatment prophylactically intravenously, almost all in the US.

A safety study (NEPA 17-05) to assess the safety and to describe the efficacy of IV fosnetupitant/palonosetron combination compared to oral Akynzeo® for the prevention of chemotherapy-induced nausea and vomiting in initial and repeated cycles of anthracycline-cyclophosphamide (AC) chemotherapy in women with breast cancer has been completed recently. A total of 402 patients enrolled and treated: 202 with oral Akynzeo® and 200 with the IV combination. Overall, the safety profiles of the two treatments were similar. Also, efficacy results were consistent between the two treatment groups; complete response rates were similar in all phases and all cycles. Additional measures including no emetic episodes, no rescue medication use, and no significant nausea followed similar patterns.

[redacted]

A study (NEPA-19-13) in healthy volunteers was designed with the aim to investigate the possibility to shorten the injection duration as compared to the 30-min IV infusion of the approved lyophilized powder formulation. The new formulation, a solution for infusion, with a qualitative composition identical to the one already authorized, was to be administered in study Part A to define the shortest safe and tolerable duration of IV bolus injection among 3 durations tested in decreasing order: 15, 5 and 2 min (or 15, 5 and 10 min in case 5 min did not prove to be safe and tolerable). The selected injection duration was then to be used in study Part B. The pre-set stopping rules in study Part A were fulfilled by one subject in the first cohort of treated subjects; therefore, the study was prematurely terminated for safety reasons.

Based on sales data (oral hard capsules and IV formulations), [redacted] patients have been treated with Akynzeo worldwide (see Table 20 Cumulative number of patients exposed to Akynzeo in post-marketing setting divided by geographical region and pharmaceutical form. below), considering for each patient an average of 6 cycles of chemotherapy preceded by antiemetic prophylaxis with Akynzeo.

Collectively, there is no evidence of any change in the clinical pattern of Akynzeo ADRs or of any new qualitative or quantitative safety concern from post-marketing experience.

The newly available safety data do not change the established favourable benefit-risk profile of Akynzeo.

Neither sponsored clinical trials nor long term follow-up studies are ongoing with oral Akynzeo.

A further FDA post-marketing commitment was a Phase I study with the objective to evaluate the duration of the inhibitory effect of Akynzeo on CYP3A4 enzyme activity beyond four days after Akynzeo administration in 24 healthy volunteers. The study hypothesis was met as the inhibitory effect of NEPA fixed combination on CYP3A4 ceased between Day 8 and Day 10, as shown by the outcome of the statistical comparisons of plasma dexamethasone pharmacokinetic parameters. Treatment emergent AEs

were observed in all subjects; however, the study safety data did not raise any safety concern for the co-administration of Akynzeo with dexamethasone up to 10 days.

Postmarketing experiences undertaken at local levels, including non-interventional studies and surveys complemented the safety data available for Akynzeo.

All together these studies generated a large amount of data and the safety data collected in a heterogeneous patient population in real world settings contributed to better characterize the tolerability of the combination. Moreover, by providing greater clarity on safety and effectiveness, these results contributed to accurately identify the risk to benefit ratio.

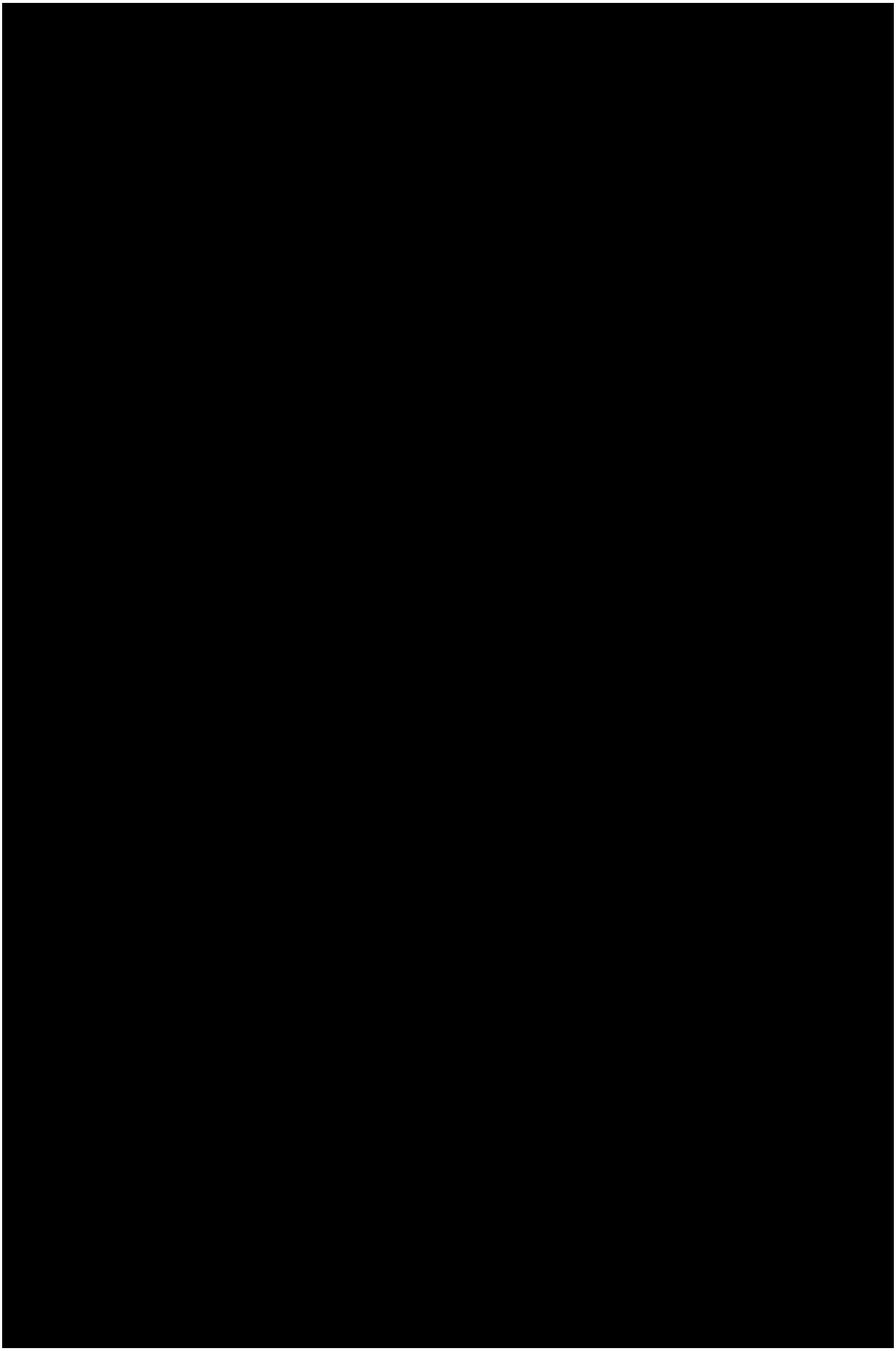
Additionally, a Patient Assistance Program, offering IV or oral Akynzeo free of charge to patients who cannot afford the medicinal product, is ongoing in the USA.

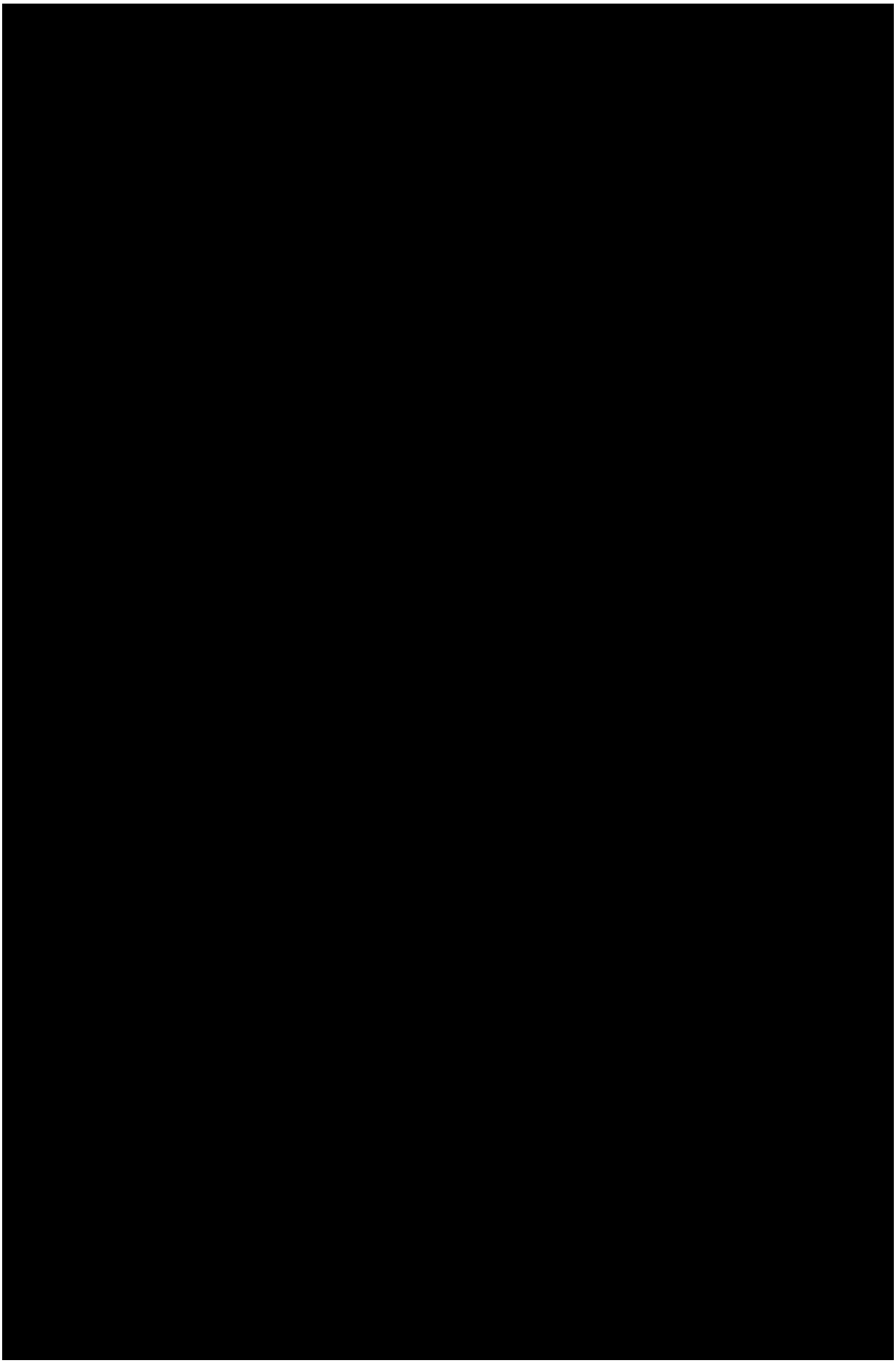
SV.1.1 Exposure

The estimates on the cumulative patients' exposure from the post-marketing experience with oral and IV Akynzeo since the first launch in the USA up to 10 October 2024 (DLP of PSUR N.16) are reported in Table 20 below.

The method applied for calculation of the number of patients exposed considers an average of 6 administrations of a medication for CINV prophylaxis during the entire course of chemotherapy for each patient (US data from IntrinsiQ, 2005 and Cancer Monitor, 2006).

Table 20 Cumulative number of patients exposed to Akynzeo in post-marketing setting divided by geographical region and pharmaceutical form.





Since the launch of Akynzeo in 2014 up to the data lock point of the last submitted PSUR N.16, a total of 100 post marketing cases coded with the PT "off label use" populate the safety data base; most of them were non-serious cases and no associated adverse reactions occurred. However, the last years an increase in the number of reported off label use cases has been identified. Most of these cases derive from the USA, are solicited from a PSP, and the off label use is mainly coded because the indication of Akynzeo is often erroneously reported as the underlying cancer diagnosis rather than CINV. Even though follow up attempts are always performed to better understand the kind of off label use, these are often unsuccessful. The Company follows a conservative approach and registers all these off label use cases in the database despite the wrongly-reported indication. Moreover, the enrollment form used in the US PSP has been modified to ensure the indication for Akynzeo can be correctly reported.

Overall, considering the total number of patients exposed to Akynzeo and the limited numbers of "off label use" cases, current post marketing data are suggestive of a correct use of the fixed combination in clinical practice in the target population candidate to receive chemotherapy at moderate or high emetogenic risk.

Such data are consistent with the results obtained by Gilmore JW et al. (2014) who evaluated a large sample of outpatients treated at community oncology practices to assess real-word outcomes including adherence to chemotherapy prophylaxis within the context of usual practice. Despite some limitations, the results of this study are comparable to and support those of a prior European Study (Aapro M et al. 2012).

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

SVI.1 Potential for misuse for illegal purposes

The pharmacologic profile of the concerned fixed combination does not suggest any potential for misuse for illegal purposes. The abuse potential of the fixed combination was addressed in non-clinical studies in baboons. The results of performed studies suggest a lack of abuse potential of the fixed combination.

In the safety IV NEPA study, the review of the TEAEs in the SOC psychiatric disorders which can be suggestive of a psychoactive effect has been conducted. The overall percentage of NEPA IV patients with TEAEs was 2.5 % compared to 6% in the oral NEPA arm; however, none of them indicates a psychotic effect, rather they are plausibly attributable to the mood alteration associated to cancer.

These results are consistent with the analysis of more than 21,000 cancer patients screened for depression using the Hospital Anxiety Depression Scale (HADS). Data showed the highest prevalence of major depression in patients with lung cancer (13.1%) followed by gynecological (10.9%), breast (9.3%), colorectal (7%), and genitourinary cancer (5.6%) (Walker J et al. Ann Oncol. 2013).

