VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Multiple myeloma (a cancer of the bone marrow) accounts for 10% of all hematologic cancers. The annual occurrence of multiple myeloma is 4.3 cases per 100,000 white men, 3 cases per 100,000 white women, 9.6 cases per 100,000 black men, and 6.7 cases per 100,000 black women.

The median age of patients with multiple myeloma is 68 years for men and 70 years for women. Only 18% of patients are younger than 50 years, and 3% of patients are younger than 40 years. The male-to-female ratio of multiple myeloma is approximately 3:2.

In the United States, African Americans are twice as likely as whites to have myeloma, with a ratio of 2:1. Myeloma is rare among people of Asian descent, with an occurrence of only 1-2 cases per 100,000 population.

Multiple myeloma survival ranges from 1 year to more than 10 years. Survival is higher in younger people and lower in the elderly.[1]

Mantle cell lymphoma (MCL, fast-growing type of B-cell non-Hodgkin lymphoma that usually occurs in middle-aged or older adults) accounts for almost 2-10% of all non-Hodgkin lymphomas (NHLs, blood cancers). The exact occurrence of MCL is difficult to estimate due to the lack of uniformity in classification and diagnosis procedures.

NHL is the seventh commonest cancer and represents approximately 4% of all cancers diagnosed worldwide. Over the last 20 years, the occurrence of NHL has increased by approximately 40%. The white population is at higher risk thank the black population. The median age is 60 years of age and the male:female ratio is 4:1. [3]

VI.2.2 Summary of treatment benefits

The average survival time for patients (682 patients) with previously untreated multiple myeloma in an international study, treated with bortezomib in addition to melphalan and prednisone was 56.4 months compared with treatment with melphalan and prednisone (43.1 months).

In another study, bortezomib combined with dexamethasone (240 patients) was compared to vincristine-doxorubicin-dexamethasone (242 patients) as induction therapy prior to stem cell transplantation in patients with previously untreated multiple myeloma. Bortezomib with dexathesone was significantly more efficient in terms of post-induction response rate and post-transplant response rates.

In a study on 669 patients with relapsed or refractory multiple myeloma, bortezomib led to a significant longer time to progression, a significantly prolonged survival and a significantly higher response rate compared to treatment with dexamethasone.

Four open-label, phase II, clinical trials, bortezomib administration in subjects with mantle cell lymphoma (n=227) led to response rates between 30%-50%, with duration exceeding 6 months in heavily pre-treated patients. Reasonable toxicity: with gastrointestinal, thrombocytopenia, neutropenia, fatigue, dizziness, neuropathy, and myalgia was reported.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. However, the safety and efficacy of bortezomib was not studied in patients with cardiac impairment or with NYHA Class III or IV impairment and in patients with ECOG>2.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Heart failure	Acute development or exacerbation of heart failure has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Heart failure is an uncommon adverse reaction for bortezomib, affecting up to 1 in 100 people.	Patients with risk factors for or existing heart disease should be closely monitored.
Hepatotoxicity	Liver failure that have been reported in patients receiving bortezomib and concomitant medicinal products and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hepatitis, swelling of the liver,	Yes, by monitoring for early signs. Special attention should be paid to patients with pre-existing moderate to severe liver problems.

Risk	What is known	Preventability
	bleeding from the liver, Budd-Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins) and obstruction of the bile duct. Such changes may be reversible upon discontinuation of bortezomib.	
Acute hypersensitivity reaction	Serious allergic reaction (anaphylactic shock) were reported during bortezomib treatment, signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse.	By contraindicating bortezomib to patients with known hypersensitivity to this substance or to boron. Also, by monitoring for early signs, the risk may be minimised.
Tumour lysis syndrome (a group of metabolic complications that can occur after treatment of cancer)	There is a risk of complications of tumour lysis syndrome because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells. The patients at risk of tumour lysis syndrome are those with large tumours prior to treatment. Symptoms of tumor lysis syndrome are muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath.	Patients at risk should be monitored closely and appropriate precautions taken.
Peripheral motor neuropathy (including paralysis) (disease affecting motor nerves-that control muscles)	Dose modification is recommended in patients with neuropathy (numbness, tingling, or pain in the hands or feet). The following symptoms may appear: a burning sensation, hyperesthesia (abnormal increase in sensitivity to stimuli of the sense), hypoesthesia (reduced sense of touch or sensation), paraesthesia (numbness, tingling or pins and needles), discomfort,	Yes, by monitoring for early signs. Special attention should be paid to patients receiving bortezomib in combination with medicinal products known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.

