VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Multiple myeloma

Multiple myeloma is a cancer of plasma cells (a type of white blood cells) in which abnormal plasma cells multiply uncontrollably in the bone marrow and occasionally in other parts of the body. The average age of people with multiple myeloma is about 65 years. Although its cause is not certain, the increased occurrence of multiple myeloma among close relatives indicates that heredity plays a role. Exposure to radiation is thought to be a possible cause, as is exposure to benzene and other solvents[4].

Normally, plasma cells make up less than 1% of the cells in the bone marrow. In multiple myeloma, typically the majority of bone marrow elements are cancerous plasma cells. The overabundance of these cancerous plasma cells in the bone marrow leads to the increased production of proteins that suppress the development of other normal bone marrow elements, including other white blood cells, red blood cells, and platelets (cell-like particles that help the body form blood clots)[4].

Collections of cancerous plasma cells develop into tumors within bones. The cancerous cells also secrete substances that cause loss of bone, most commonly in the pelvic bones, spine, ribs, and skull. Infrequently, these tumors develop in areas other than bone, particularly in the lungs, liver, and kidneys[4].

VI.2.2 Summary of treatment benefits

Bortezomib is a proteasome inhibitor. Proteasome is a protein degradation "machine" within the cell that can digest a variety of proteins into small pieces called polypeptides and amino acids). By interfering with the proteasome function, bortezomib can kill cancer cells. Bortezomib is used for the treatment of multiple myeloma in patients older than 18 years[3].

Patients with multiple myeloma, who had not been treated before, lived for an average of 20.7 months without their disease getting worse when they received bortezomib together with melphalan and prednisone. This compared with 15.0 months in the patients receiving only melphalan and prednisone[3].

Patients with multiple myeloma, who had been treated before, lived for an average of 6.2 months without their disease getting worse when they received bortezomib. This compared with 3.5 months in the patients receiving only dexamethasone[3].

The study that compared bortezomib given under the skin with bortezomib given into a vein showed that the percentage of patients who responded partially or completely to treatment was the same (42%) when using either route of administration, *i.e.* under the skin or into a vein[3].

Studies also showed the benefit of bortezomib-containing combinations in patients who were candidates for high-dose chemotherapy with a blood stem-cell transplant. In one of these studies that compared bortezomib *plus* dexamethasone with standard combinations of other anticancer drugs, around 15% of patients given bortezomib *plus* dexamethasone responded, compared with 6% of those given standard anticancer combinations. In another study, bortezomib *plus* thalidomide and dexamethasone produced a response in 49% of patients, compared with about 26% for a treatment containing bortezomib *plus* other anticancer drugs, and 17% of those given thalidomide and dexamethasone alone[3].

The bortezomib-dexamethasone combination was also shown to be beneficial in patients with worsening disease that had come back or failed to respond to at least one other treatment, with 70% of the patients responding to treatment with bortezomib-dexamethasone[3].

VI.2.3 Unknowns relating to treatment benefits

No formal evaluations of the clinical pharmacology and dose finding of bortezomib in combination with dexamethasone and thalidomide induction therapy in patients with second primary malignancies have been performed. These warnings are included into section 4.4 of the proposed SmPC.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe lung problem (Acute diffuse infiltrative pulmonary disease)	Acute infiltrative lung disease is a term used to describe a number of different disorders that affect the interstitial space of lung, *i.e.* the tissue and space around the air sacs of the lungs. These are disorders that affect the lungs, preventing the body from getting enough oxygen. Up to 1 in 1000	Bortezomib should not be given to patients with severe lung problem.

	patients taking bortezomib might develop acute infiltrative lung disease, the symptoms may includes difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing.	
Allergic reactions (Acute hypersensitivity reaction)	Up to 1 in 1000 patients taking bortezomib might develop allergic reactions. Serious allergic reactions (anaphylactic shock) may develop. Signs of serious allergic reactions 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 and collapse.	Bortezomib must not be used in people who are allergic to bortezomib or to any of the other ingredients.
Damage to nerves controlling organs such as the bladder, eyes, gut, heart and blood vessels (*Autonomic neuropathy*)	Up to 1 in 1000 patients taking bortezomib might develop autonomic neuropathy, such as postural hypotension, *i.e.* low blood pressure, sudden fall of blood pressure on standing which may lead to fainting.	It is recommended that patient should avoid standing while experience low blood pressure.
Heart failure (*Cardiac failure*)	Heart failure is a disorder in which the heart pumps blood inadequately, leading to reduced blood flow, back-up (congestion) of blood in the veins and lungs, and other changes that may further weaken the heart. Treatment with bortezomib may cause or worsen heart rhythm problems and heart failure; the symptoms may include chest pressure or pain, palpitation, swelling of the ankles or feet, or shortness of breath. Heart failure has been reported (up to 1 in 100 patients) during bortezomib treatment.	Patients with a chance of developing heart disease or with existing heart disease should be closely monitored.
Liver damage caused by a drug, chemical or other agent (*Hepatotoxicity*)	Up to 1 in 100 patients taking bortezomib might develop hepatotoxicity. Symptoms vary depending on the degree of exposure and hence extent of the liver damage or injury. Mild liver damage may cause few if any symptoms whereas severe damage can ultimately result in liver failure. Symptoms of liver problems include a yellow discoloration of the eyes and skin (jaundice) and changes in liver enzymes measured in blood test.	The liver function tests should be closely monitored in patients with liver problem.
Shingles (Herpes zoster infection)	Herpes zoster commonly known as shingles, is a viral disease characterized by a painful skin rash with blisters in a limited area on one side of the body (left or right), often in a stripe. Up to 1 in 10 patients taking bortezomib might develop shingles.	Early symptoms of Shingles should be monitored by both patients and doctors.