A clinical evaluation of drug abuse potential was undertaken involving all trials where netupitant was administered either alone or in combination with palonosetron. Palonosetron is known to have no abuse potential. Overall, out of the 3,592 patients assessed in 27 clinical studies, only 8 patients (0.22%) who were treated with netupitant alone or in combination with palonosetron reported any symptom that could potentially be considered psychoactive. Six of the 8 patients were receiving either dexamethasone or other potentially confounding medications, including midazolam; all frequencies of specific symptoms were 0.08% or less, suggesting that there is no evidence that netupitant alone or in combination have any abuse potential.

Taking int account the above information and the fact that NEPA IV 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

IV NEPA fixed combination contains fosnetupitant and palonosetron. The proposed formulation, a concentrate solution for infusion, contains the same strengths of the active ingredients as a clear solution in a single-dose vial. The route of administration and the indications are the same of the approved IV powder formulation. Qualitative composition of the proposed formulation is the same of the approved powder formulation, except for water for injection.

From the first human dose of fosnetupitant intravenously and throughout the course of the two clinical trials in cancer patients (the safety study NEPA 15-18 and the PK study NEPA 15-19) with IV NEPA fixed combination, safety information has been collected and reviewed to identify and characterize as much as possible any potential safety signal and risk related to the compound. These activities have been undertaken to optimize the benefit/risk balance of the compound, improve individual patient outcomes, and assure safe use of the medicine in the proposed indication.

One of the components of IV NEPA fixed combination is palonosetron 0.25 mg, a 5-HT_3 RA 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 about 6,000 cancer patients and from individual spontaneous reporting in the frame of post-marketing surveillance activities raised no signals (qualitatively or quantitatively) of unexpected toxicity for palonosetron IV formulation.

There were no changes to the already known safety profile of palonosetron considering that post-marketing data largely contributed to characterize its safety profile, particularly in cancer patients treated worldwide.

Fosnetupitant, the other component of IV NEPA fixed combination is rapidly converted to netupitant; 235 mg as free base is the equivalent dose of fosnetupitant yielding similar netupitant exposure to oral netupitant 300 mg, the dose of the oral fixed combination.

The pharmacology of fosnetupitant is attributable to netupitant and its active metabolites. Therefore, the clinical program conducted with the IV fosnetupitant/palonosetron combination complements the clinical program conducted with the oral netupitant/palonosetron combination.

The safety profile of oral Akynzeo® was extensively evaluated during the clinical development program which included approximately 2,500 cancer patients, of which 1,442 received a dose of netupitant and palonosetron. No remarkable safety findings were observed when the oral fixed combination was administered in repeated cycles of chemotherapy. Post-marketing data collected so far also provide safe foundation for confident prescribing of this medicine.

As discussed in Module SVI, no safety concerns can be envisaged from the use of the combination 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).

In the next section, the substance to which each safety concern is attributable has been indicated.

Potential risks associated with the concomitant use of drugs likely interfering with the metabolic pathway of the fixed combination medicine that would lead to clinical implications such as lower therapeutic efficacy or greater toxicity identified to this point in time will be thoroughly detailed with specific reference to the drug-drug interaction studies conducted with dexamethasone, benzodiazepines, rifampicin and ketoconazole.

Each combination (IV and oral) comprises two active ingredients fosnetupitant and palonosetron and netupitant and palonosetron, respectively. Fosnetupitant IV is rapidly converted to netupitant and the pharmacological effects of fosnetupitant can be entirely interpreted as due to its conversion to netupitant.

The safety concerns (potential risks and missing information) identified at the time of the RMP (version 2.7) approval for the oral and IV fixed combination in the frame of the MAA will be discussed and presented in the pertinent module for the ingredients netupitant and palonosetron.

Potential for harm from overdose

As for any other medicinal drug, the potential for both intentional and accidental overdose exists.

This condition may occur when any of the Akynzeo formulation is given daily prior to each chemotherapy cycle lasting more days.

Safety information for doses exceeding the intravenous dose of 235 mg of fosnetupitant and the oral dose of 300 mg mainly derives from the thorough QT/QTc study.

Study NETU-07-20 evaluated the potential ECG effects in healthy volunteers by using clinical and supra-therapeutic doses of the fixed combination, (200 mg/0.50 mg; 600 mg/1.50 mg) compared to placebo and positive control, moxifloxacin. A total of 60 AEs were reported by 49 of the 200 exposed subjects. Except for 1 severe AE (syncope) which was assessed as unlikely related to the fixed combination, all AEs were mild or moderate in intensity. The frequency of AEs increased with increasing netupitant/palonosetron doses. Subjects in the 600 mg netupitant and 1.50 mg palonosetron group reported mainly headache (5 events) and constipation (2 events) as study drug-related events.

Doses of palonosetron up to 6 mg, 12 times the recommended oral dose of 0.5 mg have been used in clinical studies. The highest-dose group showed a similar incidence of AEs compared to the lower-dose groups and no dose response effects were observed.

A clinical study evaluating the potential ECG effects, tested doses up to 2.25 mg palonosetron (i.e. 9-fold higher than the marketed dose of 0.25 mg) in healthy volunteers. In the safety population, 15 AEs were reported in the intravenous 0.25 mg palonosetron group, 23 in the intravenous 0.75 mg palonosetron group, and 20 in the intravenous 2.25 mg palonosetron group. The number of AEs did not differ notably among the treatment groups. Headache was the AE reported more frequently in all study groups (13.1% overall). In 0.25 mg palonosetron group, 9.1% of subjects suffered from headache, 17.4% in 0.75 mg palonosetron 0.75 mg group and 8.7% in 2.25 mg palonosetron group. No clear dose-related effects were observed for the occurrence of constipation (6.8%, 6.5%, and 8.7% in palonosetron 0.25 mg, 0.75 mg and 2.25 mg groups, respectively). These results indicate the absence of dose response effects of palonosetron.

The clinical impact of excessive drug consumption would probably lead to symptoms which are likely to be self-limiting.

No signs of increased safety issues were 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.

Akynzeo powder for infusion should be reconstituted and the concentrate solution only diluted; the risk of accidental overdose is highly unlikely to occur since both the concentrate and the diluent vials are not overfilled; only one single administration is recommended prior to each chemotherapy cycle.

Moreover, it should be used within 24 hours after reconstitution and the use is restricted to secure environment (hospital, clinics) under direct nurse monitoring and physician supervision.

In addition to the registered pack size containing 1 capsule in a cardboard carton, an additional pack size of 4 capsules of Akynzeo was approved by the EMA on 21 September 2017. This multiple unit pack is distributed and sold only to hospitals for exclusive use in patients undergoing chemotherapy in accordance to the approved posology and method of administration. This pack size of 4 capsules is intended to allow treatment of more patients simultaneously.

The potential risk for overdose associated to the Akynzeo formulations should be very limited since the fixed combinations are 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.

At the cut-off date of the last submitted PSUR one non-serious case of overdose has been reported to occur with oral Akynzeo in the post-marketing surveillance. The patient scheduled to receive Akynzeo on Day 1 and on Day 8 of the first chemotherapy cycle, erroneously took the second dose of Akynzeo on Day 3 instead of Day 8 and experienced flushing of cheeks that resolved five days later.

Overall, this suggests that the measures in place are adequate to this purpose.

Potential for transmission of infectious agents

Active substances fosnetupitant, netupitant and palonosetron hydrochloride are not of human or animal origin.

The excipients are the same for of both IV formulations and are not of human or animal origin, no Class 1, 2 or 3 solvents are used in the manufacture. There are no novel excipients in the IV formulations and all excipients are tested and compliant with USP/NF and/or Ph.Eur. compendial analytical procedures.

With the exception of the gelatine capsule (hard gelatine capsule and soft capsule shell) of the oral fixed combination, there are no other excipients of human or animal origin used in the manufacturing process of netupitant/palonosetron fixed combination capsules. The capsules comply with FDA and European pharmaceutical regulatory statutes. The capsules also comply with transmissible spongiform encephalopathy (TSE) and bovine spongiform encephalopathy (BSE) regulations.

Manufacturing processes of drug substances and drug product 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, the potential for transmission of infections agents due to the nature of the manufacturing process or the materials involved is considered substantially very low.

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.

As for the IV NEPA combination, it is recognized that parenteral administration requires preparation, dilution or reconstitution prior to use and any of these steps may be the cause or determine medication errors. It is known that treatments given by the IV route are associated with the highest rates of preparation and administration errors due to issues such as incompatibility with diluents or by injecting bolus doses faster than the recommended slower infusion time.

The potential risk from medication error associated with the reconstitution of the fixed combination of the IV formulation or associated to the intravenous injection cannot be predicted at the present time since the dilution and preparation of the final formulation is under the responsibility of the healthcare professional assigned to this task.

IV formulation "concentrate for solution for infusion" does not need to be reconstituted, allowing a faster and easier preparation of the solution to be infused, and reducing the potential risk of preparation and administration errors.

Currently the labelling of the product is designed and intended to provide key information on the optimum preparation and administration of the product. Measures to prevent the potential for risks from medication errors have been considered. For this purpose, the proposed SmPC for the IV NEPA combination thoroughly details the instructions to be followed for the reconstitution and dilution of IV NEPA including the procedure of flushing the infusion line with the same carrier solution to ensure complete drug administration and distinct information related to incompatible solutions. Additionally, the proposed SmPC indicates that the product should be administered intravenously only and clearly states that it should not be administered by intramuscular or subcutaneous route.

Moreover, to prevent potential risks associated to other circumstances, e.g. the precautions to be observed for the storage are reported in the SmPC and in the package information leaflet (PIL).

Individual vials of Akynzeo powder for concentrate for solution for infusion are placed in a carton for added protection from light and for protection during shipping and have to be stored in refrigerated conditions at 2°-8°C and once reconstituted the final solution should be administered within 24 hours.

Handling and storage of the new proposed pharmaceutical form (concentrate for solution for infusion) is easier compared to the lyophilised powder (the liquid formulation can be stored at room temperature while the lyophilised powder must be stored between 2 and 8°C).

Stability testing has been conducted on drug product packaged in the proposed commercial packaging components. As shown by the stability data, the container-closure systems are compatible with IV NEPA fixed combination. The stability of the solution has been verified in the range of 2.2-13 mg/mL and it is stable at room temperature for 1 day.

The commercial combination capsules are packaged in aluminum/aluminum blister packs for sunlight protection and do not require being stored in special conditions. A shelf life of 4 years is currently approved.

Post-marketing experience will constitute an important source of information on the real-life use of the combination in clinical practice. Medication errors cause a large number of 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 in order to evaluate the adoption and implementation of measures to mitigate and prevent such risk and its potential complications.

In the PSURs an analysis and discussion of the report of medication errors, either during the reference period and cumulatively, will be performed to evaluate the pattern of these potential medication errors and whether they represent a safety issue for which further risk minimization measures are necessary to mitigate the risk.

Post marketing safety data of oral hard capsules and IV Akynzeo have been reviewed to identify any cases notified so far. The Standardized MedDRA query "medication error" (broad) was used to detect and retrieve such cases.

Since Akynzeo commercialization in 2014 up to the data lock point (10 October 2024), a total of 65 individual reports that contain at least one medication error event of Akynzeo oral hard capsules and IV formulations have been collected, including eight cases with also the coded PT off label use. The total number of cumulatively reported cases of oral Akynzeo is 61, and 4 cases have been reported with the IV formulation. The most frequent PT was inappropriate schedule of product administration (17 events), followed by product prescribing error (5 events), product administration error (5 events), intercepted medication error (4 events), circumstances or information capable of leading to medication error (4 events), medication error (4 events) product use in unapproved indication (3 events), product dose omission (3 events) and product use issue (3 events) . Two events each were reported for product use complaints, intercepted product prescribing error, incorrect dosage administration, incorrect dose administration, and accidental overdose. One event each was reported for expired product administered, incorrect route of product administration, intercepted product preparation issue, occupational exposure to product, overdose, product dispensing error, wrong product administered.

These reports originate from France (N=17), Germany (N=10), Australia (N=8), USA (N=5), Israel (N=4), India (N=3), Brazil (N=3), Norway (N=3), Canada (N=2), United Kingdom (N=2) and 1 report each from Belgium, Finland, Ireland, Philippines, Denmark, Netherlands, China, Hong Kong respectively.

Seven (7) out of sixty-five (65) cases were serious, including one involving a female patient with breast cancer who experienced several clinically significant symptoms more likely related to chemotherapy (epirubicin, cyclophosphamide, mesna) rather than to Akynzeo, which was administered 27 hours after chemotherapy (an inappropriate schedule of drug administration). A similar case involving a female patient with breast cancer was also reported. After the administration of Akynzeo and during the first course of chemotherapy with epirubicin, the patient experienced serious dyspnea. This was likely related to chemotherapy, as Akynzeo was administered more than an hour before the chemotherapy began. In one case, a reported medication error was related to concomitantly administered dexamethasone and not to Akynzeo. In another case, Akynzeo was administered after chemotherapy (an inappropriate schedule of product administration), and serious nausea and vomiting were reported. These symptoms could have been due to chemotherapy’s emetogenicity, as Akynzeo was taken after the chemotherapy.

The most commonly reported PT was “inappropriate schedule of product administration” (17 events). The reasons for inappropriate scheduling of Akynzeo administration include situations, where the medication was administered at a higher frequency than prescribed. There were instances of drug administration, with patients taking one capsule daily for several days. Delayed administration occurred when Akynzeo was given several hours later than planned. Incorrect timing was noted when Akynzeo was received on the evening of the first day of chemotherapy, leading to the intake of two dosage forms. Consecutive dosing happened when patients took Akynzeo for three consecutive days. Additional doses were administered the following day. Irregular dosing patterns included taking Akynzeo every other day. Post-chemotherapy administration occurred when Akynzeo was taken after chemotherapy. Premature administration was noted when Akynzeo was taken more than one hour before chemotherapy. Lastly, extended delays were observed when Akynzeo was received 27 hours after chemotherapy. The majority of cases that contain the event “inappropriate schedule of product administration” were not associated with ADRs. Three cases that contained the event “inappropriate schedule of product administration” were considered serious and briefly described above. There were two cases that contained the non-serious event of dizziness (a listed event that was reported when Akynzeo was administered daily for several consecutive days); vomiting and asthenia when Akynzeo was taken for several consecutive days. Due to the lack of information reported, the assessment of the causal relationship was not possible. Two cases containing the event “drug ineffective” were also reported, including one situation where the patient started Akynzeo administration after chemotherapy. Another lack of efficacy case was poorly documented, without any details that allowed proper causality evaluation.

