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 liquid concentrate for solution for infusion), which are identical for qualitative composition and the second summary for the oral Akynzeo (hard capsules).

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

Annex 1 – EudraVigilance Interface

Not required to be submitted in e-CTD

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

Not applicable

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

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

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

4b) Follow-up form for Serotonin Syndrome

4c) Follow-up form for Teratogenic effects

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

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable

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.

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.

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.

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

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.

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.

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**