Risk	What is known	Preventability
	pain or weakness.	
Autonomic neuropathy (malfunction of the autonomic nervous system that controls a number of functions in the body, such as heart rate, blood pressure, digestive tract peristalsis, and sweating, amongst others)	Dose modification is recommended in patients with autonomic neuropathy. Autonomic neuropathy may contribute to some adverse reactions such as sudden fall of blood pressure on standing which may lead to fainting and severe constipation. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.	Yes, by monitoring for early signs.
Acute diffuse infiltrative pulmonary disease (lung disease affecting the the tissue and space around the air sacs of the lungs)	Acute diffuse infiltrative pulmonary disease of unknown cause such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (life-threatening reaction in adults to injuries or acute infections to the lung) were reported in patients receiving bortezomib. Some of these events have been fatal. The symptoms may include: difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, wheezing. It is recommended to have a pre-treatment chest radiograph to serve as a baseline for potential post-treatment lung problems.	By contraindicating bortezomib to patients with acute diffuse infiltrative disease, the risk may be minimised.
Pericardial disease (inflammation of the pericardium-the fibrous sac surrounding the heart)	Pericarditis (main symptom is chest pain) is an uncommon side effect affecting up to 1 in 100 people who take bortezomib.	By contraindicating bortezomib to patients with pericardial disease, the risk may be minimised.
Pulmonary hypertension (increase of blood pressure in the pulmonary artery, pulmonary vein, or pulmonary capillaries)	New or worsening pulmonary symptoms (e.g., cough, shortness of breath, swelling of your feet, fainting) may occur during treatment with bortezomib, in which case a prompt diagnostic evaluation should be performed and patients treated appropriately. It	Yes, by monitoring for early signs.

Risk	What is known	Preventability
	should be considered whether bortezomib therapy can be continued.	
Herpes zoster infection (shingles)	Shingles (localised including around the eyes or spread across the body) is a common adverse reaction affecting up to 1 in 10 people taking bortezomib. It was proven that when administering antiviral prophylaxis in patients receiving bortezomib, the risk of shingles is significantly reduced.	Antiviral prophylaxis should be considered in patients being treated with bortezomib.
Posterior reversible encephalopathy syndrome (a syndrome characterized by headache, confusion, seizures and visual loss)	Posterior reversible encephalopathy syndrome a severe reversible brain condition which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. Treatment with bortezomib should be discontinued if Posterior reversible encephalopathy syndrome develops.	Yes, by monitoring for early signs.
Optic neuropathy (damage to the optic nerve) and different degrees of visual impairment (up to blindness)	Irritated or inflamed eyes, excessively wet eyes, painful eyes, dry eyes, eye infections, discharge from the eyes, abnormal vision, bleeding of the eye are uncommon side effects affecting up to 1 in 100 people taking bortezomib.	Yes, by monitoring for early signs.
Thrombocytopenia (reduction in blood platelets which increases risk of bleeding or bruising) and thrombocytopenia associated with bleeding	Treatment with bortezomib is often associated with blood toxicities, including thrombocytopenia which can increase the risk of bleeding without obvious injury. Taken more than twice, bortezomib is associated with fatal thrombocytopenia.	Yes, by monitoring the blood cell count.
Neutropenia and neutropenia with associated infection (abnormally low number of a	Treatment with bortezomib is often associated with blood toxicities, including neutro-	Yes, by monitoring the blood cell count.