The second most commonly reported PTs (five reported events each) were "product prescribing error" and "product administration error."

Regarding the PT "product prescribing error," the following situations were reported, none of which were associated with ADRs: a patient was prescribed to receive Akynzeo 12 hours before chemotherapy. In another case, the prescription included three different dose forms of Akynzeo to be administered before chemotherapy, with one capsule to be taken before each chemotherapy session on a three-day cycle. There was a case of medication error when Akynzeo was administered together with ondansetron. In the following case, the therapy was charted incorrectly, resulting in the patient not taking Akynzeo until 16-24 hours after chemotherapy.

The PT "product administration error" was reported in five cases. In one case, the patient received Akynzeo capsules but did not receive chemotherapy within the recommended one-hour window. In another case, Akynzeo was mistakenly administered to a patient who was also receiving ondansetron, aprepitant, and dexamethasone simultaneously. One case described a situation where the patient was advised by her doctor to take Akynzeo as an antiemetic before her chemotherapy course, but the drug was not administered. In one instance, the patient was accidentally given Akynzeo orally along with Aloxi intravenously. The last case involved a female patient who was scheduled to receive oral Akynzeo on the day of her chemotherapy. However, the capsule was not administered: the blister pack had five compartments, four of which were empty. The nurse mistakenly cut out an empty compartment and placed it in the patient's cup with her other medications. This patient experienced non-serious nausea the day after chemotherapy. No other ADRs were reported in cases that involved the PT "product administration error".

The third most reported PTs (four reported events each) were "circumstances or information capable of leading to medication error," "intercepted medication error," and "medication error." The PT "circumstances or information capable of leading to medication error" was reported in the following situations: in two cases, the patient was prescribed Akynzeo, one capsule daily for nausea, but did not start the treatment; another case report indicated an issue with Akynzeo packaging (the patient mistakenly believed there was a tablet in one of the blister sections, but it was actually empty); in the last case, the physician recommended using Akynzeo on non-chemotherapy days, but the patient hadn't started due to the high cost of the medication. Only in the last case were the non-serious events of nausea, vomiting, and eating disorders reported; these events were considered not related to Akynzeo since the product was not administered.

The PT "intercepted medication error" was reported in four cases: in two of them, the pharmacist realized that the recommended dosage of Akynzeo in the SmPC differed from the one prescribed by the physician, contacted the physician for clarification, and ensured the patient received the correct dosage of Akynzeo. In one case, the pharmacist inquired if the capsules could be opened for a patient with swallowing difficulties. The last case referred to a situation where the capsule was opened by the nurse. No ADRs were associated with the "intercepted medication error" event.

The PT "medication error" was reported in four cases: in one case, the patient received both Aloxi and Akynzeo, leading to a double dose of palonosetron with no ADRs reported. Another case described a situation where the patient took Akynzeo 4-5 hours after chemotherapy, leading to post-chemotherapy non-serious nausea and vomiting. Another case referred to a patient who opened and swallowed the contents of an Akynzeo capsule; no ADRs were reported in this case either. The last serious case that contained the event "medication error" described above in this section referred to dexamethasone and not to Akynzeo.

The PTs "product dose omission in error," "product use in unapproved indication" and "product use issue" were reported in three cases each. The PT "product dose omission in error" was considered when the patient arrived at the hospital without having taken Akynzeo, resulting in a delay in their chemotherapy

treatment. In two other cases, patients did not receive their treatment because the medication was missing from the packaging; none of these cases were associated with ADRs. The PT "product use issue" was considered in one serious case reported from India, where Akynzeo was used off-label to treat a 14-year-old patient with osteosarcoma. Another case referred to a situation where Akynzeo ran out. The last case involved Akynzeo being taken as premedication for chemotherapy scheduled for the following day. In both cases, no ADRs were associated with the medication error events.

The remaining cases classified under the standardized MedDRA query "medication error" (broad) were not linked to ADRs, except for the following instances:

- a patient who took Akynzeo for five consecutive days experienced constipation, classified under the PT "incorrect dosage administered";

- another case involved an incorrect dose of dexamethasone, not Akynzeo, leading to an insufficient antiemetic effect of Akynzeo when combined with an unspecified EC-containing chemotherapy. This was also classified under the PT "incorrect dosage administered";

- in a case of overdose, a patient took two capsules of Akynzeo within 72 hours and experienced flushing of the cheeks the following day;

- a patient mistakenly took Akynzeo instead of Aloxi, resulting in non-serious reactions of vomiting and headache, classified under the PT "wrong product administered".

In six (6) cases extracted from the Safety Database under the standardized MedDRA query "medication error" (broad), capsules were opened due to reported difficulties with swallowing or because a nurse needed to administer them via a PEG tube. In one case, a pharmacist inquired whether the capsules could be opened. In none of these cases ADRs associated with the medication error were reported. The new NEPA oral suspension formulation will simplify administration for those patients who struggle with swallowing capsules.

Considering the overall exposure of more than 2.31 million patients treated worldwide with Akynzeo since its first launch in 2014, the number of cases containing medication errors events is very limited. Cumulatively, sixty-five (65) cases of medication errors have been received and in most of them no adverse events have been reported. At present, the potential for medication error is considered low and these cases do not show the same pattern, therefore they do not represent a safety concern.

Currently pack size limitation seems adequate to reduce the risk of medication errors as well the key information on the posology and method of administration described in the relevant sections of the SmPC.

Potential for off label use

The indication for the IV and oral hard capsules fixed combination of Akynzeo is the prevention of nausea and vomiting induced by highly or moderately emetogenic chemotherapy in cancer patients. This implies that the administration of the drug is intended only for this specific patient setting and the drug prescription is restricted to oncologists who daily manage chemotherapy protocols including chemotherapeutic agents with high or moderate emetogenic potential.

However, updated ASCO guidelines published in 2025 recommend as optimal treatment for CINV prophylaxis in patients receiving a single-day dose of low emetogenic potential chemotherapeutic agents a single dose of a 5-HT3 RA or a single 8 mg dose of dexamethasone.

In 2023 the MASCC/ESMO guidelines for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting in advanced cancer patients have been updated and further recommendations also

for chemotherapy with low or minimal emetogenic potential were included. 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).

The likelihood of the use of Akynzeo in the above described conditions cannot be entirely ruled out as the oncologist could prescribe the combination also to patients receiving such agents.

The safety profile of the IV formulation has been evaluated in cancer patients receiving repeated cycles of highly emetogenic chemotherapy. No particular safety issues emerged; in addition, considering the pharmacological properties and the mechanism of action of each single component it is unlikely that the pattern of adverse event/reactions may differ from that observed in patients treated in the clinical trial. However, since no efficacy and safety data have been collected for this setting of patients where alternative therapeutic options are available and recommended by guidelines, the intentional use of the IV formulation in this condition not covered by the terms of its marketing authorization constitutes an off-label use risk.

Since the launch of Akynzeo up to 10 October 2024, a total of 100 cases of off-label use involving both oral hard capsules and IV formulations have been reported. Most of these cases were non-serious, with no associated ADRs.

Specifically, forty-four (44) off-label use cases were reported with the IV formulation of Akynzeo, all except one case originating from the USA. Of these, thirty-three (33) cases the underlying cancer diagnosis, rather than CINV, was mistakenly reported by physicians. The company adopts a conservative approach, registering all off-label use cases in the database despite the reported incorrect indication. Among these thirty-three (33) cases, only one was associated with ADRs and was considered serious due to a fatal outcome. This case involved a 64-year-old female patient who received Akynzeo intravenously during each chemotherapy cycle. No relevant medical history, concomitant conditions, or medications were reported. The enrollment form indicated that Akynzeo was used for non-approved FDA indications, specifically ICD codes 171.6/49.5 for malignant neoplasm of connective and soft tissue of the pelvis and 276.51/E86.0 for dehydration. It was unclear if these referred to the patient's current conditions, so the company classified it as off-label use. The patient's death was confirmed one month later during a follow-up call. Due to the lack of detailed information in the reports, including the administered chemotherapy, other concomitant medications, and the patient’s medical history, a comprehensive causality evaluation was not possible. However, there was no indication of a relationship between Akynzeo and the death by unknown cause.

In eight (8) out of forty-four (44) reported off-label use cases involving the IV formulation of Akynzeo, the off-label use was attributed to incorrect administration frequency or dosage of dexamethasone, with no associated ADRs reported. The remaining three (3) cases involved situations where Akynzeo was administered multiple times per cycle or, in one instance, given to a patient without subsequent chemotherapy.

A total of fifty-six (56) out of 100 off-label use cases of Akynzeo capsules were reported, with nineteen (19) classified as serious. The seriousness of these events was not linked to off-label use. The reported off-label events included: daily administration of one Akynzeo capsule, co-administration with an incorrect dose of dexamethasone, the reported indication for various cancers such as colon neoplasia, intrahepatic bile duct carcinoma, breast cancer, squamous cell carcinoma, osteosarcoma, and gastric

cancer, instead of for CINV, as described earlier in this section. Additionally, Akynzeo was administered in various patterns, including a single dose or daily for three consecutive days. In one instance, Akynzeo was given to a 14-year-old patient with osteosarcoma.

The remaining thirty-seven (37) non-serious cases reported with Akynzeo capsules involved off-label use. These cases referred to situations where Akynzeo was administered to manage severe nausea and vomiting due to severe diabetic gastroparesis, post-operative nausea, and prior to procedures like gastric bypass surgery or the insertion of intragastric balloons. Akynzeo has been administered to paediatric patients, including 12-year-old and 15-year-old individuals. In several cases, Akynzeo was used along with dexamethasone in dosing regimens different from the recommended ones. Akynzeo was taken for three consecutive days after chemotherapy, starting one day post-chemotherapy. Additionally, Akynzeo was used before resminostat treatment, which is not included in the emetic risk classification.

"Off-label" also includes the intentional use of alternative routes of administration to that specified in the product license. For patients with swallowing difficulties or gastric tube feeding Akynzeo capsules does not represent the optimal choice for emesis prevention because of the size of the capsule. In three (3) out of fifty-six (56) cases the capsules were crushed, opened, or administered via a feeding tube. The newly developed oral suspension of NEPA will allow for easier administration to patients who have difficulties swallowing or cannot swallow the available capsule form, thus avoiding the need for intravenous infusion.

Despite a few cases of off-label use for post-operative nausea reported from post-marketing settings, the potential for off-label use in the prevention of postoperative nausea and vomiting (PONV), motion sickness and radiotherapy induced nausea and vomiting (RINV) is very small because there are therapeutic alternatives approved for use in these indications.

Considering the post-marketing experience, the risk of an off-label use is also unlikely to occur in PONV, because of the population (surgical patient) which is different from cancer patients and the availability of effective therapeutic alternatives. In addition, the treating physician is usually a surgeon or an anaesthesiologist and prophylactic treatments are commonly administered under the close supervision of health care professionals in the operating room.

Off-label use might occur if the drug is taken to prevent 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-HT_3 RAs are the most effective and used agents either as prevention and treatment of RINV.

The risk for this potential off-label use of the fixed combination 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, the potential risk of an off-label use of the fixed combination cannot be excluded considering the setting of patients to be treated.

Breakthrough CINV is vomiting and/or nausea that occurs within five days of chemotherapy administration despite the use of prophylactic antiemetic agents. This type of CINV usually requires immediate treatment or requires "rescue" with additional antiemetics. In clinical practice it is suggested treating breakthrough CINV with an agent from a drug class that was not used in the prophylactic regimen and recommended continuing the breakthrough medication if nausea and vomiting are controlled.

Since oral NEPA data are available only for the prevention of CINV and no further studies have been conducted to show the efficacy and safety of the combination in the treatment of breakthrough or refractory CINV, the use of oral NEPA in such conditions constitutes an "off label use".

One case report of oral NEPA use in the breakthrough CINV has been notified. Reportedly nausea and vomiting persisted despite therapy; the fixed combination capsule was discontinued and patient switched to aprepitant and palonosetron with favourable outcome.

"Off-label" also includes the intentional use of alternative routes of administration to that specified in the product license. For patients with swallowing difficulties or gastric tube feeding oral NEPA does not represent the optimal choice for emesis prevention because of the size of the capsule. Opening the hard gelatin capsule Size 0 which contains three netupitant tablets plus a soft gel capsule of palonosetron is not allowed as the package information leaflet of oral NEPA indicates that the capsule can be swallowed as a whole.

The identification of cases according to the search criteria above described resulted in a total of 9 cases coded with the PT "intentional product misuse". With the exception of one patient administered the content of oral NEPA, after the opening of the capsule by the nurse, in a PEG-tube; the remaining 8 cases pertain to patients with swallowing difficulties. There were no adverse events associated with this intentional misuse of the product.

Considering that the limited number of cases notified so far were all uneventful, the SmPC statement that the hard capsule should be swallowed whole; is deemed adequate to this purpose.

Potential for risks in pregnant and lactating women

Report of the study on off-label use of medicinal products in the European Union published in February 2017 (Weda M et al. 2017) points to that off-label use in pregnant women happens or needs special attention as many medicines are not approved for use in pregnant women, have contra-indications or lack information on the safe use in pregnancy.

An analysis of the literature showed that only the administration of chemotherapy during the embryonic stage of conceptus is dangerous and can lead to the termination of the pregnancy. When the disease is diagnosed in the 2nd or 3rd trimester of gestation or when it is possible to delay the initiation of chemotherapy beyond the 14th week, the risk of severe problems for the fetus are low, and pregnancy termination is not required. The 1st trimester is the period during which the majority of organogenesis occurs and chemotherapy can exert a significant teratogenic effect, particularly on the heart, limbs, palate, neural tube, eyes, and ears. Therefore, the administration of cytotoxic drugs during the 1st trimester is particularly dangerous because it is frequently associated with the development of malformations, embryo death, and spontaneous abortion.

