Aprepitant

80 mg and 125 mg

Hard Capsules

1.8.2 Safety Risk Management Plan

Active substance(s) (INN or common name):	Aprepitant
Pharmaco-therapeutic group (ATC Code):	Antiemetics and antinauseants (A04AD12)
Name of Marketing Authorization Holder or Applicant:	Sandoz
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	[Nationally completed name] 80 mg and 125 mg Hard Capsules
Version number	1.0
Data lock point for this RMP	13 Dec 2016
Date of final sign off	13 Dec 2016

1.1 Part VI.2 Elements for a Public Summary

1.1.1 Part VI.2.1 Overview of disease epidemiology

Chemotherapy (cancer treatment with drugs)-induced nausea (a feeling that vomiting will occur) and vomiting [throwing up], called CINV, continues to have a great impact on the quality of life of patients receiving some anti-cancer treatment. CINV can be defined as acute (sudden onset), delayed or expected beforehand. Acute CINV occurs within 24 hours after chemotherapy infusion. Delayed CINV begins 24 hours or more after chemotherapy infusion and can last up to several days. According to a study, 38% of patients receiving a new chemotherapy regimen develop acute CINV and as many as 64% develop delayed CINV. More than 90% of patients who experience acute or delayed CINV also reported an impact on daily activities. Chemotherapies with highly emetogenic (capacity to induce vomiting) drugs like cisplatin have a greater than 90% incidence of CINV while the incidence is 30-90% with moderately emetogenic drugs like anthracyclines (e.g. daunorubicin) [Oncolink, 2016].

1.1.2 Part VI.2.2 Summary of treatment benefits

According to a multicentered (study conducted at more than one clinic) prospective (study in which the subjects are first identified and then followed forward periodically), double-blind study in which neither the participants nor the experimenters know the particular treatment being received), double-dummy (technique for retaining the blinding of a clinical trial), conducted in 866 breast cancer patients treated with chemotherapy that included cyclophosphamide 750-1,500 mg/m^2; or 500-1,500 mg/m^2 and doxorubicin (< 60 mg/m^2) or epirubicin (< 100 mg/m^2), addition of aprepitant 125 mg to standard antiemetic (preventing vomiting) regimen containing ondansetron 8 mg, and dexamethasone 20 mg, was superior in comparison with ondansetron and dexamethasone alone in the proportion of patients achieving a complete response overall (51% in aprepitant vs 42% in control group) after one cycle of moderately emetogenic chemotherapy [David G, 2005]. According to a phase 3, randomized, multicenter, double-blind study, conducted in 307 pediatric cancer patients aged 6 months to 17 years, who were treated with either moderately or HEC, addition of aprepitant to ondansetron with or without dexamethasone has resulted in complete response in the delayed phase (51% in the aprepitant group vs 26% in control group containing ondansetron with or without dexamethasone) [Kang HJ, 2015].

1.1.3 Part VI.2.3 Unknowns relating to treatment benefits

It is not known whether aprepitant is excreted in human milk; therefore, breast-feeding is not recommended during treatment with aprepitant.

There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment.

1.1.4 Part VI.2.4 Summary of safety concerns

Table 4-1 Important identified risks

Risk	What is known	Preventability
Allergic reactions (Hypersensitivity)	Hives, rash, itching, difficulty breathing or swallowing	Patient is advised not to take aprepitant if allergic to aprepitant or any of the other

Risk	What is known	Preventability
	(frequency not known, cannot be estimated from the available data); are signs of an allergic reaction. Hot flush or reddening of the face or skin, rash is uncommon (may affect up to 1 in 100 people) in patients undergoing therapy with aprepitant. Sensitivity of the skin to sun, sores on skin, itching rash, Stevens-Johnson syndrome (reaction affecting the skin and the mucous membranes leading to redness and peeling of the skin over large areas of the body) or toxic epidermal necrolysis (a rare condition that causes large portions of the skin's outermost layer to detach from the layers of skin below) were rare (may affect up to 1 in 1,000 people) in patients undergoing therapy with aprepitant.	ingredients of this medicine. Patient is advised to stop taking aprepitant and immediately consult a doctor if the patient notices any of the mentioned side effects, which may be serious, and for which patient might require urgent medical treatment.
Interaction of aprepitant with birth control pills (Drug interaction: hormonal contraceptives)	Birth control medicines which can include birth control pills, skin patches, implants, and certain Intrauterine devices (a small contraceptive device, often 'T'-shaped, often containing either copper or levonorgestrel, which is inserted into the uterus) that release hormones may not work adequately when taken together with aprepitant. The efficacy of birth control medicines may be reduced during and for 28 days after administration of aprepitant.	Another or additional non-hormonal form of birth control methods should be used during treatment with aprepitant and for 2 months following the last dose of aprepitant.

Table 4-2 Important potential risks

Risk	What is known
Potential for errors of prescription, dispensing or use of medicine (Potential for medication errors)	Patient should always take this medicine or give this medicine to the child exactly as told by the doctor, pharmacist or nurse. Patient should check with the doctor, pharmacist or nurse if not sure about the dose.

Risk	What is known
	Aprepitant should always be taken together with the medicines that prevent nausea and vomiting. After the treatment with aprepitant, the doctor might ask the patient to continue taking other medicines including a corticosteroid (group of drugs mainly used to reduce inflammation and suppress the immune system) such as dexamethasone and a '$5HT_3$ antagonist' (such as ondansetron) for preventing nausea and vomiting. The recommended oral dose of aprepitant is Day 1: one 125 mg capsule 1 hour before you start your chemotherapy session, and; Days 2 and 3: one 80 mg capsule each day If no chemotherapy is given, patient should take aprepitant in the morning and if chemotherapy is given, then the patient should take aprepitant 1 hour before starting with the chemotherapy session. The aprepitant capsule should be swallowed whole with some liquid and can be taken with or without food. Patient should contact the doctor for advice in case of a missed dose. Patient should not take more capsules than what it was recommended by the doctor. Doctor should be consulted immediately, if the child or patient has taken too many capsules.

Table 4-3 Missing information

Risk	What is known
Use in pregnancy	For aprepitant, no clinical data on exposed pregnancies are available. This medicine should not be used during pregnancy unless clearly necessary. Before taking aprepitant, patient should ask for a doctor's advice if the patient is pregnant, might be pregnant or planning to have a baby.
Use in children less than 12 years of age	It is advised not to give aprepitant 80 mg and 125 mg capsules to children under 12 years of age, because the use of 80 mg and 125 mg capsules have not been studied in this population.
Use in patients with moderate or severe liver damage (Use in patients with moderate or severe hepatic impairment)	There are limited data in patients with moderate liver damage and no data in patients with severe liver damage. Aprepitant should be used with caution in these patients.

1.1.5 Part VI.2.5 Summary of risk minimization measures by safety concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

1.1.6 Part VI.2.6 Planned post authorization development plan

None

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

N/A (first submission)