Bortezomib Fresenius Kabi, 3.5 mg powder for solution for injection

Part VI: Summary of the risk management plan

Summary of risk management plan for Bortezomib Kabi

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

Bortezomib Kabi SmPC and its PL give essential information to healthcare professionals and patients on how Bortezomib Kabi should be used.

I. The medicine and what it is used for

Bortezomib Kabi is authorised for –

- Bortezomib Fresenius Kabi as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.

- Bortezomib Fresenius Kabi in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

- Bortezomib Fresenius Kabi in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

- Bortezomib Fresenius Kabi in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

It contains bortezomib as the active substance and is available for intravenous or subcutaneous administration. Further information about the evaluation of Bortezomib Fresenius Kabi benefits can be found in European public assessment report (EPAR), including in its plain-language summary, available on the EMA website, under the medicines.

https://www.ema.europa.eu/en/medicines/human/EPAR/bortezomib-fresenius-kabi

The link will be active once EPAR is published.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Bortezomib Kabi, together with measures to minimise such risks and the proposed studies for learning more about Bortezomib Kabi risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 patient (e.g. with or without prescription) can help to minimise its risks.

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

In addition to routine risk minimisation measures, there are additional (proposed) risk minimization measures for Medication / dispending errors (Annex 6, HCP education material). These proposed measures are to inform HCPs of how to correctly prescribe, dispense, reconstitute and administer bortezomib and how to minimise the occurrence of medication errors.

Medication/dispensing errors

In order to prevent medication errors, IV administered SC or vise a versa as well as drug administration and dosing errors:

- education of HCPs
- a reconstitution, dosing and administration booklet,
- reconstitution poster,
- a dosing slide rule and
- training of medical representative

Confusion with administering the incorrect regimens in the transplant induction setting

- proper training of all Medical Science Liaisons (MSLs) on the different bortezomib treatment schedules approved for transplant induction. MSLs shall be able to offer on-site training and relevant recommendations
- an educational programme and specific tools for HCPs who are involved in the prescription and administration of bortezomib combination regimens in the transplant induction
- the schedules, doses and number of cycles for each of the 2 combinations shall be clearly described and graphically represented in educational materials and should also remind the need to implement the Thalidomide Pregnancy Prevention Program

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*. There are routine pharmacovigilance activities beyond adverse reactions reporting, aggregate reports, review in PSURs and signal detection for following risks:

- Progressive Multifocal Leukoencephalopathy
- Second primary malignancies with BzTD induction therapy
- Optic neuropathy and different degrees of visual impairment (up to blindness)
- Medication errors

The routine pharmacovigilance activities include follow-up forms with questionnaires to gather more information for cases and close monitoring at regular intervals for early detection and risk minimization.

If important information that may affect the safe use of Bortezomib Kabi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Bortezomib Kabi are risks that need special risk management activities to further investigate or minimise 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 Bortezomib Kabi. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	– Heart failure – Hepatotoxicity – Acute hypersensitivity reactions – Tumour lysis syndrome – Peripheral motor neuropathy (including paralysis) – Autonomic neuropathy – Acute diffuse infiltrative pulmonary disease – Pericardial disease – Pulmonary hypertension – Herpes zoster infection – Posterior reversible encephalopathy syndrome (PRES) – Optic neuropathy and different degrees of visual impairment (up to blindness) – Thrombocytopenia and thrombocytopenia with associated bleeding – Neutropenia and neutropenia with associated infection
Important potential risks	– Progressive multifocal leukoencephalopathy – Ventricular rhythm abnormalities – Guillain-Barre syndrome – Other central nervous system disorders – Medication/dispensing errors
Missing information	– Safety in patients with cardiac impairment or with NYHA Class III or IV impairment – Safety in patients with ECOG>2 – Second primary malignancies with BzTD induction therapy

II.B Summary of important risks

Important identified risk – Heart failure	
Evidence for linking the risk to the medicine	Reports of Heart failure from bortezomib derived from bortezomib such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Fluid retention may be a predisposing factor for signs and symptoms of heart failure.

Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Hepatotoxicity	
Evidence for linking the risk to the medicine	Reports of hepatotoxicity from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with moderate or severe hepatic impairment
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Bortezomib Fresenius Kabi" and section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Acute hypersensitivity reactions	
Evidence for linking the risk to the medicine	Reports of Acute hypersensitivity reactions from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients, hypersensitive to bortezomib or any of the excipient in formulation.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.3 "Contraindications". Listed in SmPC section 4.8 "Undesirable effects":

	Guidance in PL section 2 "What you need to know before use Bortezomib Fresenius Kabi "and section 4 "Possible side effects". Additional risk minimisation measures Not applicable