Outside this period, the influence of chemotherapy in fetal and child outcomes is significantly lower, and the risk of malformations has not been explicitly demonstrated. Major malformations are reported in 1.3% of children born to mothers with cancer who had been treated with chemotherapy after the 1st trimester, which is a risk value similar to the general population without chemotherapy treatment. Moreover, although it has been reported that the eyes, genitalia, central nervous system, and hematopoietic systems remain vulnerable to continued exposure to cytotoxic drugs during the last months of gestation, and intrauterine growth retardation is a possible complication of that exposure, results from several studies have shown that chemotherapy administered during the 2nd or 3rd trimester of pregnancy has little effect on the long-term outcome of the child, which favors its use to control cancer in pregnant women. Although these data seem reassuring and promising, other factors should be considered. Severe neutropenia can occur in pregnant women with cancer treated with chemotherapy. Usually this condition is treated with granulocyte colony stimulating factor but the effectiveness and safety of this compound during pregnancy has not definitively been established (Esposito S et al. 2016).

There were 2 scattered cases of exposed pregnancy to netupitant-palonosetron during the clinical development program of the oral fixed combination. Both pregnancies and deliveries were uneventful, and newborns were healthy. During the Phase I bioequivalence study of the oral suspension formulation, a pregnancy was identified during a follow-up visit in a healthy female volunteer enrolled in the study. It was reported that an artificial abortion was performed due to personal decision (no medical reasons). No ADRs were reported.

Three cases have been collected in the post-marketing surveillance of the oral hard capsules formulation through the application of SMQs Pregnancy and neonatal topics. One case involves a female patient with ovarian cancer who was incorrectly administered oral fixed combination daily for 5 consecutive days at the second trimester of pregnancy; another case refers to a female with breast cancer given oral fixed combination prior to the first cycle of chemotherapy at the 26-week of gestation. At the second cycle of chemotherapy there was a switch to ondansetron. The third case includes PTs "foetal exposure during pregnancy" and "small for dates baby". The case referred to a male foetus, whose parent, a 31-year old female was under chemotherapy treatment. The foetus was exposed to Akynzeo via transplacental route of administration (oral use as parent route of administration) during 32.4 - 35.4 gestational week at third trimester of gestation period along with uromitexan, dexamethasone, epirubicin. Considering that several medications were administered concomitantly, the contribution of each one, if any, could not be determined and the role of Akynzeo was evaluated as possibly related.

In the current version of the SmPC it is clearly reported that women of childbearing potential should not be pregnant or become pregnant while on treatment with the oral fixed combination. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must use effective contraception during therapy and up to one month after treatment with this medicinal product.

The combination is contraindicated during pregnancy as reported in the SmPC since safety in human pregnancy has not been established for either palonosetron or fosnetupitant/netupitant, and animal reproduction studies do not always predict human responses. Effects in embryofetal development and in the pre- and post-natal development study in rats were observed only at the high dose level of fosnetupitant. Preclinical data in rabbit studies indicates a potential teratogenic effect of netupitant due to the observations of foetal abnormalities without safety margin; however, the relevance of these findings in humans is unknown.

In the unlikely event that cases are reported to the Company concerning the fixed combination administration to pregnant woman, the case will be fully documented and logged into the safety database for active monitoring of pregnancy until delivery (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 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 and gynecologists of the detected risks.

Risks associated with pharmacokinetic and pharmacodynamics interactions

Fosnetupitant

In vitro studies indicated that fosnetupitant is rapidly hydrolyzed to netupitant by non-saturable hydrolytic enzymes such as phosphatases, largely distributed throughout the body in blood and tissues. Rapid hydrolysis of fosnetupitant was demonstrated in human liver, lung, kidney and intestine S9 fraction in the presence and in the absence of NADPH. Conversion of fosnetupitant to netupitant is not thought

to involve CYP450 enzymes because it can occur in the absence of NADPH. Indeed, as for other quaternary amine prodrugs resulting from phosphonoxomethyl derivatization of tertiary amine functionality, a two-step bioreversion process is expected to occur in vivo for fosnetupitant. First step consists in a phosphatase-catalized dephosphorylation to give the resultant hydroxymethyl quaternary ammonium intermediate. In a second step, this latter, highly unstable at neutral pH, may undergo spontaneous non-enzymatic chemical breakdown to release the parent tertiary amine netupitant. Lack of CYP450 enzymes involment in fosnetupitant metabolism prevents any potential interaction between fosnetupitant and CYP450 inhibitors and inducers.

In human liver microsomes, fosnetupitant shows moderate-to-weak inhibition of CYP2C9 (IC50 = 27.9 µM) and CYP2C19 (IC50 = 46.1 µM). No relevant interactions were observed with other CYP450 isoforms. In vitro studies indicated also that fosnetupitant is a moderate-to-weak inhibitor of few transporters, i.e., the uptake transporters OATP1B3 (IC50 = 17.34 µM) and OATP1B1 (IC50 = 19.01 µM), and the efflux transporter MDR1/P-gp (47% inh. at 50 µM). However, the outcome of a physiologically-based pharmacokinetic (PBPK) modeling on the Simcyp platform (Certara, USA) using a single adjusting compartment (SAC) predicted no clinically relevant interaction between fosnetupitant and CYP2C9 and CYP2C19 substrates, such as warfarin and omeprazole, respectively. Prediction of the magnitude of interaction of fosnetupitant with S-warfarin (CYP2C9 substrate) or omeprazole (CYP2C19 substrate) following coadministration of the victim drug with a single IV dose of 235 mg fosnetupitant infused over 30 minutes, indicated no increase in S-warfarin and omeprazole exposure, with geometric mean Cmax and AUC ratios of 1.00.

In vitro studies showed that fosnetupitant is a moderate-to-weak inhibitor of few transporters, i.e., the uptake transporters OATP1B3 (IC50 = 17.34 µM) and OATP1B1 (IC50 = 19.01 µM), and the efflux transporter MDR1/P-gp (47% inhibition at 50 µM). No in vivo interaction between fosnetupitant and rosuvastatin (OATP1B1 and OATP1B3 substrate) as well as between fosnetupitant and digoxin (P-gp substrate) was predicted based on the PBPK model mentioned above. Hence, no influence on the PK profile of OATP1B1/3 and P-gp transporter substrates is expected due to concomitant administration of fosnetupitant.

In conclusion, no drug interaction is expected between fosnetupitant and drugs which are inhibitors or inducers of CYP450 isoforms and transporters. Similarly, an interaction between fosnetupitant and drugs which are substrates of CYP450 enzymes or transporters can be ruled out.

Netupitant / palonosetron

The drug-interaction program designed for the netupitant/palonosetron fixed combination development was based on two primary principles: 1) evaluations based on metabolic/mechanistic pathways and, 2) evaluations of agents which will be routinely co-administered.

Data available from non-clinical and clinical DDI study indicated that there is no PK interaction between netupitant and palonosetron.

The interaction potential of palonosetron has 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 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.

Metabolism of netupitant is hepatic and mainly mediated by CYP3A4 isoform. Netupitant and its metabolites M1, M2, M3 competitively inhibits CYP3A4 and *in vitro* and *in vivo* studies results indicate drug interaction potential with CYP3A4 substrates. Other CYP isoenzymes (e.g., CYP1A2, CYP2C19 and CYP2D6) were not inhibited by netupitant. Netupitant and its metabolites, M1, M2 and M3, are not inducers of CYP1A2, CYP2C9, CYP2C19 and CYP3A4.

The assessment of the potential Time Dependent Inhibition (TDI) of netupitant towards CYP3A4 was investigated in vitro up to the concentration of 250 µM using Human Liver Microsomes (HLM). Erythromycin was used as a positive control. Netupitant, in the range of concentrations tested (50-250 µM), did not show any TDI effect towards CYP3A4.

In the framework of oral Akynzeo approval in USA, FDA recommended to perform the following studies:

a) *In vivo* drug interaction study to evaluate the duration of inhibitory effects of Akynzeo on CYP3A4 enzyme activity beyond 4 days after Akynzeo administration. It was a randomized, two-period, two-sequence, cross-over study in healthy subjects. A total of 24 healthy male subjects were dosed and completed the study observation period. The study results showed that the inhibitory effect of Akynzeo on CYP3A4 ceased between Day 8 and Day 10, as indicated by the outcome of the statistical comparisons of plasma dexamethasone pharmacokinetic parameters. Treatment emergent adverse events were reported during the study in all subjects. However, no unexpected treatment emergent adverse reaction was detected throughout the study, thus confirming the safety profile of Akynzeo as observed in the previous studies. No clinically significant change in laboratory parameters, vital signs, body weight or ECGs due to a single dose of Akynzeo was observed. The study safety data did not raise any safety concern for the co-administration of Akynzeo with dexamethasone up to 10 days.

b) *In vitro* study to evaluate the potential of netupitant to act as a substrate for P-gp transporter in a bi-directional transport assay system. It was conducted to evaluate the potential of netupitant to act as a substrate for P-gp transporter in a bi-directional transport assay system. The study results showed that netupitant at 1, 10 and 100 µM has medium to high permeability and an efflux ratio lower than 2. The presence of P-gp inhibitors (50 µM Verapamil and 12.5 µM Cyclosporin A) in the incubation of netupitant at 1 µM did not affect significantly the permeability and the efflux ratio of test item. Overall these results indicate a low potential for netupitant to be a substrate for P-gp.

c) An 8-week GLP toxicology study with fertility evaluation in neonatal rats treated with netupitant alone. The results of this study showed that daily oral gavage for 8 weeks to juvenile male and female rats of netupitant at dose levels of 0, 3, 10 and 30 mg/kg/day resulted in no relevant safety findings. The only adverse sign of toxicity consisted of an increased incidence and severity of macrophage foci in the mesenteric lymph nodes at 30 mg/kg/day in both sexes. In the fertility assessment phase of the study, there were no treatment-related changes. For the toxicity assessment of netupitant, based on adverse effects observed in the mesenteric lymph node from

both sexes at 30 mg/kg/day, the No-Observed Adverse Effect Level (NOAEL) of the test substance for males and females was considered to be 10 mg/kg/day. For the fertility assessment of netupitant, in the absence of any treatment-related finding, the NOAEL of the text substance for males and females was considered to be 30 mg/kg/day.

Interaction with CYP3A4 inhibitors and inducers (due to netupitant)

Results of drug-drug interaction studies showed that when Akynzeo is used concomitantly with another CYP3A4 inhibitor, netupitant plasma concentrations could be elevated. It can be anticipated that the high concentration of netupitant might lead to an increased observation of AEs such as headache, somnolence. This is only a theoretical hypothesis merely based on the safety results of a study in overactive bladder patients treated with doses of netupitant from 50 mg up to 200 mg in comparison with placebo for 8 weeks.

Conversely, when Akynzeo is used concomitantly with medications that induce CYP3A4 activity, netupitant plasma concentrations could be reduced and this may result in decreased efficacy. In this case the diminished efficacy of netupitant in cancer patients may not guarantee an adequate control of nausea and vomiting resulting in repeated emetic episodes, that in the most severe and persistent forms, may be complicated by electrolytes disorders, symptomatic dehydration and malnutrition. Nausea may affect appetite, the ability to eat, the taste and determine weight loss.

These unpleasant effects may cause a delay of the next chemotherapy cycle and/or a reduction of the agents to be given which ultimately impact the course of the malignant disease.

Given the importance of CYP3A4 in the metabolism of a variety of drugs, an understanding of this phenomenon is crucial in minimizing the potential for interactions between drugs; therefore, a warning to inform about this risk is included in the SmPC. The concomitant use of the fixed combination with strong inhibitors (ketoconazole) or strong inducers (rifampicin) should be avoided to mitigate such risk.

Interaction with CYP3A4 substrates (e.g., corticosteroids and benzodiazepines) (due to netupitant)

Co-administration of a single dose of netupitant (300 mg) with a dexamethasone regimen (20 mg on Day 1, followed by 8 mg b.i.d. from Day 2 to Day 4) significantly increased the exposure to dexamethasone in a time and dose dependent manner. The $AUC_{0\text{-}24}$ (Day 1), the $AUC_{24\text{-}36}$ (Day 2) and the $AUC_{84\text{-}108}$ and $AUC_{84\text{-}\infty}$ (Day 4) of dexamethasone increased 2.4-fold, with co-administration of 300 mg netupitant. The pharmacokinetic profile of netupitant was unchanged when administered in combination with dexamethasone.

Increased exposure to dexamethasone levels may induce acute psychosis disorders, headache and gastrointestinal disorders, ranging from mild to severe forms such as pancreatitis or bleeding.

In oncology clinical practice, dexamethasone, along with other active antiemetic drugs, is one of the most widely used corticosteroids to prevent chemotherapy induced nausea and vomiting. To avoid the development of undesirable effects, it is strongly recommended in the SmPC that dexamethasone dose should be reduced by approximately 50% when co-administered with the netuputant/palonosetron fixed combination.

To comply with FDA recommendation, a study to investigate the duration of CYP3A4 inhibition up to 10 days after administration of a single capsule of NEPA fixed combination using dexamethasone as a probe substrate was conducted. Netupitant's inhibitory effect on CYP3A4 was evident in the plasma dexamethasone PK profiles on Days 1 and 4, as observed in a previous drug-drug interaction study.

Inhibition was still present on Day 6, whereas it remarkably decreased on Day 8. On Day 10, netupitant's inhibitory effect on CYP3A4 was no longer appreciable.

The outcome of this study suggests that there is no need to modify the current recommended dosage of dexamethasone reported in the SmPC of oral Akynzeo.

