# 7 Part VI: Summary of the risk management plan (RMP) Bortezomib, 1 mg, 2.5 mg and 3.5 mg, Powder for solution for injection

This is a summary of the RMP for bortezomib powder for solution for injection 1 mg, 2.5 mg and 3.5 mg. The RMP details important risks of bortezomib powder for solution for injection, how these risks can be minimized, and how more information will be obtained about bortezomib powder for solution for injection's risks and uncertainties (missing information).

Bortezomib powder for solution for injection's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how bortezomib powder for solution for injection should be used.

Important new concerns or changes to the current ones will be included in updates of bortezomib powder for solution for injection's RMP.

## 7.1 Part VI: I. The medicine and what it is used for

Bortezomib powder for solution for injection is a ‘proteasome inhibitor’. Proteasomes play an important role in controlling cell functioning and growth. By interfering with their function, bortezomib can kill cancer cells.

Bortezomib is used for the treatment of multiple myeloma (a cancer of the bone marrow) in patients older than 18 years:

- alone or together with other medicines (dexamethasone, pegylated liposomal doxorubicin), in patients whose disease is worsening after receiving at least one prior treatment and for whom blood stem cell (cells capable of giving rise to indefinitely more cells of the same type) transplantation was not successful.
- in combination with medicines (melphalan and prednisone), in patients whose disease has not been previously treated and is unsuitable for high-dose chemotherapy with blood cell transplant.
- in combination with medicines (dexamethasone or dexamethasone together with thalidomide), in patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

Bortezomib is also used for the treatment of mantle cell lymphoma (a type of cancer affecting the lymph nodes) in patient ≥18 years in combination with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone, for patients whose disease has not been previously treated and for whom blood stem cell transplantation is unsuitable.

It contains bortezomib as the active substance and is given by intravenous ((IV) or subcutaneous (SC) route of administration in the form of powder for solution for injection (1 mg, 2.5 mg and 3.5 mg).

## 7.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of bortezomib powder for solution for injection, together with measures to minimize such 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 PL and SmPC addressed to patients and HCPs;
- 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 patient (e.g. with or without prescription) can help to minimize its risks.

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

In the case of bortezomib powder for solution for injection, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, if applicable, 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 bortezomib powder for solution for injection is not yet available, it is listed under 'missing information' below.

### 7.2.1 Part VI – II.A: List of important risks and missing information

Important risks of bortezomib powder for solution for injection 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 bortezomib powder for solution for injection. 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).

**Table 7-1 List of important risks and missing information**

| | |
|---|---|
| Important identified risks | Heart failure |
| | Hepatotoxicity |
| | Acute hypersensitivity reaction |
| | Tumor 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 (PML) |
| | Ventricular rhythm abnormalities |
| | Guillain-Barré syndrome |
| | Other central nervous system (CNS) disorders |
| | Medication/dispensing errors |
| Missing information | Safety in patients with cardiac impairment or with New York heart association (NYHA) Class III or IV impairment |
| | Safety in patients with eastern cooperative oncology group (ECOG)>2 |
| | Second primary malignancies with bortezomib, thalidomide, dexamethasone (BTD) induction therapy |

### 7.2.2 Part VI – II.B: Summary of important risks

**Table 7-2 Important identified risk: Heart failure**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 recommending close monitoring in patients with risk factors for or existing heart disease<br><br>PL section 2 Recommendations are given to not use the bortezomib if there is a certain severe heart problem<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-3 Important identified risk: Hepatotoxicity**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures |

| | |
|---|---|
| | SmPC sections 4.4, 4.8 and 5.2<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 recommending instructions to monitor patients with moderate or severe hepatic impairment for toxicities<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-4 Important identified risk: Acute hypersensitivity reaction**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.3 and 4.8<br><br>PL sections 2 and 4<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-5 Important identified risk: Tumor lysis syndrome**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 recommending close monitoring in patients with high tumor burden prior to bortezomib treatment<br><br>PL section 2 Instructions to contact doctor or pharmacist before using bortezomib if symptoms of tumor lysis syndrome occur<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-6 Important identified risk: Peripheral motor neuropathy (including paralysis)**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.2, 4.4 and 4.8<br><br>PL sections 2 and 4 |