Low levels of neutrophils, a type of white blood cell that fights infection (*Neutropenia* and *neutropenia* with associated infection)	Bortezomib can cause low levels of white blood cells (infection-fighting cells). More than 1 in 10 patients taking bortezomib might experience a reduction in the number of white blood cells. If the number of white blood cells becomes low, there is a higher risk for infections.	Blood tests should be checked regularly before and during the treatment with bortezomib. Tell your doctor if you develop a fever or believe you have an infection.
Visual nerve damage [*Optic neuropathy* and different degrees of visual impairment (up to blindness)]	Optic neuropathy refers to damage to visual nerve. The main symptom is loss of vision, with colors appearing subtly washed out in the affected eye and other vision problems. Up to 1 in 1000 patients taking bortezomib might develop optic neuropathy.	It is recommended that patients be carefully monitored for symptoms of visual impairment.
Disease affecting the sac that surrounds the heart (*Pericardial disease*)	The pericardium is a thin tissue sac that surrounds the heart. Up to 1 in 100 patients taking bortezomib might develop pericarditis, including pericardial effusion, *i.e*. too much liquid building up around the heart.	Bortezomib should not be given to patients with pericardial disease
Nerve damage in the hands and feet [*Peripheral motor neuropathy* (including *paralysis*)]	Treatment with bortezomib is very commonly (more than 1 in 10 patients) associated with peripheral motor neuropathy, which is predominantly sensory. The symptoms of peripheral motor neuropathy might include sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage or feeling weak. However, cases of severe motor neuropathy have been reported. The incidence of peripheral motor neuropathy increases early in the treatment and has been observed to peak during cycle 5.	Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving bortezomib in combination with thalidomide and appropriate dose reduction or treatment discontinuation should be considered. Patients experiencing new or worsening peripheral motor neuropathy should undergo neurological evaluation.
A reversible brain disorder [*Posterior reversible encephalopathy syndrome* (PRES)]	There have been reports of a reversible condition involving the brain, called PRES, in up to 1 in 100 patients treated with bortezomib. Patients with PRES can have seizures, high blood pressure, headaches, tiredness, confusion, blindness, or other vision problems. Brain imaging, preferably Magnetic Resonance Imaging, is used to confirm the diagnosis.	In patients developing PRES, bortezomib should be stopped.
High blood pressure in the arteries of the lungs (*Pulmonary hypertension*)	There have been rare reports (up to 1 in 1000 patients) of pulmonary hypertension in patients receiving bortezomib. Some of these events have been fatal. Symptoms include cough, shortness of breath, wheezing or difficulty breathing.	The patients should inform their doctor(s) if they experience any cough, shortness of breath, wheezing, or difficulty breathing. In patients developing pulmonary

		hypertension, bortezomib should be stopped.
Low blood platelets count and bleeding problems (*Thrombocytopenia* and thrombocytopenia with associated bleeding)	More than 1 in 10 patients taking bortezomib might experience a reduction in the number of platelets. If platelets become very low, there is an increased risk of bleeding, which may make you be more prone to bruising, or to bleeding without obvious injury (e.*g.*, bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver).	Blood tests should be checked regularly before and during the treatment with bortezomib. If platelets become very low, the doctor may recommend a platelet transfusion, or change the dose and/or schedule of bortezomib.
Complications due to breakdown of cancer cells (*Tumour lysis syndrome,* TLS)	Because bortezomib is a cytotoxic agent and can rapidly kill malignant plasma cells, TLS may occur. Up to 1 in 100 patients taking bortezomib might experience TLS, which is caused by the breakdown products of dying cells and include high potassium, high phosphates and low calcium in the blood, and consequent acute uric acid nephropathy and acute renal failure.	The patients at risk of TLS are those with high tumour burden prior to treatment. The doctor should monitor the blood and urine for any signs of this syndrome. If TLS develops, the doctor will take appropriate steps to treat it.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Guillain-Barré Syndrome	Guillain-Barré Syndrome has been reported in patients treated with bortezomib[1]. However, no adequate information on causal association between the use of bortezomib and the occurrence of Guillain-Barré Syndrome is available.
Medication/Dispensing errors	<u>Subcutaneous administration instruction</u> Bortezomib is a cytotoxic agent. Therefore, caution should be used during its handling and preparation. Bortezomib 3.5 mg can be administered both intravenously (into a vein) and subcutaneously (under the skin) while bortezomib 1 mg can be administered only intravenously. Bortezomib must not be administered into your spinal fluid (intrathecally). <u>Confusion with administering the incorrect regimens in the transplant induction setting</u> If the patients have not been treated before for multiple myeloma, they will receive bortezomib intravenously together with the medicines dexamethasone, or dexamethasone *plus* thalidomide as induction treatment before they receive high dose chemotherapy and blood stem cell transplantation.