Results of the drug-drug interaction studies with erythromycin and midazolam showed that exposure to erythromycin and midazolam was increased approximately 1.3 and 2.4 fold, respectively, when each was co-administered with netupitant. The pharmacokinetic profile of netupitant was unaffected by the concomitant administration of either midazolam or erythromycin.

Benzodiazepines such as alprazolam, triazolam and midazolam are mainly metabolized thru Phase I metabolism by CYP3A4. These drugs are commonly prescribed for insomnia since they facilitate sleep onset and the overall duration of sleep. Successive doses of midazolam lead to bioaccumulation of its hydroxy-metabolites and may prolong the drug's sedative effects.

An increased exposure to these benzodiazepines when given concomitantly to the fixed combination may cause an altered (depressed) mental status, residual daytime sedation, drowsiness, dizziness, light-headedness, cognitive impairment, motor incoordination. It is not expected to induce signs and symptoms of severe toxicity (comatose status) with respiratory compromise, even though the doses required to produce respiratory compromise are difficult to quantify and depend upon many factors, including tolerance, weight, age, and genetics.

Summing up, the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam) should be considered in clinical practice when co-administering these agents with the fixed combination. No further actions were foreseen to minimize the above described risk; the SmPc provides details about the results of the drug-drug interaction studies.

Possible interaction with BCRP substrates (due to netupitant)

In vitro studies indicate that netupitant is not a BCRP substrate. However, netupitant and its metabolites M1, M2 and M3 are inhibitors of the BCRP transporter. The effects of netupitant on concomitant BCRP substrates were not studied in humans. Besides being an efflux trasporter in the gut, BCRP is reported to participate in the biliary and renal excretion of drugs. On the basis of the low netupitant solubility and the inhibition constant (Ki) for BCRP determined in vitro, inhibition of the efflux transporter BCRP by netupitant at intestinal level cannot be excluded, although this is predicted to be unlikely and, should it occur, of scarce clinical relevance. Netupitant is not expected to interact with BCRP at liver and renal levels. Therefore, drug-drug interaction between netupitant and BCRP substrates is unlikely and in vivo DDI studies with the concomitant administration of netupitant and probe BCRP substrates, such as rosuvastatin, are unnecessary. Details provided in the SmPC are deemed adequate for the purpose to inform about this unlikely interaction.

Possible interaction with UGT-2B7 substrates (due to netupitant)

UDP-glucuronosyltransferase (UGT) UGTs enzymes are found in human hepatic and extra hepatic tissues, such as the intestinal epithelial layer.

UGT2B7 is the major enzyme isoform for the metabolism of morphine to the main metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Netupitant, M1 M2 and M3 inhibitory potential on different UGT isoforms was tested in human liver microsomes or recombinant UGTs. Results showed that netupitant may act as inhibitor of the UG2B7 isoform involved in the metabolism of several

compounds, including opioids and other oral substrates of this enzyme such as zidovudine and valproic acid.

In vivo interactions with UGT1A1, 1A3, 1A6, 1A9 and 2B17 are unlikely. Despite the significant inhibition of the isoform UGT2B7 produced by netupitant in vitro, no interaction can be predicted in vivo between netupitant and UGT2B7 substrates at hepatic level. In fact, considering that netupitant Cmax after oral administration of 300mg is approximately 1μM and netupitant free fraction in plasma is <1 %, the calculated unbound Cmax (Cmax,u) reached in plasma is 0.01μM. Therefore, taking into consideration the lowest IC50 value measured for UGT2B7 (0.735 μM), [I]/Ki results to be 0.014 (where [I]=Cmax,u), a value below the 0.02 cut-off defined by the EMA Guidance on the Investigation of Drug Interactions (2012) that exclude the need for in vivo DDI studies with probe substrates. Based on this result, an in vivo interaction of netupitant with UGTs at hepatic level is unlikely. The predicted in vivo contribution of the three metabolites M1, M2 and M3 to the inhibition of UGT2B7 is considered irrelevant due to the lower Cmax and the higher IC50s compared to netupitant. An in vivo interaction upon netupitant administration is considered possible at intestinal level only during the absorption phase of orally administered drugs with poor/moderate oral bioavailability which are mainly metabolized by UGT2B7. In fact, netupitant is orally administered at a dose of 300 mg; assuming that the maximum concentration in the intestinal lumen ([I]) corresponds to the netupitant solubility in FaSSIF (93.3 μM), the ratio [I]/Ki is >10 for UGT2B7 ([I]/Ki = 93.3 μM/ 0.735 mM = 127).

The magnitude of such an inhibitory effect in the clinical setting is not established. Therefore, as reported in the SmPC, caution is recommended when netupitant is combined with an oral substrate of this enzyme (e.g., zidovudine, valproic acid, morphine).

Based on the acknowledged low affinity of substrates for UGT enzymes, as well as the potential for multiple UGTs to metabolize the drugs, it is anticipated that the likelihood of a pharmacokinetic drug-drug interaction between netupitant and UGT2B7 substrates cleared by glucuronidation is low.

Overall, netupitant interaction with UGT enzymes is expected to have scarce clinical relevance, if any. No in vivo interaction studies are envisioned. Details provided in the SmPC are deemed adequate for the purpose to inform about this possible interaction; no additional risk minimization measures are envisioned.

Possible interaction with P-gp substrates (due to netupitant)

Digoxin is a substrate of P-glycoprotein (P-gp), an efflux transporter mainly expressed by epithelial cells with excretory roles in the intestine, kidneys and liver. Drugs that induce or inhibit P-gp have the potential to alter digoxin pharmacokinetics. In the presence of a P-gp inhibitor, digoxin serum concentrations may increase more than 50%. Considering that digoxin is a drug with a narrow therapeutic index, the risk of drug related adverse events due to an increase of circulating concentrations needs to be considered. There is evidence from in vitro studies that netupitant is a weak inhibitor of the P-glycoprotein (P-gp) transporter. Interaction of netupitant for P-gp transport can be expected at concentrations ≥ 5 μM. Considering that netupitant Cmax after administration of 300 mg oral netupitant approaches 1μM, no drug-drug interaction is expected in vivo between netupitant and P-gp substrates at renal and hepatic levels. P-gp inhibition at intestinal level may increase the oral bioavailability of P-gp substrate drugs that are scarcely bioavailable. This is not the case for digoxin, a P-gp substrate with good oral bioavailability (>70%), or other P-gp substrates that may be co-administered with Akynzeo. Hence, no clinically relevant impact of netupitant on digoxin rate and extent of absorption is expected. Differently, dabigatran etixilate, another P-gp substrate, has a low oral bioavailability (about 7%). In this case, an exposure increase in the presence of netupitant may occur.

In a specific in vivo drug-drug interaction study concurrent administration of netupitant with digoxin in human healthy volunteers did not affect the systemic exposure to digoxin at steady-state; digoxin Cmax point estimate was 9% higher with netupitant co-administration, an increase that was considered to be of scarce clinical significance. No change in digoxin exposure occurs with the co-administration of oral netupitant, even at a dose 50% greater than that recommended (300 mg). Moreover, after netupitant administration, on Days 8-12, mean trough digoxin concentrations appeared to be stable, confirming that there was no effect of netupitant on digoxin concentrations. Also, the excretion of digoxin in urine was 55% without netupitant and 57% after netupitant co-administration, demonstrating again the lack of a drug-drug interaction.

The influence of physio-pathological covariates, namely gender, age and renal status, on the gender has a minor impact, if any, on the pharmacokinetic profile of digoxin and netupitant.

Age was also investigated as a covariate with potential impact on the metabolism of digoxin when coadministered with netupitant. Aging is known to be associated both with a decline in basal metabolic rate and a mild or moderate degree of renal insufficiency that lead to a decreased clearance of creatinine. Changes of digoxin PK profile are mainly the results of decreased CLCR and metabolism rate which determine a decrease in digoxin CL, and a decreased lean body mass which determines a decrease in digoxin volume of distribution.

Results of netupitant PK parameters in elderly prove that the observed modest increase in netupitant exposure is not expected to affect P-gp secretory activity at hepatic and renal level. Therefore, no interaction between netupitant and digoxin is envisioned in the elderly. Decreased digoxin clearance and increased digoxin exposure are predicted in the elderly receiving digoxin alone as compared to healthy adults; however, the concomitant administration of netupitant is not anticipated to affect digoxin PK in the elderly.

The main route of elimination of digoxin is the renal excretion, since only about 25% is eliminated by non-renal routes. Therefore, impaired kidney function is the most important condition with an influence on the pharmacokinetics of digoxin. To reduce the risk of under- and overtreatment in patients with impaired renal function, dose adjustment is necessary based on serial measurements of steady-state plasma concentration of digoxin. Netupitant is mainly eliminated through hepatic metabolic pathway with renal clearance accounting for less than 5% of clearance. The co-administration of netupitant with digoxin is not predicted to alter the PK profile of digoxin in patients with impaired renal function.

The use of digoxin in cancer patients is believed to be not different in the presence of netupitant; however, cancer patients with reduced renal function due to any reason would be expected to have appropriate monitoring of digoxin as part of their clinical care. No speculations regarding P-gp substrates in the gut, such as dabigatran, are currently possible. Routine risk minimization measures reported in the SmPC are considered adequate to this purpose and no additional risk minimization measures were envisaged.

Important identified risks (severe hypersensitivity reactions and severe constipation) and other important potential risks have been removed with the official approval of the EU-RMP version 2.7.

Paediatric safety issues

No Paediatric Investigational Plan (PIP) was conducted for the Akynzeo® hard capsules, as a waiver was granted by the EMA on 24th January 2012 (EMEA-001198-PIP01-11, decision number P/0014/2012), for all subsets of the paediatric population. The waiver was granted on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients, in the condition "Prevention of chemotherapy-induced nausea and vomiting".

In November 2017, in response to an application of a Paediatric Investigation Plan including a deferral for the IV formulation (ref. EMA/556599/2017), the paediatric committee concluded that there is no need to study the fixed combination of fosnetupitant/palonosetron in neonates. Consequently, a waiver for conducting studies in neonates was granted (EMA Decision P/0140/2018 dated 7 May 2018). This is also in line with the fact that IV palonosetron is only approved from 1 month of age onward.

The Pediatric Committee issued a positive decision on the proposed PIP in May 2018. Since then, the originally approved PIP has undergone some modifications, the most recent of which was submitted on 29 May 2023. This major modification was aimed at shifting the required adequate and well controlled safety and efficacy study clinical study from oral NEPA to IV NEPA and investigate IV NEPA also as multiple dose administration during multi day chemotherapy regimens. The changes to the proposed PIP are based on the consideration that data from an adequate and well controlled efficacy and safety study with IV NEPA would be clinically more appropriate than such data on oral NEPA and that data obtained from both a single and multiple administration of the antiemetic in the single and multiday chemotherapy regimen would have a greater clinical importance.

[redacted]

At present the lack of paediatric data constitutes missing information.

Missing information

Effects in children

The efficacy and safety of the IV and oral fixed dose formulation has not been established. Preliminary safety and efficacy results were obtained from the PK/PD dose finding study for oral hard capsules formulation (NEPA-15-31). Please refer to the above section "Paediatric safety issues "for further details.

Other missing information has been removed following official approval of the EU-RMP version 2.7.

Risks linked to the disposal of the used product

Not applicable; the IV products have to 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 21 shows the safety concerns identified in the initial and approved version of the RMP for oral Akynzeo.

Important identified risks	Severe hypersensitivity reactions, including anaphylaxis, anaphylactic/anaphylactoid reactions and shock Severe constipation (due to palonosetron)
Important potential risks	QT/QTc interval prolongation Convulsive events (due to palonosetron) Serotonin syndrome (due to palonosetron) Liver transaminases increase Effects of interaction with CYP3A4 substrates (e.g. corticosteroids and benzodiazepines) (due to netupitant) Effects of interaction with CYP3A4 inhibitors and inducers (due to netupitant) Phospholipidosis (due to netupitant) Teratogenic effects Effects of interaction with BCRP substrates (due to netupitant) Effects of interaction with UGT-2B7 substrates (due to netupitant) Effects of interaction with P-gp substrates (due to netupitant)
Missing information	Effects in children Effects in patients with severe hepatic impairment Effects in patients with end-stage renal disease undergoing haemodialysis Effects in patients aged 75 years or more Effects on fertility Effects on pregnancy and lactation

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

Medication error occurred neither with the IV nor with the oral fixed combination formulation during the clinical development program, therefore the real-life use in the post-marketing environment will be helpful to identify some medication errors. As discussed in the previous section, it is known that the intravenous (IV) formulation which requires preparation, dilution or reconstitution prior to use may be subject to medication errors.

The proposed new formulation, a liquid solution form for IV injection, does not require reconstitution, hence, it reduces the risks due to preparation and avoids potential inaccuracies in the total dose of active ingredients to be infused.

At present, since the SmPC provides accurate information on the preparation, dilution, storage and drug dispensing, potential risks from medications errors are not considered for inclusion among the safety specification. Accurate analysis of each individual spontaneous report of medication error will be conducted as well as diligent efforts to collect any information useful for a root cause analysis in order to assess if further actions are necessary to mitigate the risk.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Torsade de pointes

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).

In the safety study comparing IV and oral NEPA (NEPA 15-18), across all cycles, the percentage of patients with a QTcB post-baseline value >500 msec and baseline value ≤500 msec was similar for both treatment groups and less than 1.0% overall at each timepoint. No events of Torsade de pointes were recorded.

Warning and precaution concerning the potential issue of QT prolongation is reported in the EU SmPC of IV and oral Akynzeo, in particular for patients with cardiac or eletrolytes abnormalities or for patients taking anti-arrhythmic medicinal products or other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Nevertheless, due to the clinical relevance of this medical condition, it is 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 any case originating from any source.

Serotonin syndrome (due to palonosetron)

Serotonin syndrome (SS) is a potentially life-threatening drug reaction precipitated by the use of 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.

Serotonin syndrome represents a potential safety concern since palonosetron is a component of the combination. Post-marketing cases have been notified following exposure to palonosetron or oral Nepa concomitantly with other serotoninergic agents.