Important identified risk – Tumour lysis syndrome	
Evidence for linking the risk to the medicine	Reports of Tumour lysis syndrome from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib Fresenius Kabi" and section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Peripheral motor neuropathy (including paralysis)	
Evidence for linking the risk to the medicine	Reports of Peripheral motor neuropathy (including paralysis) from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with pre-existing severe neuropathy
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration" and 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures

	Not applicable

Important identified risk – Autonomic neuropathy	
Evidence for linking the risk to the medicine	Reports of Autonomic neuropathy from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with pre-existing neuropathy
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Acute diffuse infiltrative pulmonary disease	
Evidence for linking the risk to the medicine	Reports of Acute diffuse infiltrative pulmonary disease of bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with pre-existing pulmonary complications
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.3 "Contraindications", 4.4 "Special warnings and precautions for use", Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Pericardial disease	
Evidence for linking the risk to the medicine	Reports of Pericardial disease from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological

	studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patient with existing cardiac disease
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Pulmonary hypertension	
Evidence for linking the risk to the medicine	Reports of Pulmonary hypertension from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with underlying cardiac or blood pressure disorders
Risk minimisation measures	Routine risk minimisation measures Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Herpes zoster infection	
Evidence for linking the risk to the medicine	Reports of Herpes zoster infection from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Immunocompromised state of patient due to underlying malignancy / chemotherapy
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" and Listed in SmPC section 4.8 "Undesirable effects":

	Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Posterior reversible encephalopathy syndrome	
Evidence for linking the risk to the medicine	Reports of Posterior reversible encephalopathy syndrome from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with past history of seizures, memory loss, trouble thinking, difficulty with walking or loss of vision.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Optic neuropathy and different degrees of visual impairment (up to blindness)	
Evidence for linking the risk to the medicine	Reports of Optic neuropathy and different degrees of visual impairment (up to blindness) from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with underlying optical disorder or PRES.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Thrombocytopenia and thrombocytopenia with associated bleeding

Evidence for linking the risk to the medicine	Reports of Thrombocytopenia and thrombocytopenia with associated bleeding from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with relapsed multiple myeloma and underlying haematologic disorder.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use" and 4.9 "Overdose" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important identified risk – Neutropenia and neutropenia with associated infection	
Evidence for linking the risk to the medicine	Reports of Neutropenia and neutropenia with associated infection from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with relapsed multiple myeloma and underlying haematologic disorder.
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use" and 4.9 "Overdose" Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects" Additional risk minimisation measures Not applicable
Important potential risk – Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	Reports of Progressive multifocal leukoencephalopathy of bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with prior or concurrent immunosuppressive therapy.
Risk minimisation measures	Routine risk minimisation measures

	Guidance in SmPC section 4.4 "Special warnings and precautions for use", Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important potential risk – Ventricular rhythm abnormalities	
Evidence for linking the risk to the medicine	Reports of Ventricular rhythm abnormalities of bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with pre-existing cardiac rhythm disorders
Risk minimisation measures	Routine risk minimisation measures Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important potential risk – Guillain-Barre syndrome	
Evidence for linking the risk to the medicine	Reports of Guillain-Barre syndrome from bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients having immune-mediated disease and on vaccinations
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important potential risk – Other central nervous system disorders	
Evidence for linking the risk to the medicine	Reports of Other central nervous system disorders of bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Patients with pre-existing central nervous disorders
Risk minimisation measures	Routine risk minimisation measures Listed in SmPC section 4.8 "Undesirable effects": Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures Not applicable

Important potential risk – Medication/dispensing errors	
Evidence for linking the risk to the medicine	Reports of medication/dispensing errors of bortezomib derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.
Risk factors and risk groups	Incorrect method of administration or dispensing of product
Risk minimisation measures	Routine risk minimisation measures Listed in SmPC section 4.2 "Posology and method of administration" Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional risk minimisation measures (Annex 6): • Education of HCP; reconstitution, dosing and administration booklet, reconstitution poster; dosing slide rule; training of medical representative • Proper training of all medical science liaison (MSL) or equivalent, on the different bortezomib treatment schedules approved for transplant induction • An educational programme and specific tools for HCPs who are involved in the prescription and administration of bortezomib combination regimens in the transplant induction

Missing information: Safety in patients with cardiac impairment or with NYHA Class III or IV impairment

Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use" Guidance in PL section 2 "How to use Bortezomib Fresenius Kabi" Additional risk minimisation measures Not applicable

Missing information: Safety in patients with ECOG>2	
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration" Guidance in PL section 2 "How to use Bortezomib Fresenius Kabi " Additional risk minimisation measures Not applicable
Missing information: Second primary malignancies with BzTD induction therapy	
Risk minimisation measures	Routine risk minimisation measures Guidance in SmPC section 4.2 "Posology and method of administration": Additional risk minimisation measures Not applicable

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 Bortezomib Kabi.

II.C.2 Other studies in post-authorisation development plan

There are no on-going or closed studies for Bortezomib Kabi**.**