VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Epidemiology of Mantle cell lymphoma (MCL)

MCL is a cancer of b-cells (lymphocytes) - a type of blood cell that protects against infection as part of the defence (immune) system. Population-based studies of MCL occurrence rate by basic demographic characteristics are limited to the past 15-20 years and to Europe and the US. In both regions, average occurrence rates of about 0.5 cases per 100,000 person-years were reported, with a male-to-female ratio of 2.3-2.5:1, and a median age at diagnosis of close to 70 years. Some data suggest a possible increase in MCL occurrence rate over the last 20 years, but the observation may also reflect improved diagnostics. The causes of MCL are not known. Moderate associations with MCL risk have been reported for Borrelia burgdorferi infection, family history of blood or blood cell related cancers (hematopoietic malignancies), and genetic variation in the interleukin-10 and tumor necrosis factor genes, but findings remain unconfirmed (Smedby KE, 2011).

Epidemiology of multiple myeloma (MM)

MMs are a less frequent cancer site among both sexes. On a worldwide scale, it is estimated that about 86000 cases occur every year, accounting for about 1 in 100 of all new cancer cases. About 63000 people are reported to die from the disease each year, accounting for about 1 in 100 of all cancer deaths. Geographically, the frequency is very unevenly distributed in the world with the highest occurrence rate in the industrialised regions of Australia / New Zealand, Europe and North America. Occurrence rate and death rate seem to be stable in Asian countries and to increase slowly over the decades among whites in the western countries (Becker N, 2011).

VI.2.2 Summary of treatment benefits

Clinical efficacy in the treatment of Multiple myeloma (MM)

In one clinical study the effectiveness and safety of bortezomib retreatment was studied in MM patients who had relapsed after achieving at least a partial response to prior bortezomib based therapy. Patients received up to eight cycles of bortezomib (± dexamethasone). Forty out of 100 patients achieved response to retreatment. In conclusion, bortezomib retreatment was effective and tolerable in relapsed MM patients. (Maria T. Petrucci, 2013)

Clinical efficacy in the treatment of Mantle cell lymphoma (MCL)

Bortezomib and gemcitabine have each shown activity as single agents in MCL, which is incurable. The purpose of one clinical study was to determine the effectiveness and safety of the combination of bortezomib and gemcitabine in patients with relapsed or MCL resistant to treatment (refractory). Patients were treated with gemcitabine 1000 mg/m(2) on days 1 and 8 and bortezomib 1.0 mg/m(2) intravenous on days 1, 4, 8, and 11, on a 21-day schedule. Sixty out of 100 patients achieved response to this treatment. Bortezomib and gemcitabine is an active combination in relapsed and MCL resistant to treatment (refractory) with clinically meaningful results. (Kouroukis CT, 2011)

VI.2.3 Unknowns relating to treatment benefits

No or very limited information is available regarding treatment benefits of bortezomib in patients over 65 years and below the age of 18 years. Also no data is available for use of bortezomib in pregnant and breast-feeding woman and effects of bortezomib on ability to reproduce.

VI.2.4 Summary of safety concerns

1.1.Important identified risks

Risk	What is known	Preventability
Heart failure	Heart failure has been reported in patients treated with bortezomib. Fluid retention may be a predisposing factor for signs and symptoms of heart failure	Yes Patients with risk factors for or existing heart disease should be closely monitored.
Harmful effects on liver (Hepatotoxicity)	Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment. Rare cases of hepatic failure 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, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib.	Yes. Patients with moderate to severe liver problems should be treated with bortezomib at reduced doses and closely monitored for harmful effects. Medicine should be stopped. Patient should inform treating doctor, if he/she has moderate to severe liver problems.
Allergic reaction (Acute hypersensitivity reaction)	It is a set of undesirable reactions produced by the normal defence system, including allergies. These reactions may be damaging, uncomfortable, or occasionally life-threatening. Bortezomib and its excipients can cause allergic reaction. Severe cases of allergic reactions have been reported with bortezomib (affecting up to 1 in 100 patients).	Yes. Bortezomib must not be used in patients allergic to bortezomib, boron or any of the other ingredients of this medicine. Patients should contact their doctor immediately if they develop any of the following signs and symptoms which could indicate an allergic reaction: difficulty