| | |
|---|---|
| | SmPC section 4.4 and PL section 2 recommending patients to undergo neurological evaluation if experiencing symptoms of neuropathy<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-7 Important identified risk: Autonomic neuropathy**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.2, 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>SmPC section 4.2 where instructions to consider discontinuing bortezomib therapy if a patient develops a severe autonomic neuropathy<br><br>PL section 2 recommending patients to undergo neurological evaluation if experiencing symptoms of neuropathy<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-8 Important identified risk: Acute diffuse infiltrative pulmonary disease**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.3, 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 recommending chest radiograph to monitor pre- and post-treatment pulmonary changes<br><br>PL section 2 Recommendations are given to contact the doctor immediately if a patient suffers from coughing and breathing difficulties or tightness in the chest<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-9 Important identified risk: Pericardial disease**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.3 and 4.8 |

| | |
|---|---|
| | PL sections 2 and 4<br><br>PL section 2 Recommendations are given to talk to doctor or pharmacist if patient experience heart problems<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-10 Important identified risk: Pulmonary hypertension**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC section 4.8<br><br>PL sections 2 and 4<br><br>PL section 4 Recommendations are given to contact the doctor immediately if a patient suffers from coughing and breathing difficulties or tightness in the chest<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-11 Important identified risk: Herpes zoster infection**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>SmPC section 4.4<br>antiviral prophylaxis is recommended in patients being treated with bortezomib<br><br>PL section 4<br>where instructions are given to contact the doctor/pharmacist if a patient develops herpes virus infection and related signs & symptoms<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-12 Important identified risk: PRES**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.4 and 4.8 |

| | |
|---|---|
| | PL sections 2 and 4<br><br>SmPC section 4.4 recommending brain imaging such as MRI to be performed to confirm diagnosis. If patients develop PRES, bortezomib therapy should be discontinued<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-13 Important identified risk: Optic neuropathy and different degrees of visual impairment (up to blindness)**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.8<br><br>PL section 4 where instructions are given to tell the doctor straight away if a patient notices any visual loss or disturbances<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-14 Important identified risk: Thrombocytopenia and thrombocytopenia with associated bleeding**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.2, 4.4, 4.8 and 4.9<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 and PL sections 2, 4 recommending complete blood cell count monitoring throughout and before initiating treatment with bortezomib<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-15 Important identified risk: Neutropenia and neutropenia with associated infection**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.2, 4.4 and 4.8<br><br>PL sections 2 and 4 |

| | |
|---|---|
| | SmPC section 4.4 and PL sections 2, 4 recommending complete blood cell count monitoring and patients for potential signs and symptoms of neutropenia associated infections<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-16 Important potential risk: PML**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC section 4.4<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 and PL section 2 recommending monitoring and testing of patients at regular intervals for new or worsening of serious brain infections<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-17 Important potential risk: Ventricular rhythm abnormalities**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.4 and 4.8<br><br>PL section 4<br><br>SmPC section 4.4 recommending close monitoring of patients with risk factors or existing heart disease<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-18 Important potential risk: Guillain-Barré syndrome**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>None<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-19 Important potential risk: Other CNS disorders**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC section 4.8<br><br>PL section 4<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-20 Important potential risk: Medication/dispensing errors**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.2, 4.4, 4.9 and 6.6<br><br>PL sections 3 and 5<br><br>SmPC sections 4.2, 6.6 and PL section 3, 5 providing detailed description on how to use bortezomib from IV and SC administration<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>• Reconstitution, dosing and administration booklet<br>• Reconstitution poster<br>• Dosing slide rule<br>• Induction transplant regimens graph |

**Table 7-21 Missing information: Safety in patients with cardiac impairment or with NYHA Class III or IV impairment**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 recommending close monitoring of patients with risk factors or existing heart diseases<br><br>PL section 2 recommendations to talk to doctor or pharmacist if patient suffers from heart problems<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-22 Missing information: Safety in patients with ECOG>2**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures |

| | |
|---|---|
| | None<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

**Table 7-23 Missing information: Second primary malignancies with BTD induction therapy**

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures<br>SmPC sections 4.4 and 4.8<br><br>PL sections 2 and 4<br><br>SmPC section 4.4 recommending close monitoring in patients with high tumor burden prior to bortezomib treatment<br><br>Legal status: Prescription only<br><br>Additional risk minimization measures<br>None |

## 7.2.3 Part VI – II.C: Post-authorization development plan

### 7.2.3.1 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 bortezomib powder for solution for injection.

### 7.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for bortezomib powder for solution for injection.