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Summary of the risk management plan (RMP) for Bortezomib Accord (bortezomib)

This is a summary of the risk management plan (RMP) for Bortezomib Accord, which details the measures to be taken in order to ensure that Bortezomib Accord is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Bortezomib Accord, which can be found on Bortezomib Accord's EPAR page.

Overview of disease epidemiology

Bortezomib Accord is a medicine used to treat adults with multiple myeloma and mantle cell lymphoma.

Multiple myeloma

Multiple myeloma (also known as plasma cell myeloma) is a cancer of a type of white blood cell called plasma cells. The risk of multiple myeloma is higher in older people, males and black people. The risk is 2–3 times higher in those people whose parents, siblings or children have myeloma. This risk may be tripled in patients who have undergone organ transplantation.

It is estimated that about 86,000 cases of multiple myeloma occur annually worldwide, accounting for about 0.8% of all new cancer cases. About 63,000 patients are reported to die from the disease each year, accounting for 0.9% of all cancer deaths.

Mantle cell lymphoma

Mantle cell lymphoma belongs to a group of cancers called non-Hodgkin lymphomas that affect a type of white blood cell called B lymphocytes, or B cells. It is a rare disease that affects less than 1 in 100,000 people throughout the world. Mantle cell lymphoma occurs more frequently in older adults, the average age at diagnosis being in the mid-60s. It is more common in men than women, and white people are at a higher risk than black people.

Summary of treatment benefits

Bortezomib Accord contains the active substance bortezomib and is available in vials as a 3.5 mg powder to be made up into a solution for injection into a vein or under the skin. Bortezomib Accord is a 'generic medicine'. This means that Bortezomib Accord is similar to a 'reference medicine' already authorised in the European Union (EU) called Velcade.

Because Bortezomib Accord is a generic medicine, its benefits and risks are taken as being the same as the reference medicine's. No additional studies have been performed with Bortezomib Accord as this is a generic medicine that is given by injection and contains the same active substance as the reference medicine, Velcade.

Unknowns relating to treatment benefits

Bortezomib Accord has not been studied in patients with severe heart failure (NYHA class III or IV), in patients who can no longer fully care for themselves or are completely disabled (with ECOG status above 2) and patients with other primary cancers following treatment with Velcade, thalidomide and dexamethasone.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Heart failure	Heart failure has been reported in patients treated with bortezomib (affecting up to one in 100 patients). Fluid retention is a risk factor for heart failure.	Patients with risk factors for or existing heart disease should be closely monitored. Before starting therapy with Bortezomib Accord, patients should inform their doctor of previous or existing heart or blood pressure problems.
Liver toxicity (hepatotoxicity)	Bortezomib can cause swelling of the liver, bleeding from the liver or alteration of liver function. Rare cases of hepatic failure have been reported in patients receiving bortezomib at the same time as other medicines and with serious underlying medical conditions. Patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal.	Before starting treatment with Bortezomib Accord, patients should inform their doctor of previous or existing liver problems including hepatitis. Patient with moderate or severe liver impairment should receive a reduced dose of Bortezomib Accord. If patients develop hepatitis or have increased liver enzymes in their blood treatment with Bortezomib Accord should be interrupted. Doctors should carefully check patients with a history of hepatitis B for signs of active hepatitis B. Prevention with an antiviral medicine should be considered.
Severe allergic reaction (acute hypersensitivity reaction)	Severe cases of allergic reactions have been reported with bortezomib (affecting up to 1 in 100 patients).	Bortezomib Accord 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

Risk	What is known	Preventability
		develop any of the following signs and symptoms which could indicate an allergic reaction: difficulty 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 condition that is caused by the breakdown of cancer cells (tumour lysis syndrome)	Bortezomib can result in the cancer cells being destroyed very quickly, which can disturb the blood flow (tumour lysis syndrome). Symptoms may include muscle pain, muscle cramps and weakness, pain in the limbs, shortness of breath, confusion, memory impairment or loss, partial or total loss of vision. Symptoms of tumour lysis syndrome have been reported uncommonly (in up to 1 patient in 100) in patients treated with bortezomib for multiple myeloma or mantle cell lymphoma.	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.
Nerve damage which may affect sensation, movement, gland or organ function (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.	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 nerves that manage involuntary body functions such as blood pressure, heart rate, bowel	Bortezomib can lead to postural hypotension (sudden fall of blood pressure when standing up) and abnormal bowel function (such as constipation or diarrhoea).	Bortezomib Accord should be used with caution in patients with a history of syncope (fainting) when receiving medicines known to be associated with hypotension (low blood pressure), or who