The prospective of an increase in use of IV or oral NEPA in different cancer settings, also in combination with other drugs makes the issue of the risk profile important for these drugs.

Serotonin syndrome is not an idiopathic drug reaction, but it is predictable and preventable, and therefore patient safety would be served if it is mentioned in the product labelling. 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.

Teratogenic effects

Fosnetupitant had no relevant effects on fertility up to 39.47 mg/kg/day. Studies conducted in order to assess the potential for embryofoetal developmental toxicity were carried out in both rats and rabbits. Effects in embryofetal development were observed mainly at high dose level. In the rat studies no malformations were detected in the foetuses of the low and mid-dose groups (3.95 and 13.16 mg/kg/day respectively). One foetus with malformation (hindlimb malrotated) and one dead foetus were observed in the high dose group. At skeletal examination of foetuses, no ossification of pubis was
detected in 6 foetuses of the high dose group (39.47 mg/kg/day). For studies in rabbits there were no treatment-related effects for the skeletal examination of foetuses at any dose level. A slight increase in

intrauterine deaths was recorded in treated groups with statistically significance in the mid- and high dose groups (6.25 and 12.5 mg/kg/day respectively).
An increased incidence of positional foetal abnormalities of the limbs and paws, fused sternebrae and agenesis of accessory lung lobe were observed following daily administration of netupitant in rabbits at 10 mg/kg/day and higher during the period of organogenesis. In a pilot dose range finding study in rabbits, cleft palate, microphtalmia and aphakia were observed in four foetuses from one litter in the 30 mg/kg/day group. The relevance of these findings in humans is unknown.

Limited clinical data are available that can contribute to better understand and assess the impact and the consequences of fixed combination administration in pregnant patients.

Considering the above, teratogenic effects are considered an important potential risk.

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

The list of safety concerns presented in the RMP version 3.0 is the same as in the version 2.7. The list of safety concerns was reviewed in RMP version 2.7 in line with the current guidance and definitions on important identified and potential risks and missing information. Detailed rationales were also provided in the RMP version 2.7. The safety concerns outlined in RMP version 3.0 are also proposed for inclusion in RMP version 4.0.

There is no evidence of any change in the clinical pattern of Akynzeo ADRs or of any new qualitative or quantitative safety concern. No regulatory requests were received since the approval of the previous RMP version 3.0. Therefore, and based on the evaluation of the cumulative safety data collected up to the DLP of this RMP, the DLP of the last submitted PSUR and the PRAC assessment of this PSUR, the MAH considers there are no reasons to support the reclassification of the risks or the identification of new safety concerns.

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

None

Important potential risks

Table 22 Torsade de pointes due to QT/QTc prolongation

Torsade de pointes due to QT/QTc prolongation	
Potential mechanisms	Preclinical studies indicated the potential to cause prolongation of the QT interval by both palonosetron and netupitant. At all dose levels tested in ICH E14 compliant studies, neither palonosetron nor netupitant did induce clinically relevant prolongation of the QT/QTc interval. Results also provided evidence to the effect that combining netupitant with palonosetron did not confer a risk of QT-liability or modify the QT-safety of palonosetron. 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. 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.
Evidence source and strength of evidence	Studies in healthy volunteers showed no relevant effects on the QT parameters and no clinically important QT prolongations were observed in the safety study in both treatment groups. 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. In the IV NEPA program, mean changes from baseline in the ECG parameters were small and generally similar in the two treatment groups. The frequency of patients with new QTcF interval values > 500 ms or increases from baseline > 60 ms was very low and comparable between treatment groups. No new abnormal U waves across treatment cycles were detected. Regular ECG monitoring in well over 1000 cancer patients over a number of cycles in phase 2/3 clinical trials provides further evidence on the satisfactory cardiac safety of the oral combination of netupitant and palonosetron. The numbers of subjects with categorical QT responses were far lower than those subjects who had (in all likelihood, chemotherapy-induced) non-specific ST-segment or T-wave changes (5-17%), thus further excluding an adverse electrophysiological pharmacological effect on cardiac repolarization due to the anti-emetic treatment. The interpretation of outlier results in a setting of oncologic patients needs to take into account the confounding effect of several risk factors including

Torsade de pointes due to QT/QTc prolongation	
	electrolyte imbalance, comorbidities and comedication in addition to chemotherapy. Recommended assessment criteria that could indicate a potential safety signal include a change in QTcF from baseline to > 500 msec in more than 5% of patients and from baseline of > 60 msec in more than 15% of patients. Whether following a single cycle or following multiple cycles, the data did not breach these recommended thresholds for outlier analysis in both clinical development programs. The above results denote a satisfactory cardiac safety profile for the IV and oral NEPA fixed combination. In the Cardiac Disorders and Investigations SOCs at the data lock point of the last submitted PSUR of Akynzeo there are no adverse reactions denoting this type of abnormalities or more serious events.
Risk factors and risk groups	Risk factors include drug interaction, pre-existing cardiac disease, e.g. cardiac ischaemia, cardiomyopathies, congenital long QT syndrome, or electrolytes abnormalities or treatment with drugs known to prolong QT interval, hypothyroidism and hypoglycaemia. Female sex and older age are also associated with longer QT intervals. Furthermore a wide range of chemotherapy agents including histone deacetylase inhibitors, nilotinib, ponatinib, vandetanib, crizotinib, vemurafenib, taxanes has been associated with arrhythmia effects.
Preventability	Patients with known pre-existing cardiac disease should be monitored closely for any signs of QT/QTc interval prolongation or any other cardiovascular effects of the fixed combination. Patients should talk to their doctor before taking the fixed combination if they have a personal or family history of alterations in heart rhythm or they have other heart diseases or an imbalance of blood electrolytes (e.g. potassium and magnesium). To avoid the occurrence of serious complications, the risk of QT prolongation must be carefully evaluated by physicians not only by adopting the appropriate correction formula but also by considering treatment-related toxicities and by assessing the pharmacologic characteristics of other drugs that are administered with a curative or palliative intent but prolong QT (antiemetics, antibiotics, antifungals, antipsychotics, and others).
Impact on the benefit-risk balance of the product	In light of the safety results of the clinical trials with both fixed combination drugs, the actual impact is considered very limited; the palonosetron postmarketing experience, even considering the underreporting, and the satisfactory cardiac safety profile emerged from the review of the clinical data are encouraging; therefore also the expected impact of this potential risk for the fixed combination formulations is low. The benefit/risk ratio is expected to be not affected by this concern; QT liability will be judiciously scrutinized in this respect.
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. There are no post-marketing case reports with this type of reaction for oral Akynzeo. 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. Serious adverse drug reactions related to complications of QT/QTC prolongation following exposure to the fixed combination will be analyzed in order to assess the overall impact on public health.

Table 23 Serotonin syndrome (due to palonosetron)

Serotonin syndrome (due to palonosetron)	
Potential mechanisms	Serotonin syndrome 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.

Serotonin syndrome (due to palonosetron)	
	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. 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.
Characterisation of the risk	A retrospective analysis of serotonin syndrome (SS) registered in the French pharmacovigilance database between January 1, 1985 and May 27, 2013 was conducted (Abadie D et al. 2015). Only cases whose clinical symptoms fulfilled Sternbach, Radomski, or Hunter SS diagnostic criteria were retained for the analysis. 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 inhibitors (9.1%, mainly venlafaxine), tricyclic antidepressants (8.6%, mainly clomipramine), and some monoamine oxidase inhibitors (6.2%, mainly moclobemide). Nonpsychotropic 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 serotonin syndrome 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, in particular of comedications that may have triggered the reaction. One post-marketing case has been notified involving a female patient who suffered from SS associated to depression and suicide attempt seven days after the intake of one capsule of Akynzeo. Another post-marketing case pertains to a male patient, who experienced serotonin syndrome on the same day he received Akynzeo. From the sign-off date of the RMP version 3.0 to the DLP of this RMP, there were two spontaneous, poorly documented cases of SS reported from Australia and South Africa. The lack of essential information about the patients' medical histories and concomitant medications does not allow a thorough evaluation of the potential risk of SS.
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 serotonin syndrome 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 the benefit/risk ratio of the fixed combination.

Serotonin syndrome (due to palonosetron)	
Public health impact	Polypharmacy is pandemic and the incidence of serotonin syndrome may be on the rise. So far, it is not possible to estimate the potential public health impact, without further characterization of the relevance of this risk to the fixed combination administration.

Table 24 Teratogenic effects

Teratogenic effects	
Potential mechanisms	Unknown mechanism in humans as no studies conducted in pregnant women with the fixed combination. Preclinical data are not predictive of the potential effects in humans. Ondansetron has an effect on a developing fetus because it easily crosses the placental barrier. It has also been found to take longer to leave neonatal bodies immediately after birth than it does the mother's body. There is no information in humans concerning the mechanism of palonosetron and the potential teratogenic effects.
Evidence source and strength of evidence	Signal of birth defects following in-utero exposure during the first trimester of pregnancy arised from recent publication on ondansetron (Zambelli-Weiner A et al. 2019). Analyzed dataset contained 1,149,145 live births from 1,004,175 mothers. Of these, 76,330 infants were exposed to ondansetron in-utero during the first trimester (5,557 exposed exclusively in medical settings), and 61,830 infants were diagnosed with structural defects. First trimester exposure to ondansetron was associated with increased risk of cardiac (OR: 1.52 95% CI: 1.35-1.70) and orofacial cleft defects (OR: 1.32 95% CI: 0.76-2.28) in offspring compared to women with no antiemetic exposure during pregnancy. Another based retrospective cohor study nested in the 2000-2013 was conducted from the US nation wide Medicaid AnalyticeXtract. The cohort consisted of 1.816.414 pregnancies contributed by 1.502.895 women enrolled in Medicaid from 3 months before the last menstrual period through 1 month or longer after delivery; infants were enrolled in Medicaid for at least 3 months after birth. The final date of follow-up was December 31,2013. Analyses were conducted between November 1,2017, and June 30,2018. This study also suggests that first trimester ondansetron use in pregnancy is associated with a small but significant increased risk of orofacial cleft defects (aRR 1.24, 95% CI: 1.03-1.48) but found no statistical significant association between ondansetron and cardiac malformation(adjusted RR 0.99; 95% CI: 0.93-1.06) or congenital malformations overall (aRR 1.01, 95% CI: 0.98-1.05) (Huybrechts KF et al. 2018). Other two studies in the past have suggested an increased risk in specific major birth defects with first-trimester ondansetron use (Anderka M et al. 2012, Danielsson B et al. 2014).
Characterisation of the risk	Nausea and vomiting of pregnancy affect approximately 80% of pregnancies, beginning as early as 5 weeks of gestation and typically ending before the second trimester. Among affected women, 15% use prescription or over-the-counter medications for treatment. Although not approved for nausea and vomiting of pregnancy, ondansetron has become the most commonly used prescription antiemetic for this condition in the United States. Taylor et al assessed ondansetron and other antiemetic use among pregnant women delivering live births between 2001 and 2015. In over 2.3 million pregnancies, the prevalence of ondansetron was 15.2 percent, use was highest in the first trimester (Taylor et al. 2017). Zambelli -Weiner and coll. analyzed at national level dataset that contained 1,149,145 live births from 1,004,175 mothers. Of these, 76,330 infants were exposed to ondansetron in-utero during the first trimester (5,557

Teratogenic effects	
	exposed exclusively in medical settings), and 61,830 infants were diagnosed with structural defects. Risk was highly elevated for atrioventricular septal defects (OR: 2.68 95% CI: 1.61-4.47) and diaphragmatic hernia (OR: 2.49 95% CI: 1.18-5.25) (Zambelli-Weiner A et al. 2019). In Huybrecht and coll. study 88.467 (4.9%) pregnant women were exposed to ondansetron during the first trimester. There was no association between exposure to ondansetron during the first trimester of pregnancy and increased risk of cardiac malformations or congenital malformations overall, after accounting for potentially confounding conditions. Given the large cohort size, the estimates were precise with an upper bound of the 95% CI of the adjusted relative risk of 1.06 for cardiac malformations and of 1.05 for congenital malformations overall. There was a small increase in the risk of oral clefts associated with ondansetron exposure (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24) with the upper bound of the 95% CI of the adjusted relative risk at 1.48, corresponding to 5 additional cases per 10 000 prenatally exposed livebirths. These findings were consistent across a broad range of sensitivity analyses. The study by Anderka and coll. used data from the National Birth Defects Prevention case control study from 1997 to 2004 to examine risks with nausea and vomiting of pregnancy and its treatments for the most common non-cardiac defects in the dataset. These included cleft lip with or without cleft palate, cleft palate alone, neural tube defects, and hypospadias. Ondansetron was associated with an increased risk for cleft palate alone based on seven exposed cases (adjusted odds ratio, 2.37; 95% confidence interval, 1.18-4.76) (Anderka M et al.2012). The study published in 2014 used data from the Swedish Medical Birth Register from 1998 to 2012 to identify 1,349 infants whose mothers reported taking ondansetron in early pregnancy. While no overall increased risk of major birth defects was found with early pregnancy ondansetron use, compared with no such use, there was a significant increased risk noted for cardiovascular defects, particularly cardiac septum defects (any cardiac defect OR, 1.62; 95% CI, 1.04-2.14; cardiac septum defects risk ratio, 2.05; 95% CI, 1.19-3.28).3 No cases of cleft palate were reported among exposed cases in that study (Danielsson B et al. 2014).
Risk factors and risk groups	Women suffering from nausea and vomiting in the first trimester of pregnancy. Risk factor is represented by the off-label use of antiemetics in morning sickness affecting pregnant women or in the most severe form of hyperemesis gravidarum. It should be noted that ondansetron use increased from less than 1 percent of pregnancies in 2001 to 22.2 percent in 2014, according to an FDA article published in February 2017. The agency attributed much of the increase to oral ondansetron beginning in 2006.
Preventability	The use of the fixed combination is contraindicated during pregnancy. Women of childbearing potential should not be pregnant or become pregnant while on treatment with Akynzeo. A pregnancy test should be performed on all pre-menopausal women prior to treatment. Women of childbearing potential must use effective contraception during therapy and up to one month after treatment with this medicinal product. Patients should tell their doctor if they are pregnant or planning to become pregnant.
Impact on the benefit-risk balance of the product	No human data are available for each individual component of the fixed combination, i.e. palonosetron and netupitant, or for the combination. Further characterization of this potential risk is necessary to evaluate the impact on the benefit/risk ratio of the fixed combination.

