SUMMARY OF THE RISK MANAGEMENT PLAN (CH)
AKYNZEO, INTRAVENOUS

Active substance:	Fosnetupitant and palonosetron (Fixed combination), intravenous
Pharmaco-therapeutic group (ATC Code):	Antiemetics and antinauseants, serotonin (5HT3) and neurokinin-1 (NK1) receptor antagonists (ATC Code A04AA55)
MAH/Applicant name:	Vifor (International) Inc.
Medicinal Product(s) to Which this RMP Refers:	1
Product(s) concerned (brand name(s)):	Akynzeo 235 mg/0.25 mg concentrate for solution for infusion

Data lock point for this module	10 October 2019
Version number of RMP when this module was last updated	2.8 (corresp. to initial in CH)

EXECUTIVE SUMMARY

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, intravenous 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 authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Akynzeo, intravenous in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Vifor (International) Inc. is fully responsible for the accuracy and correctness of the content of the published summary RMP of Akynzeo, intravenous.

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Akynzeo, intravenous is 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.

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.

The incidence of acute and delayed CINV was investigated in 298 eligible patients receiving either highly or moderately emetogenic chemotherapy treatment regimens (HEC resp. MEC) from 14 oncology practices in six countries. 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 emesis and nausea appeared without the onset of acute symptoms in 38% and 33% of HEC patients, respectively, and in 19% and 21% of MEC patients, respectively.

VI.2.2 Summary of treatment benefits

No pivotal efficacy trials have been conducted with Akynzeo, intravenous itself.

For the fosnetupitant component, a bioequivalence approach (study PNET-12-23) was used to determine the dose of fosnetupitant that produces a similar netupitant exposure as oral netupitant 300 mg (Akynzeo, hard capsules) for the acute (0-24 h) and delayed (24-120 h) phase of chemotherapy-induced nausea and vomiting. Cohorts of 10 subjects received intravenous fosnetupitant single doses of 19.5 mg to 390 mg. In each cohort, two subjects were given the oral reference product Akynzeo, hard capsules. The results showed that the dose of 260 mg fosnetupitant leads to a netupitant exposure that corresponds to that after a dose of 300 mg netupitant from Akynzeo, hard capsules.

For the palonosetron component, a study determined the non-inferiority of intravenous palonosetron 0.25 mg, administered over 30 minutes compared to administration over 30 seconds, in preventing nausea and vomiting in the acute phase (0-24 h) of HEC (study PALO-15-17). In total, 425 patients (infusion n = 214; bolus n = 211) received the study drug and the HEC. In the group with intravenous palonosetron infusion, 82.7% of the patients achieved a complete response in the acute phase, in comparison with 86.3% of the patients in the group with intravenous palonosetron bolus, which proved the non-inferiority of a 30-minute infusion compared to the 30-second bolus dose.

VI.2.3 Unknowns relating to treatment benefits

Pregnant females: Safety in human pregnancy has not been established for either palonosetron or netupitant.

Pediatric population: No data are available with Akynzeo, intravenous.

Elderly: No dose adjustment is required in elderly patients.

Hepatic impairment: No dose adjustment is required in patients with slightly or moderately impaired liver function. However, patients with severely impaired liver function should not be treated with Akynzeo, intravenous due to limited data.

Renal impairment: Dose adjustment is not deemed to be necessary in patients with slightly or moderately impaired kidney function. In case of severely impaired kidney function, total exposure to palonosetron increased by 28% compared to healthy subjects.

Race: Different ethnicity does not represent a safety concern.

VI.2.4 Summary of safety concerns

Important identified risks

None.

Important potential risks

Risk	**What is known**
Torsade de pointes due to QT/QTc prolongation	Studies in healthy volunteers showed no relevant effects on the QT parameters and no clinically important QT prolongations were observed in treatment groups of a safety study. 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 exact mechanism is unknown.
Serotonin syndrome (due to palonosetron)	The occurrence of serotonin syndrome has been considered as a potential class effect of the anti-emetics belonging to the class of the 5-HT3 receptor antagonists. Serotonin syndrome is a potentially life-threatening drug reaction that may produce a spectrum of specific symptoms including cognitive, autonomic, and somatic effects, which can be of variable intensity. As palonosetron belongs to the same substance class, it is prudent to consider serotonin syndrome an important potential risk.
Teratogenic effects	Based on several studies, ondansetron use during the first trimester of pregnancy has been inconsistently associated with birth defects in infants following in-utero exposure, such as cardiac defects or orofacial cleft defects. Although the preclinical data with Akynzeo are not predictive of potential effects in pregnant women, it is prudent to consider teratogenic effects an important potential risk as palonosetron belongs to the same substance class than ondansetron.

Missing information

Risk	What is known
Effects in children	No safety and efficacy data are available so far for Akynzeo, intravenous (only preliminary data from a dose finding study with Akynzeo, hard capsules). 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.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a product information which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. The measures in these documents are known as routine risk minimisation measures.

The Swiss Product Information for Akynzeo, intravenous can be found at www.swissmedicinfo.ch.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

A Paediatric Investigation Plan has been agreed by the Paediatric Committee of the EMA on 19 October 2018 and modified on 26 June 2020. This clinical study development plan for children includes studying Akynzeo, intravenous in children and adolescents from 1 month to 18 years of age in the prevention of chemotherapy-induced nausea and vomiting.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.8 (corresp. to initial in Switzerland)	At time of authorisation 01/09/2022	Identified Risks: none Potential Risks: Torsade de pointes due to QT/QTc prolongation, Serotonin syndrome (due to palonosetron), Teratogenic effects Missing information: Effects in children	n.a.