Summary of Risk Management Plan (RMP)

Akynzeo IV 235 mg / 0.25 mg

Concentrate for solution of infusion

Fosnetupitantum, Palonosetronum
(Antiemetics and antinauseants, serotonin (5HT3) and neurokinin-1 (NK1) receptor antagonists (ATC Code A04AA55))

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Based on Helsinn Birex Pharmaceuticals Ltd. RMP version 3.0
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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Akynzeo IV 235 mg / 0.25 mg is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Akynzeo IV 235 mg / 0.25 mg in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Medius AG, Muttenz is fully responsible for the accuracy and correctness of the content of the published summary RMP of Akynzeo IV 235 mg / 0.25 mg.

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 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_Cprolongation	
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 lifethreatening 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 $5HT_3$ 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 $5\text{-}HT_3$ 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.