Teratogenic effects	
Public health impact	So far, it is not possible to estimate the potential public health impact, without further characterization of the relevance of this risk to the fixed combination administration, the indication of which is limited to the prevention of CINV.

SVII.3.2. Presentation of the Missing Information

Effects in children

Anticipated risk/consequence of the missing information	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. No safety and efficacy data are available so far for the IV fixed combination and limited data for the oral fixed combination. As observed in adults, the frequency of nausea and vomiting in children is related to the emetogenic risk of the particular chemotherapeutic agent or combination of drugs being administered. The emetogenicity of chemotherapeutic regimens prescribed in patients 1-19 years has been assessed by extrapolation from adult data or through a retrospective analysis evaluating the severity of CINV in one week after administration of chemotherapy (Small BE et al. 2000). Another retrospective analysis was conducted by Holdsworth (Holdsworth MT et al. 2006). The majority of regimens were considered to have the same emetogenicity in children and adults, even if in many cases they would rarely be administered in adults as they are specific for cancer common in childhood. 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. From birth to adulthood, the body size and weight of an average child increases up to 20-fold, and the magnitude of dose variation administered throughout childhood may be 100-fold. Drug formulations used in pediatric pharmacotherapy should be adapted to children's needs to suit their age, size, physiologic condition, and treatment requirements. The need for drug formulations tailored to children in all the target age groups is obvious since the oral fixed combination formulation is not suitable for use in pediatrics, while the IV formulation might be preferable as the intravenous route is used in clinical practice to administer chemotherapy. However, as detailed above, there are several factors to be considered, mainly the pharmacokinetic and pharmacodynamic response in young patients which is mandatory to investigate according to the specific age category in order to identify the effective and safe dosage for this setting of patients. Details of the proposed pediatric investigational plan agreed with the competent authorities are described above in the pertinent section. Results obtained from the completed PK/PD dose finding study are preliminary and

	further investigation is warranted to get more robust data on the safety profile and efficacy of the combination in this setting of patients.

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 underneath.

Table 25: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Torsade de pointes due to QT/QTc prolongation Serotonin syndrome (due to palonosetron) Teratogenic effects
Missing information	Effects in children

Part III: Pharmacovigilance Plan

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

III.1 Routine pharmacovigilance activities

At present, taking into consideration the information provided on safety concerns for Akynzeo in previous sections and as also agreed with relevant competent authorities, routine pharmacovigilance activities are considered adequate to monitor the safety concerns for both the IV and the oral fixed combination.

As part of the routine pharmacovigilance activities, specific adverse reaction follow-up questionnaires for three safety concerns, Torsade de pointes due to QT/QT_C prolongation, serotonin syndrome and teratogenic effects have been generated to obtain structured information on reported suspected adverse reactions.

Details are provided underneath.

Focused follow-up questionnaire of QT/QTc interval prolongation and 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 job aid in the form of data collection check-list has been generated to facilitate the prompt collection of complete or of missing additional pertinent information from the reporting sources of the cases. 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. 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 as a check-list against which to verify both completeness and pertinence of the initial medical information received with a clinically significant adverse drug reaction report.

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 check-list 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.

Focused follow-up questionnaire for the cases of exposure during pregnancy and pregnancy outcome

The mother may have a serious illness which requires treatment, or a condition that untreated may pose significant risk to the foetus. In order to optimise the knowledge about any potential teratogenic or embryotoxic/foetotoxic effects of the medicinal product and the doses at which such effects might develop, it is necessary to gather information about medicinal products taken by pregnant women. Safety concerns related to ondansetron and the risk of birth defetcs emphasise the need for data collection on exposure during pregnancy and the importance of pregnancy databases in revealing potential teratogenic or embryotoxic/foetotoxic signals.

To evaluate the potential risk of teratogenic effects with the medicinal product, pro-active monitoring is carried out by means of a questionnaire that is utilized on a regular basis by Helsinn pharmacovigilance personnel as a check-list to to collect data on both the exposure and the outcome of pregnancy.

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 combination. No new important risks have been identified for the approved product, i.e. the IV formulation of the fixed combination. Likewise, no new important risks can be foreseen for the proposed liquid solution, identical as qualitative composition to the one already approved, except for water for injection.

V.1. Routine Risk Minimisation Measures

Table 26 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 Section 4.8 PL section 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. 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: Legal status: Prescription only medicine
Serotonin syndrome (due to palonosetron)	Routine risk communication:

Safety concern	Routine risk minimisation activities
	None Routine risk minimisation activities recommending specific clinical measures to address the risk: Advice is given for monitoring of patients with serotonin-syndrome like symptoms in SmPC Section 4.4. Specific information on the serotonin syndrome when the fixed combination is administered with other serotoninergic agents is included in SmPC Section 4.5. 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: Legal status: Prescription only medicine
Teratogenic effects	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: A contraindication for the use of the product during pregnancy is included in SmPC Section 4.3. Advice is given to female patients in SmPC Section 4.6 concerning fertility and pregnancy. Information about studies in animals showing reproductive toxicity including teratogenic effects in rabbit without safety margin is included in SmPC Section 5.3. Information to patients on the importance of not becoming pregnant, being pregnant or breast feed when taking the product is given in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Effects in children	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: The lack of efficacy and safety data in children and adolescent below 18 years is included in SmPC Section 4.2 Advice to not use the product in children and adolescent below 18 years is included in PL section 2

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine

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 27 Summary table of pharmacovigilance activities 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 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

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Serotonin syndrome (due to palonosetron)	Routine risk minimisation measures: SmPC Section 4.5 SmPC Section 4.4 where advice is given for monitoring of patients with serotonin-syndrome like symptoms. PL section 2 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

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Teratogenic effects	Routine risk minimisation measures: SmPC Section 4.3 (contraindication in pregnancy), 4.6, 5.3 PL section 2 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow up questionnaire form to collect information on exposure and pregnancy outcome
Effects in children	Routine risk minimisation measures: SmPC Section 4.2 PL section 2 Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Part VI: Summary of the risk management plan

A separate RMP Part VI is provided for the IV Akynzeo formulations and the oral Akynzeo in the RMP.

The first summary refers to both, the IV pharmaceutical forms of Akynzeo (powder for concentrate for solution for infusion and concentrate for solution for infusion), which are identical for qualitative composition and the second summary for the oral Akynzeo pharmaceutical forms (hard capsules and oral suspension).

Summary of risk management plan for IV Akynzeo

This is a summary of the risk management plan (RMP) for IV Akynzeo (powder for concentrate for solution for infusion and concentrate for solution for infusion).

The RMP details important risks of IV Akynzeo, how these risks can be minimised, and how more information will be obtained about IV Akynzeo's risks and uncertainties (missing information).
IV Akynzeo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how IV Akynzeo should be used.

This summary of the RMP for IV Akynzeo 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 IV Akynzeo's RMP.

I. The medicine and what it is used for

IV Akynzeo is indicated in adults for the:

- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

IV Akynzeo contains fosnetupitant and palonosetron as active substances and it is given by intravenous route.

Further information about the evaluation of IV Akynzeo’s benefits can be found in IV Akynzeo’s 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 IV Akynzeo, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products are the following:

- 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 IV Akynzeo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Akynzeo IV 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 IV Akynzeo can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of IV Akynzeo. 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 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 potential risks	Torsade de pointes due to QT/QTc prolongation Serotonin syndrome (due to palonosetron) Teratogenic effects
Missing information	Effects in children

II.B Summary of important risks

Important potential risk: Torsade de pointes due to QT/QT_C prolongation	
Evidence for linking the risk to the medicine	Studies in healthy volunteers showed no relevant effects on the QT parameters and no clinically important QT prolongations were observed in the safety study in both treatment group. 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. The risk in this particular 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.
Risk factors and risk groups	Risk factors include drug interaction, pre-existing cardiac diseases, e.g. cardiac ischaemia, cardiomyopathies, congenital long QT syndrome,

	electrolytes abnormalities or treatment with drugs known to prolong QT interval, hypothyroidism and hypoglycaemia. Female sex and older age are also associated with longer QT intervals. Furthermore a wide range of chemotherapy agents including histone deacetylase inhibitors, nilotinib, ponatinib, vandetanib, crizotinib, vemurafenib, taxanes has been associated with arrhythmic effects.
Risk minimisation measures	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 Additional risk minimisation measures: No additional risk minimisation measures

Important potential risk: Serotonin syndrome (due to palonosetron)	
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 minimisation measures SmPC Section 4.5 SmPC Section 4.4 where advice is given for monitoring of patients with serotonin-syndrome like symptoms. PL section 2 Additional risk minimisation measures: No additional risk minimisation measures

Important potential risk: Teratogenic effects	
Evidence for linking the risk to the medicine	The occurrence of teratogenic effects has been considered in view of the recent published data of the anti-emetic ondansetron belonging to the class of the 5-HT_3 RAs that have suggested an increased risk in specific major birth defects with first-trimester ondansetron use. This increase

	was entirely accounted for by a dramatic rise in oral ondansetron use beginning in 2006.
Risk factors and risk groups	Women suffering from nausea and vomiting in the first trimester of pregnancy. Risk factor is represented by the off-label use of antiemetics in morning sickness affecting pregnant women or in the most severe form of hyperemesis gravidarum.
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.3 (contraindication in pregnancy), 4.6 and 5.3 PL section 2 Additional risk minimisation measures: No additional risk minimisation measures

Missing information: Effects in children	
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.2 PL section 2 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 for IV Akynzeo.

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

There are no studies required for IV Akynzeo.

Summary of risk management plan for oral Akynzeo

This is a summary of the risk management plan (RMP) for oral Akynzeo. The RMP details important risks of oral Akynzeo, how these risks can be minimised, and how more information will be obtained about oral Akynzeo's risks and uncertainties (missing information).
Oral Akynzeo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how oral Akynzeo should be used.

This summary of the RMP for oral Akynzeo 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 oral Akynzeo's RMP.

I. The medicine and what it is used for

Oral Akynzeo is indicated in adults for the:

- Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy.

- Prevention of acute and delayed nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Oral Akynzeo contains netupitant and palonosetron as active substances and it is given by mouth.

Further information about the evaluation of oral Akynzeo’s benefits can be found in oral Akynzeo’s 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 oral Akynzeo together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products are the following:

- 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 oral Akynzeo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of oral Akynzeo 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 oral Akynzeo can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of oral Akynzeo. 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 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 potential risks	Torsade de pointes due to QT/QTC prolongation Serotonin syndrome (due to palonosetron) Teratogenic effects
Missing information	Effects in children

II.B Summary of important risks

Important potential risk: Torsade de pointes due to QT/QT_C prolongation	
Evidence for linking the risk to the medicine	Studies in healthy volunteers showed no relevant effects on the QT parameters and no clinically important QT prolongations were observed in the safety study in both treatment group. 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. The risk in this particular 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.
Risk factors and risk groups	Risk factors include drug interaction, pre-existing cardiac diseases, e.g. cardiac ischaemia, cardiomyopathies, congenital long QT syndrome, or electrolytes abnormalities or treatment with drugs known to prolong QT

	interval, hypothyroidism and hypoglycaemia. Female sex and older age are also associated with longer QT intervals. Furthermore a wide range of chemotherapy agents including histone deacetylase inhibitors, nilotinib, ponatinib, vandetanib, crizotinib, vemurafenib, taxanes has been associated with arrhythmia effects.
Risk minimisation measures	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 Additional risk minimisation measures: No additional risk minimisation measures

Important potential risk: Serotonin syndrome (due to palonosetron)	
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 minimisation measures SmPC Section 4.5 SmPC Section 4.4 where advice is given for monitoring of patients with serotonin-syndrome like symptoms. PL section 2 Additional risk minimisation measures: No additional risk minimisation measures

Important potential risk: Teratogenic effects	
Evidence for linking the risk to the medicine	The occurrence of teratogenic effects has been considered in view of the recent published data of the anti-emetic ondansetron belonging to the class of the 5-HT_3 RAs that have suggested an increased risk in specific major birth defects with first-trimester ondansetron use. This increase was entirely accounted for by a dramatic rise in oral ondansetron use beginning in 2006.

Risk factors and risk groups	Women suffering from nausea and vomiting in the first trimester of pregnancy. Risk factor is represented by the off-label use of antiemetics in morning sickness affecting pregnant women or in the most severe form of hyperemesis gravidarum.
Risk factors and risk groups	Routine risk minimisation measures SmPC Section 4.3, 4.6 and 5.3 PL section 2 Additional risk minimisation measures: No additional risk minimisation measures

Missing information: Effects in children	
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.2 PL section 2 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 oral Akynzeo.

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

There are no studies required for oral Akynzeo.

Part VII: Annexes

Table of contents

4c) Follow-up form for Teratogenic effects

Drug:	**NETUPITANT/PALONOSETRON FDC** **Exposure during Pregnancy and Pregnancy Outcome**

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

☐ Date of Akynzeo (OS or IV) administration prior to the start date of last menses

- ☐ In case of repeated administrations, please retrieve the total number of Akynzeo capsules or injections administered prior to the start date of last menses
- ☐ Gestational age at the time of first drug exposure
- ☐ Estimated date of delivery
- ☐ Specific tests, e.g. amniocentesis, foetal ultrasound, cardiotocography, chorionic villi biopsy performed or planned during the pregnancy and provide results
- ☐ Concomitant medications administered during pregnancy. Please collect dosage, frequency, start and stop date, reason for administration
- ☐ Pregnancy outcome date and type (e.g. uneventful, induced termination, spontaneous abortion, stillbirth, miscarriage, neonatal birth, birth defects). In case of abortion, neonatal death, birth defects, please retrieve information on reason(s) for abortion, causes of neonatal death, details of birth defects (e.g. cleft lip/palate, congenital heart defects, esophageal atresia, hypospadias)
- ☐ Presence of parents or maternal risk factors that may increase the likelihood of a baby developing birth defects, e.g. family history, diabetes, obesity during pregnancy, smoking, alcohol use, other substances consumption
- ☐ N. of previous pregnancies and foetal abnormalities (if any).