	The two bortezomib combination regimens in the Transplant Induction Setting (bortezomib *plus* dexamethasone, and bortezomib *plus* dexamethasone and thalidomide) are different in the duration of a treatment cycle and number of cycles. Further instructions for prescribing and administration including the cycles' length and number of cycles are included in the educational materials.
Other brain and spinal cord disease (Other central nervous system disorders)	Other central nervous system disorders (such as encephalopathy) have been reported in patients treated with bortezomib.
A serious brain infection (*Progressive multifocal leukoencephalopathy*, PML)	PML is a rare infection of the brain that is caused by the virus called John Cunningham (JC). Very rare cases with PML and death have been reported in patients treated with bortezomib. Most cases of PML were diagnosed within 12 months of their first dose of bortezomib. Symptoms may begin gradually and usually worsen progressively. They vary depending on which part of the brain is infected. Memory loss, trouble thinking, difficulty with walking or loss of vision. These may be signs of a serious brain infection and the doctor may suggest further testing and follow-up. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If a diagnosis of PML is suspected, the treatment with bortezomib should be stopped.
Heart rhythm abnormal (Ventricular rhythm abnormalities)	There have been isolated cases of heart rhytm abnormal (QT-interval prolongation in electrocardiogram, ECG) in clinical studies. However, it is unknown whether the change in ECG is related to the use of bortezomib. Up to 1 in 100 patients taking bortezomib might develop heart rhythm abnormal.

Important missing information

Risk	What is known
Second primary malignancies with dexamethasone and thalidomide induction therapy	There are no adequate information concerning second primary malignancies associated the use of bortezomib combined with dexamethasone and thalidomide. In addition, second primary malignancies are an identified risk of thalidomide.
Use in patients with heart disease	No adequate information on the use of bortezomib in patients with heart disease is available. However, heart failure has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.
Use in patients with Eastern Cooperative Oncology Group (ECOG)>2	Eastern Cooperative Oncology Group (ECOG) performance status is an attempt to quantify cancer patients' general well-being and activities of daily life. Bortezomib has not been studied in patients with ECOG performance status >2.

VI.2.5 Summary of additional risk minimisation measures by safety concern

The educational materials for healthcare professionals regarding the prescribing, dispensing, handling or administration of bortezomib, will be provided during the national phase of the procedures.

The educational materials will consist of the following[2]:

1. Reconstitution, dosing and administration booklet
2. Reconstitution poster
3. Dosing Slide Rule
4. Induction Transplant Regimens Graph.

The Reconstitution, dosing and administration booklet will contain the following key elements:

- bortezomib 3.5 mg can be administered both intravenously and subcutaneously while bortezomib 1 mg can be administered only intravenously
- different reconstitution requirements for intravenous (IV) or subcutaneous (SC) use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted bortezomib (both IV and SC use) required for different body surface areas (cross reference to Dosing Slide Rule)
- advice on method of administration for both IV and SC use, including the need to rotate injection sites for SC use
- storage precautions for reconstituted solution
- potential risks of administration errors including overdosing, underdosing and that inadvertent intrathecal administration has resulted in death
- to report any adverse event, or medication error experienced with the administration of bortezomib 3.5 mg.

The Reconstitution poster will contain the following key elements:

- different reconstitution requirements for bortezomib 3.5 mg IV or SC use
- need to handling the medicinal product in sterile setting
- storage precautions for reconstituted solution
- advice on how to reduce the risk of mix-up of IV and SC reconstituted syringes
- that bortezomib is to be given only by IV or SC injections; no other route of administration is allowed
- that bortezomib 1 mg is only for IV use
- to report any adverse event, or medication error experienced with the administration of bortezomib 3.5 mg.

Dosing Slide Rule will contain the following key elements:

- a dose-calculation tool that enables prescribers to input a patient's height and weight in order to calculate the body surface area (BSA) and thereby to determine the appropriate bortezomib dose
- different reconstitution requirements for intravenous (IV) or subcutaneous (SC) use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted bortezomib (both IV and SC use) required for different body surface areas.

Induction Transplant Regimens Graph will contain the following key elements:

- instructions for prescribing and administration including the cycles' length and number of cycles, to minimise the risk of medication and dispensing errors potentially induced by the existence of the two different bortezomib combination regimens in the Transplant Induction Setting (bortezomib *plus* dexamethasone, and bortezomib *plus* dexamethasone and thalidomide).
- to remind that patients receiving bortezomib in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide, with reference to the SmPC of thalidomide for additional information.

VI.2.6 Planned post authorisation development plan (if applicable)

No post-authorization development is planned.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.