Risk	What is known	Preventability
		breathing, chest pain or chest tightness, feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue or throat, which may cause difficulty in swallowing.
A serious condition that can happen when cancer treatment causes cancer cells to die quickly (Tumour lysis syndrome)	Tumour lysis syndrome is a serious condition that can happen when cancer treatment causes cancer cells to die quickly. Because bortezomib can rapidly kill malignant (invasive) plasma cells, the complications of tumour lysis syndrome may occur. Symptoms of tumour lysis syndrome are muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath. The patients at risk of tumour lysis syndrome are those with high tumour burden before the treatment.	Yes. Since the patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment, these patients should be monitored closely and appropriate precautions taken. Patients should inform their doctor if they have symptoms of tumour lysis syndrome.
Damage to peripheral nerves [Peripheral motor neuropathy (including paralysis)]	Patients receiving bortezomib may experience very common side effects due to nerve damage (which may affect more than 1 in 10 people) such as sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands and feet. In patients receiving bortezomib for multiple myeloma the following side effects have been reported uncommonly (in up to 1 in 100 people): paralysis, seizure (fit), falls, movement disorders, abnormal or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling and twitching.	Yes Patients should be carefully monitored for symptoms of nerve damage. Patients experiencing new or worsening nerve damage may require a change in dose or the way the medicine is given (patients may receive the medicine under the skin instead of through a vein).
Damage to the autonomic nerves (Autonomic neuropathy)	Bortezomib may lead to autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.	Yes. Patients should be monitored closely and appropriate precautions taken.

Risk	What is known	Preventability
		Dose modification is done on the basis of severity of neuropathy.
Lung disease (Acute diffuse infiltrative pulmonary disease)	Cases of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving Bortezomib.	Yes. Patient should not use Bortezomib if he/she has severe lung problems. A pre-treatment chest radiograph is advised to serve as a baseline for potential post-treatment lung changes. In the event of new or worsening lung symptoms (e.g., cough, dyspnoea), rapid diagnostic evaluation should be performed and patients treated appropriately. The benefit/risk ratio should be considered before continuing bortezomib treatment.
Inflammation of the lining around heart or fluid around heart (Pericardial disease)	Cases of Pericarditis (inc pericardial effusion) have been reported very uncommon (in patients receiving bortezomib (affecting up to one in 1,000 patients).	Yes. Patient should not use Bortezomib in patients with heart problems like inflammation of the lining around heart or fluid around heart.
High blood pressure that affects the arteries in lungs and the right side of the heart (Pulmonary hypertension)	Cases of pulmonary hypertension have been reported have been reported rarely in patients receiving bortezomib (affecting up to one in 10,000 patients)	Yes. Patients should inform their doctor if they have any heart or blood pressure problems.
Herpes virus infection (Herpes zoster infection)	Herpes zoster infection (inc disseminated & ophthalmic have been reported commonly in patients receiving bortezomib (affecting up to one in 100 patients)	Yes. Patients should inform their doctor if symptoms of shingles develop (numbness, itching, tingling or a burning pain