Risk	What is known	Preventability
particular blood cells, that helps fight off infections)	penia. Due to this, infections are more likely to manifest.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Progressive multifocal leukoencephalopathy (viral disease characterized by progressive damage or inflammation of the white matter of the brain)	Very rare cases with unknown causality of John Cunningham (a type of human polyomavirus) virus infection, resulting in progressive multifocal leukoencephalopathy and death, have been reported in patients treated with bortezomib. Patients diagnosed with progressive multifocal leukoencephalopathy had prior or concurrent immunosuppressive therapy (drug to stop immune response). Most cases of progressive multifocal leukoencephalopathy were diagnosed within 12 months of their first dose of bortezomib. Patients should be monitored at regular intervals for any new or worsening neurological symptoms (relating to nervous system). It is recommended to discontinue bortezomib treatment if progressive multifocal leukoencephalopathy is diagnosed.
Ventricular rhythm abnormalities (irregular heartbeat)	Isolated cases of QT-interval (part of ECG readout) prolongation reported in studies, but causality has not been established. Increased or reduced heart rate and ventricular dysfunction uncommon side effects affecting up to 1 in 100 people taking bortezomib.
Guillain-Barré Syndrome (acute polyneuropathy, a disorder affecting the peripheral nervous system)	Guillain-Barré syndrome can be described as a collection of clinical syndromes that manifests as an acute inflammatory neuropathy with resultant weakness and diminished reflexes. Guillain-Barré syndrome is considered to be a postinfectious, immune-mediated disease targeting peripheral nerves. Administration of certain vaccinations and other systemic illnesses has also been associated with Guillain-Barré syndrome. Case reports exist regarding numerous medications and procedures; however, whether any causal link exists is unclear.[2]
Other central nervous system disorders	Seizures (fits) have been reported in patients without previous history of seizures or epilepsy (brain function disorder that causes fits or seizures). Special care is required when treating patients with any risk factors for seizures. Some nervous system disorders (other than the one described above) might be to be associateed with bortezomib treatment and these could manifest by headache, vertigo, light headedness, a feeling of weakness or loss of consciousness, seizures, falling, movement disorders, abnormal or change in, or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching, bleeding in the brain.
Medication/Dispensing errors	Treatment with bortezomib must be administered by a health care professional experienced in the use of cytotoxic medicines. Bortezomib powder has to be dissolved before administration. This will be done by a healthcare professional.

Risk	What is known (Including reason why it is considered a potential risk)
	The resulting solution is then either injected into a vein or under the skin. Injection into a vein is rapid, taking 3 to 5 seconds. Injection under the skin is in either the thighs or the abdomen. Bortezomib should not be given by other routes. Intrathecal administration (injection into the spinal canal) has resulted in death. Health care professionals must know the correct use of the two regimens (bortezomib with dexamethasone and with dexamethasone and thalidomide) used for patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

Important missing information

Risk	What is known
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment (way of classifying the extent of heart failure)	Acute development or exacerbation of heart failure has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Heart failure is an uncommon adverse reaction for bortezomib, affecting up to 1 in 100 people.
Safety in patients with ECOG>2 (performance status is an attempt to quantify cancer patients' general well-being and activities of daily life)	No safety information regarding bortezomib use in patients with ECOG>2 (capable of only limited self-care [ECOG=3] or completely disabled [ECOG=4]) is available.
Second primary malignancies (new primary cancer in a person with a history of cancer) with bortezomib-thalidomide-dexamethasone induction therapy	Patients must read the package leaflets of all medicinal products to be taken in combination with bortezomib for information related to these medicines before starting treatment with bortezomib.

VI.2.5 Summary of risk minimisation measures by safety concern

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

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.
These additional risk minimisation measures are for the following risks:

Medication/Dispensing errors

Risk minimisation measure(s)
Objective and rationale: HCPs to understand the risk of medication/dispensing errors and the procedures related to the appropriate management of this risk to minimise its occurrence.

Risk minimisation measure(s)
Proposed action: *Additional Risk Minimisation Measures for the risk of medication/dispensing error:* Educational materials: 1. Reconstitution, dosing and administration booklet 2. Reconstitution poster 3. Dosing Slide Rule 4. Induction Transplant Regimens Graph

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for bortezomib.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	16-04-2014	***Identified Risks*** Heart failure Hepatotoxicity Acute hypersensitivity reaction 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 Optic neuropathy and different degrees of visual impairment (up to blindness) ***Potential Risks*** Progressive multifocal leukoencephalopathy Ventricular rhythm abnormalities Guillain-Barré 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 bortezomib-thalidomide-dexamethasone induction therapy	First version, not approved. Educational materials proposed: 1. Booklet including both reconstitution, dosing and administration information and induction transplant regimens graph. 2. Reconstitution brochure
2.0	11-12-2014	No changes in the safety concerns	Educational materials proposed were changed according to the Authori-

Version	Date	Safety Concerns	Comment
			ty request: 1. Reconstitution, dosing and administration booklet 2. Reconstitution poster 3. Dosing Slide Rule 4. Induction Transplant Regimens Graph
3.0	31-03-2015	The following risks were added to the list of safety concerns: ***Identified Risks*** Thrombocytopenia and thrombocytopenia associated with bleeding Neutropenia and neutropenia with associated infections	The RMP was updated in relation to Day 120 Assessment Report received for procedure: DK/H/2395/001/DC from RMS Denmark.
4.0	-05-2015	No changes in the safety concerns	The RMP was updated in order to include the new indication for the use of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.