Risk	What is known	Preventability
and bladder emptying, and digestion (autonomic neuropathy)		are dehydrated due to recurrent diarrhoea or vomiting. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.
Group of lung disorders in which the tissues of the lungs become inflamed (acute diffuse infiltrative pulmonary disease)	Cases of acute diffuse infiltrative pulmonary disease (such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome) have been reported rarely in patients receiving bortezomib (affecting up to one in 10,000 patients). Some of these events have been fatal.	Bortezomib Accord must not be used in patients with acute diffuse infiltrative pulmonary disease. Before receiving Bortezomib Accord patients should have a chest X-ray. In case patients develop symptoms of acute diffuse infiltrative pulmonary disease (such as difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing) doctors should evaluate and treat patients promptly.
Disorder affecting the sac that surrounds the heart (pericardial disease)	Bortezomib can lead to inflammation of the sac that surrounds the heart or fluid around the heart causing symptoms such as chest discomfort.	Bortezomib Accord must not be used in patients with pericardial disease. Patients should inform their doctor of existing or previous heart problems.
Increase of blood pressure in the blood vessels of the lungs (pulmonary hypertension)	Bortezomib can lead to an increase in the blood pressure in the blood vessels in the lungs.	Patients should inform their doctor if they have any heart or blood pressure problems.
An infection called shingles resulting from reactivation of the varicella-zoster virus, the same virus that	Infection with varicella-zoster virus causes chickenpox. Once the illness resolves, the virus remains dormant and can reactivate later in a person's life and cause shingles. Shingles have been reported commonly (in	Patients should inform their doctor if symptoms of shingles develop (numbness, itching, tingling or a burning pain in one part of the body

Risk	What is known	Preventability
causes chickenpox (herpes zoster infection)	up to 1 in 10 people) in patients receiving bortezomib.	or face). Prevention with an antiviral medicine is recommended in patients treated with Bortezomib Accord.
A neurological syndrome called posterior reversible encephalopathy syndrome (PRES)	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.	Bortezomib Accord should be discontinued in patients developing PRES. Patients should inform their doctor in case of past history of seizures, memory loss, trouble thinking, difficulty with walking or loss of vision.
Damage to the optic nerve (optic neuropathy) and different degrees of visual impairment (up to blindness)	Bortezomib can cause abnormal vision, visual loss or visual disturbances.	Patients should inform their doctor if they develop symptoms of visual impairment.
Low blood platelet counts and 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).	Patients should inform their doctor if they have bleeding problems and/or a low number of platelets in blood. Patients have to undergo regular blood test before and during Bortezomib Accord therapy.
Low white blood cell counts and associated infection (neutropenia and neutropenia with associated infection)	Bortezomib can cause a decrease in the numbers of white blood cells. This may make patients more prone to infections or flu-like symptoms.	Patients should inform their doctor if they have a low number of white blood cells. Patients have to undergo regular blood tests before and during Bortezomib Accord therapy.

Important potential risks

Risk	What is known
A rare brain infection caused by the John Cunningham virus	Very rare cases of John Cunningham (JC) virus infection with unknown causality, resulting in PML and death, have been

Risk	What is known
(JCV) (progressive multifocal leukoencephalopathy, PML)	reported in patients treated with bortezomib. Patients diagnosed with PML had prior or simultaneous immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of the first dose of bortezomib. Patients should be monitored at regular intervals for any new or worsening symptoms or signs that may be suggestive of PML. 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. Bortezomib Accord should be stopped if PML is diagnosed.
Abnormal heart rhythm (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 (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 Accord must be given under the supervision of a healthcare professional experienced in the use of cancer chemotherapy. Bortezomib Accord 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.

Missing information

Risk	What is known
Safety in patients with severe heart problems (cardiac impairment or with NYHA Class III or IV impairment)	Bortezomib should not be used in patients with severe heart problems.
Safety in patients with ECOG	Patients with ECOG (Eastern Cooperative Oncology Group) status above 2 are patients that are capable of only limited self-care or

Risk	What is known
status above 2	are completely disabled. Further information about safety in this population is needed to provide confirmation about the presence of a risk.
Patients with other primary cancers following treatment with Velcade, thalidomide, dexamethasone	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.

Summary of 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 also describes the risks and recommendations for minimising 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'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Bortezomib Accord can be found on Bortezomib Accord's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Bortezomib Accord's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Medication/dispensing errors

Risk minimisation measure: Healthcare professional education material
Objective and rationale: To inform healthcare professionals of how to correctly prescribe, dispense, reconstitute and administer bortezomib and how to minimise the occurrence of medication errors.
Description: The healthcare professional education material will include: • Summary of Product Characteristics • Reconstitution, dosing and administration booklet • Reconstitution poster • Dosing slide rule • Induction transplant regimens graphs

Planned post-authorisation development plan

No studies are planned.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 06-2015.