Risk	What is known	Preventability
		in one part of the body or face). Prevention with an antiviral medicine is recommended in patients treated with Bortezomib
Posterior reversible encephalopathy syndrome	Bortezomib can lead to PRES, a severe reversible brain condition which causes seizures (fits), high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.	Yes. Bortezomib should be discontinued in patients developing PRES.
A disease of the eye called optic neuropathy and different degrees of eye sight problems (up to blindness) [Optic neuropathy and different degrees of visual impairment (up to blindness)]	Bortezomib can cause abnormal vision, visual loss or visual disturbances.	Yes Patient should inform doctor straight away if notices any of these symptoms.
An abnormally low levels of thrombocytes, also known as platelets, in the blood with associated bleeding (Thrombocytopenia and thrombocytopenia with associated bleeding)	Bortezomib can cause a decrease in the numbers of platelets (cells involved in clotting) in the blood. This may make patient more prone to bruising, or to bleeding without obvious injury (e.g. bleeding from the bowels, stomach, mouth and gum or bleeding in the brain or from the liver).	Yes. Doctors should check the full blood count before each dose of Bortezomib. Depending on the results of the blood test the doctor will decide how to continue the treatment.
An abnormally low concentration of neutrophils in the blood (Neutropenia and neutropenia with associated infection)	Febrile neutropenia, Neutropenia, Leukopenia,Anaemia, Lymphopenia have been reported very commonly in patients receiving bortezomib (affecting up to one in 10 patients)	Yes. Patients have to undergo regular blood tests before and during Bortezomib therapy.

1.2.Important potential risks

Risk	What is known
A rare brain infection caused by the John Cunningham virus (JCV). Symptoms include mental deterioration, vision loss, speech disturbances, ataxia (inability to coordinate movements), paralysis, and coma (Progressive multifocal leukoencephalopathy)	Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with Bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML 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 or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue Bortezomib if PML is diagnosed.
Ventricular rhythm abnormalities	Bortezomib can lead to irregular rhythm and dysfunction of the ventricles of the heart.
An immune system disorder that causes multiple inflammations of the nerves. Symptoms include tingling and weakness starting in your feet and legs and spreading to your upper body and arms. (Guillain-Barré syndrome)	Cases of Guillain-Barré syndrome have been reported in patients treated with bortezomib; however, a causal relationship has not been established.
Other disorders affecting the brain and nerves	Bortezomib can lead to seizures, falling, movement disorders, abnormal or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching, altered levels of consciousness, confusion, memory impairment or loss.
Medication/dispensing errors	Bortezomib must be given under the supervision of a healthcare professional experienced in the use of cancer chemotherapy. Bortezomib powder has to be dissolved before administration. This must be done by a healthcare professional. 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 (tummy). There have been cases of administration errors that occurred with bortezomib, where the medicine was accidentally given intrathecally (into the space that surrounds the spinal cord). Bortezomib should not be given intrathecally.

1.3.Missing information

Risk	What is known
Safety in patients with severe heart problems (cardiac impairment or with New York Heart Association (NYHA) Class III or IV impairment)	Bortezomib should not be used in patients with severe heart problems.
Safety in patients with Eastern Cooperative Oncology Group (ECOG) status above 2	Patients with ECOG (Eastern Cooperative Oncology Group) status above 2 are patients that are capable of only limited self-care or are completely disabled. Further information about safety in this population is needed to provide confirmation about the presence of a risk.
Second primary malignancies with bortezomib, dexamethasone and thalidomide induction therapy	Although chemotherapy aims to destroy tumour cells, it may also damage normal cells causing other primary cancers that are unrelated to the original tumour. Avoiding or limiting the treatment may prevent new cancers. Doctor should monitor treatment to control risks.

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

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and describes the risks and recommendations for minimizing them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as ‘routine risk minimisation measures’.

Following safety concern has the additional risk minimisation measures.

Safety Concern	Additional risk minimisation measures
Medication/dispensing errors	As part of Bortezomib Educational Programme following educational materials will be supplied to the HCPs, pharmacists and other specialised healthcare personnel involved in prescribing, dispensing and/or reconstitution of Bortezomib: • Reconstitution, Dosing and Administration Booklet • Reconstitution poster • Dosing Slide Rule As part of Transplant Induction Setting Additional Educational Programme the 'Induction Transplant Regimens Graph' will be supplied to HCPs, and other specialised healthcare personnel involved in prescribing and administration of Bortezomib.

VI.2.6 Planned post authorisation development plan

Not applicable

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
NA	NA	NA	NA