PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Kyprolis® (Carfilzomib)

This is a summary of the risk management plan (RMP) for Kyprolis. The RMP details important risks of Kyprolis, how these risks can be minimized, and how more information will be obtained about Kyprolis's risks and uncertainties (missing information).

Kyprolis's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Kyprolis should be used.

This summary of the RMP for Kyprolis should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Kyprolis's RMP.

I. The medicine and what it is used for

Kyprolis is authorized for the treatment of adult patients with multiple myeloma who have received at least one prior therapy in combination with either lenalidomide and dexamethasone or dexamethasone alone (see SmPC for the full indication). It contains carfilzomib as the active substance and it is given by intravenous route of administration.

Further information about the evaluation of Kyprolis's benefits can be found in Kyprolis's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/Kyprolis.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Kyprolis, together with measures to minimize such risks and the proposed studies for learning more about Kyprolis's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- 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 authorized 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 (eg, with or without prescription) can help to minimizes its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of Important Risks and Missing Information

Important risks of Kyprolis 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 can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Kyprolis. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet 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 (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction and cardiac arrest) Pulmonary toxicities Pulmonary hypertension Dyspnea Hypertension including hypertensive crises Acute renal failure Thrombotic microangiopathy Posterior reversible encephalopathy syndrome (PRES)
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

Important identified risk: Cardiac Toxicity (cardiac failure, myocardial ischemia, myocardial infarction and cardiac arrest)	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical trials and postmarketing data. The risk of cardiac toxicity with carfilzomib has been consistently reported from clinical trial data. An increased incidence of cardiac failure with carfilzomib has been observed from clinical trial data and the strength of this evidence is strong.
Risk factors and risk groups	The risk of cardiac failure is increased in elderly patients (≥ 75 years) and in Asian patients. Patients with NYHA Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.2 and 4.4 where advice is given on monitoring volume overload/fluid requirements/hydration • SmPC Section 4.4 where recommendation is given for stopping Kyprolis until recovery • SmPC Section 4.4 where recommendation is given for caution in treating patients with NYHA Class III and IV heart failure, recent myocardial infarctions and conduction abnormalities • SmPC Sections 4.8 and 5.3 • PL Sections 2 and 4 Additional risk minimization measures: • None

Important identified risk: Pulmonary Toxicities	
Evidence for linking the risk to the medicine	The data identifying pulmonary toxicities derive from clinical trials as well as postmarketing data. The strength of the evidence is strong.
Risk factors and risk groups	No risk factors are known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where recommendation is given evaluating and stopping Kyprolis until recovery. • SmPC Sections 4.8 and 5.3 • PL Sections 2 and 4 Additional risk minimization measures: • None

Important identified risk: Pulmonary Hypertension	
Evidence for linking the risk to the medicine	The data identifying pulmonary hypertension derive from clinical trials as well as postmarketing data. The strength of the evidence is strong.
Risk factors and risk groups	Patients with NYHA Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were excluded from clinical trials with carfilzomib, as they may be at greater risk of cardio-pulmonary complications.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where recommendation is given for stopping Kyprolis until recovery • SmPC Sections 4.8 and 5.3 • PL Sections 2 and 4 Additional risk minimization measures: • None

Important identified risk: Dyspnea	
Evidence for linking the risk to the medicine	Data to evaluate safety concerns derive from clinical trials and postmarketing data.
Risk factors and risk groups	Dyspnea was associated with either cough or lower respiratory tract infection in more than 50% of subjects. Dyspnea has also been noted within a day of dosing as part of the constellation of symptoms associated with infusion reactions. Based on a review of medical history for subjects who had an on-trial event of dyspnea or cough in clinical trials with carfilzomib, no risk factors for dyspnea or cough could be identified.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice is given to evaluate event to exclude cardiopulmonary conditions and stop Kyprolis in subjects with Grade 3 or 4 dyspnea until resolved or returned to baseline • SmPC Section 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None

Important identified risk: Hypertension Including Hypertensive Crises	
Evidence for linking the risk to the medicine	The risk of hypertension with carfilzomib has been consistently reported from clinical trial data. An increased incidence of hypertension with carfilzomib has been observed from clinical trial data and the strength of this evidence is strong.
Risk factors and risk groups	No risk factors are known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice is given to control hypertension prior to Kyprolis treatment, routine evaluate and reduce or stop Kyprolis if event not resolved • SmPC Section 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None

Important identified risk: Acute Renal Failure	
Evidence for linking the risk to the medicine	The risk of acute renal failure with carfilzomib has been consistently reported from clinical trial data. An increased incidence of hypertension with carfilzomib has been observed from clinical trial data and the strength of this evidence is strong.
Risk factors and risk groups	In clinical trials, the risk of renal failure events was higher in subjects with baseline characteristics suggestive of poor prognosis (such as increased beta-2-microglobulin and poorer overall performance status), and with impaired renal function at baseline.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 where advice is given regarding reduction for starting dose of lenalidomide in patients with baseline renal impairment and monitoring during Kypolis treatment • SmPC Section 4.4 where recommendation is given for monitoring of renal failure. • SmPC Sections 4.8, 5.2, and 5.3 • PL Sections 2 and 4 Additional risk minimization measures: • None

Important identified risk: Thrombotic Microangiopathy	
Evidence for linking the risk to the medicine	Although rare, thrombotic microangiopathy events have been observed in multiple settings. The strength of the evidence is strong.
Risk factors and risk groups	No risk factors are known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice is given for monitoring events and to discontinue Kyprolis if diagnosis suspected • SmPC Section 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None

Important identified risk: Posterior Reversible Encephalopathy Syndrome (PRES)	
Evidence for linking the risk to the medicine	Although rare, posterior Reversible Encephalopathy Syndrome (PRES) has been observed in multiple settings. The strength of the evidence is strong.
Risk factors and risk groups	No risk factors are known.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice is given to stop Kyprolis treatment if diagnosis suspected • SmPC Section 4.8 • PL Sections 2 and 4 Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Kyprolis.

II.C.2 Other Studies in Postauthorization Development Plan

There are no studies required for Kyprolis.