Annex 7- Other supporting data (including referenced material)

List of references

Annex 8 – Summary of changes to the risk management plan over time

List of all significant changes to the Risk Management Plan over time

Annex 4 - Specific adverse drug reaction follow-up forms

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

Drug:	**NETUPITANT / PALONOSETRON FDC**
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:	**NETUPITANT/PALONOSETRON FDC**
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.

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

☐ What medication has the patient taken previously?

☐ What adverse drug reactions have been previously experienced?

4c) Follow-up form for Teratogenic effects

Drug:	**NETUPITANT/PALONOSETRON FDC** **Exposure during Pregnancy and Pregnancy Outcome**

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

- ☐ Date of Akynzeo (OS or IV) administration prior to the start date of last menses
- ☐ In case of repeated administrations, please retrieve the total number of Akynzeo capsules or injections administered prior to the start date of last menses
- ☐ Gestational age at the time of first drug exposure
- ☐ Estimated date of delivery
- ☐ Specific tests, e.g. amniocentesis, foetal ultrasound, cardiotocography, chorionic villi biopsy performed or planned during the pregnancy and provide results
- ☐ Concomitant medications administered during pregnancy. Please collect dosage, frequency, start and stop date, reason for administration
- ☐ Pregnancy outcome date and type (e.g. uneventful, induced termination, spontaneous abortion, stillbirth, miscarriage, neonatal birth, birth defects). In case of abortion, neonatal death, birth defects, please retrieve information on reason(s) for abortion, causes of neonatal death, details of birth defects (e.g. cleft lip/palate, congenital heart defects, esophageal atresia, hypospadias)
- ☐ Presence of parents or maternal risk factors that may increase the likelihood of a baby developing birth defects, e.g. family history, diabetes, obesity during pregnancy, smoking, alcohol use, other substances consumption
- ☐ N. of previous pregnancies and foetal abnormalities (if any).

Annex 7- Other supporting data (including referenced material)

Reference

Aapro M, Molassiotis A, Dicato M, Peláez I, Rodríguez-Lescure Á, Pastorelli D, Ma L, Burke T, Gu A, Gascon P & F. Roila on behalf of the PEER investigators The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). Annals of Oncology 2012; 23: 1986–1992.

Abadie D, Rousseau V, Logerot S, Cottin J, Montastruc JL, Montastruc F. Serotonin Syndrome: Analysis of Cases Registered in the French Pharmacovigilance Database. J Clin Psychopharmacol. 2015 Aug; 35(4):382-8.

Anderka M et al. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Res A Clin Mol Teratol. 2012 Jan; 94(1): 22-30.

ASCO Clinical Practice Guidelines 2025, An American Society of Clinical Oncology Journal

Bender CM, McDaniel RW, Murphy-Ende K, Pickett M, Rittenberg CN, Rogers MP, et al. Chemotherapy-induced nausea and vomiting. Clinical Journal of Oncology Nursing 2002; 6(2): 94-102.

Bleyer WA, Danielson MG. Oral cancer chemotherapy in paediatric patients: obstacles and potential for development and utilisation. Drugs 1999; 58 Suppl 3: 133-40.

Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol. 2006; 24(27): 4472-8.

Boyle P, Levin B. Word cancer report 2008. Lyon, France: Word Health Organization and International Agency for Research on Cancer. 2008.

Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer. 2007; 15(5): 497-503

Danielsson B, Wikner BN, Källén B. Use of ondansetron during pregnancy and congenital malformations in the infants. Reprod Toxicol. 2014 Dec; 50: 134-7.

De Remer DL, Clemmons AB, Orr J, Clark SM, Gandhi AS. Emerging Role of Olanzapine for Prevention and Treatment of Chemotherapy Induced Nausea and Vomiting. Pharmacotherapy 2016; Vol 36, Issue N.2: 218-29.

Esposito S, Tenconi R, Preti V, Groppali E, Principi N. Chemotherapy against cancer during pregnancy. A systematic review on neonatal outcomes Medicine (2016) 95:38

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBCAN 2008. Lyon, France: International Agency for Research on Cancer; 2008.

Gilmore J W, Peacock N W, Gu A, Szabo S, Rammage M, Sharpe J, Haislip S T, Perry T, Boozan TL, Meador K, Cao X, Burke T A. Antiemetic Guideline Consistency and Incidence of Chemotherapy-Induced Nausea and Vomiting in US Community Oncology Practice: INSPIRE Study. Journal of oncology practice 2014; vol. 10, issue 1: 68 -78

Gross CP, McAvay GJ, Guo Z, Tinetti ME. The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. Cancer 2007; 109(12): 2410-9.

Grunberg SM, Deuson RR, Mavros P, Geling O, Hansen M, Cruciani G, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer 2004; 100(10): 2261-668.

Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a U.S. population. Support Care Cancer. 2011; 19(6): 843-51.

Halfdanarson TR, Jatoi A. Oral cancer chemotherapy: the critical interplay between patient education and patient safety. Curr Oncol Rep. 2010; 12(4): 247-52.

Hawkins R, Grunberg S. Chemotherapy-induced nausea and vomiting: challenges and opportunities for improved patient outcomes. Clin J Oncol Nurs. 2009; 13(1): 54-64.

Herrstedt J, Clark-Snow R, Ruhlmann CH, Molassiotis A, Olver I, Rapoport BL, 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open. 2024 Feb;9(2):102195.

Herrstedt J, Clark-Snow R. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open 2024 Feb; 9(2): 102195.

Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008; 358(23): 2482-94.

Hesketh PJ, Aapro M, Street JC, Carides AD. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. Supportive care in cancer 2010; 18(9): 1171-7.

Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacio D, Somerfield MR, Lyman GH. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017; 35:3240-3261.

Hilarius DL, Kloeg PH, van der Wall E, van den Heuvel JJ, Gundy CM, Aaronson NK. Chemotherapy-induced nausea and vomiting in daily clinical practice: a community hospital-based study. Support Care Cancer 2012; 20(1): 107-17.

Holdsworth MT, Raisch D W, Frost J. Acute and delayed nausea and emesis control in pediatric oncology patients. Cancer 2006; 106(4): 931-940.

Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda, Maryland: National Cancer Institute; 2011.

Huybrechts KF, Hernández-Díaz S, Straub L, Gray KJ, Zhu Y, Patorno E, Desai RJ, Mogun H, Bateman BT. Association of Maternal First-Trimester Ondansetron Use with Cardiac Malformations and Oral Clefts in Offspring. JAMA.2018;320(23): 2429-2437.doi:10.1001/jama.2018.18307.

Ihbe-Heffinger A, Ehlken B, Bernard R, Berger K, Peschel C, Eichler HG, et al. The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. Ann Oncol. 2004; 15(3): 526-36.

Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol. 2005; 55(3): 231-40.

Jordan K, Sippel C, Schmoll H-J. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. The oncologist 2007; 12(9): 1143-50.

Jordan K, Paul S, Heissner K. Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with Cisplatin Chemotherapy. EJCMO 2010; 1-6

King CR. Non- pharmacologic management of chemotherapy-induced nausea and vomiting. Oncol Nurs Forum 1997; 24 (7 Suppl): 41-48

Krebber AMH, Buffart LM, Kleijn G, Riepma IC, de Bree R, Leemans C. R, Becker A, Brug J, van Straten A, Cuijpers P, Verdonck-de Leeuw IM. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psycho-Oncology 2014; 23: 121–130.

Kuryshev YA, Brown AM, Wang L, Benedict CR, Rampe D. Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. J Pharmacol Exp Ther. 2000; 295(2): 614-20.

Lachaine J, Yelle L, Kaizer L, Dufour A, Hopkins S, Deuson R. Chemotherapy-induced emesis: quality of life and economic impact in the context of current practice in Canada. Support Cancer Ther. 2005 Apr 1;2(3):181-7.

Li M, Ramos LG. Drug-Induced QT Prolongation and Torsades de Pointes. 2017; 42 (7): 473-7.

Lindley CM, Bernard S, Fields SM. Incidence and duration of chemotherapy-induced nausea and vomiting in the outpatient oncology population. Journal of Clinical Oncology. 1989; 7(8): 1142-9.

Molassiotis A, Saunders MP, Valle J, Wilson G, Lorigan P, Wardley A, Levine E, Cowan R, Loncaster J, Rittenberg C. A prospective observational study of chemotherapy-related nausea and vomiting in routine practice in a UK cancer centre. Support Care Cancer. 2008; 16(2): 201-8.

Mohammed Elmadani et al, Cancer burden in Europe: a systemic analysis of the Globocan database (2022), BMC Cancer, 12 March 2025.

Navari RM. Pathogenesis-based treatment of chemotherapy-induced nausea and vomiting--two new agents. J Support Oncol. 2003; 1(2): 89-103

NCCN Guidelines, 2025, National Comprehensive Cancer Network.

Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, Clark-Snow RA, Dupuis LL, Einhorn LH, Feyer P, Hesketh PJ, Jordan K, Olver I, Rapoport BL, Roscoe J, Ruhlmann CH, Walsh D, Warr D, van der Wetering M; participants of the MASCC/ESMO Consensus Conference Copenhagen 2015. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(5):119-133.

Sedeta E. et al, Epidemiology of Non-Hodgkin Lymphoma: Global Patterns of Incidence, Mortality, and Trends, Blood (2022) 140 (Supplement 1): 5234–5235.

Siegal R.L et al, Cancer statistics 2022, CA: A Cancer Journal for Clinicians, 12 January 2022.

Small B. E., M. T. Holdsworth, et al. (). "Survey ranking of emetogenic control in children receiving chemotherapy." J Pediatr Hematol Oncol 2000; 22(2): 125-132.

Steeghs N, de Jongh FE, Sillevis Smitt PA, van den Bent MJ. Cisplatin-induced encephalopathy and seizures. Anticancer Drugs 2003; 14(6): 443-6.

Summary of Product Characteristics (SmPC): Akynzeo, 2024.

Taylor LG, Bird ST, Sahin L, Tassinari MS, Greene P, Reichman ME, Andrade SE, Haffenreffer K, Toh S. Antiemetic use among pregnant women in the United States: the escalating use of ondansetron. Pharmacoepidemiol Drug Saf. 2017 May;26(5):592-6.

Turkel SB, Nadala JG, Wincor MZ. Possible serotonin syndrome in association with 5-HT(3) antagonist agents. Psychosomatics 2001; 42(3): 258-60

Walker J, Holm Hansen C, Martin P, Sawhney A, Thekkumpurath P, Beale C, Symeonides S, Wall L, Murray G, Sharpe M. Prevalence of depression in adults with cancer: a systematic review. Annals of Oncology 2013; 24:895–900.

Weda M, Hoebert J, Vervloet M, Moltó Puigmarti C, Damen N, Marchange S, Langedijk J, Lisman J, van Dijk L. Study on off-label use of medicinal products in the European Union. February 2017; 1-193.

Zambelli-Weiner A, Via C, Yuen M, Weiner DJ, Kirby RS. First trimester ondansetron exposure and risk of structural birth defects. Reprod Toxicol. 2019 Jan;83:14-20. doi: 10.1016/j.reprotox.2018.10.010. Epub 2018 Oct 29.

Annex 8 – Summary of changes to the risk management plan over time

List of all significant changes to the Risk Management Plan over time

Version	Approval date Procedure	Change
2.3	27 May 2015 EMA/243243/2015	Part II: Module SVIII - Summary of safety concerns has been reviewed to reflect requirements in current applicable EU guidelines as follows: • Severe hypersensitivity reactions, including anaphylaxis, anaphylactic/anaphylactoid reactions and shock: Important identified risk removed • Severe constipation: Important identified risk removed • Convulsive events: Important potential risk removed • Liver transaminases increase: Important potential risk removed • Effects of interaction with CYP3A4 substrates (e.g. corticosteroids and benzodiazepines): Important potential risk removed • Effects of interaction with CYP3A4 inhibitors and inducers: Important potential risk removed • Phospholipidosis: Important potential risk removed • Effects of interaction with BCRP substrates: Important potential risk removed • Effects of interaction with UGT-2B7 substrates: Important potential risk removed • Effects of interaction with P-gp substrates: Important potential risk removed • QT/QTC prolongation: Important potential risk reclassified as Torsade de pointes due to QT/QTC prolongation • Effects in patients with severe hepatic impairment: Missing information removed • Effects in patients with end-stage renal disease undergoing haemodialysis: Missing information removed • Effects in patients aged 75 years or more: Missing information removed • Effects on fertility: Missing information removed • Effects on pregnancy and lactation: Missing information removed Content in tables of part V has been updated in line with current Guidance on the format of the RMP in the EU in integrated format (31 October 2018) Follow-up questionnaire for exposure in pregnancy and pregnancy outcome added

Version	Approval date Procedure	Change
2.7	16 March 2020	Addition of a new pharmaceutical form for the intravenous formulation. There were no changes to the list of safety concernsin version 2.7.
3.0	16 September 2021	Addition of references to SmPC/PL sections (contraindication during pregnancy - section 4.3 and animal findings - section 5.3 of the EU-SmPC) to: • Part V, table V.1 Routine Risk Minimisation Measures and table V.3 Summary of risk minimisation • Part VI, II.B Summary of important risks measures for Akynzeo oral and Akynzeo IV
4.0	11 December 2025	Addition of a new pharmaceutical form of Akynzeo, i.e., an oral suspension formulation. There were no changes to the list of safety concerns in the version 4.0.