VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Bendamustine is used alone (monotherapy) or in combination with other medicines for the treatment of patients with[3]

- chronic lymphocytic leukaemia (CLL) who cannot take fludarabine;
- indolent (slow-growing) non-Hodgkin's lymphoma (NHL) who had not, or only shortly, responded to prior rituximab treatment;
- multiple myeloma (MM) who cannot have high dose chemotherapy with a stem cell transplant and are unable to take thalidomide or bortezomib.

Chronic lymphocytic leukaemia
CLL is a type of cancer that starts from lymphocytes (lymph cells) in the bone marrow. It then invades the blood. Leukaemia cells tend to build up over time, and many people do not have symptoms for at least a few years. In time, it can also invade other parts of the body, including the lymph nodes, liver and spleen. Compared with other types of cancer, CLL gets worse slowly. CLL accounts for about 1/3 of the new cases of leukaemia[1]. CLL is the most common leukaemia in the Western world with an incidence of 4.2/100,000/year. The incidence increases to >30/100,000/year at an age of >80 years. The median age at diagnosis is 72 years. About 10% of CLL patients are reported to be younger than 55 years. The risk is slightly higher in men than women[9]. Factors such having a family history of CLL may raise the risk[1].

Indolent non-Hodgkin's lymphomas
NHL is a cancer which affects lymphocyte cells in the lymphatic system. The various types of NHL are divided into high-grade or aggressive (fast growing) and low-grade or indolent (slow growing). Anyone can be affected. Most cases occur in people over the age of 60. Men are more commonly affected than women[10]. It is calculated that, in 2012, about 7 people every 100,000 in Europe developed a NHL[8].

Multiple myeloma
MM is a cancer formed by malignant plasma cells. Normal plasma cells are found in the bone marrow and are an important part of the immune system. When plasma cells become cancerous and grow out of control, they can produce a tumour called a plasmacytoma. These tumours generally develop in a bone, but they are also rarely found in other tissues. If someone has more than one plasmacytoma, they have MM[2]. MM is the second most common form of haematological malignancy in the Western World after NHL, accounting for approximately 10% of haematological malignancies and 1% of all malignancies. It is a disease of later life with 98% of patients aged 40 or older[5]. In the United States, the lifetime risk of getting MM is 1 in 143 (0.7%).

VI.2.2 Summary of treatment benefits

Chronic lymphocytic leukaemia
The indication for use of bendamustine in CLL is supported by a single open-label clinical study (where both patients and researches knew which treatment was administered). In this study, 319 previously untreated patients with CLL requiring therapy were included. They received bendamustine or chlorambucil (another medicine used to treat CLL). In patients receiving bendamustine the CLL took longer to get worse than in patients receiving chlorambucil (21.5 *versus* 8.3 months)[4].

Indolent non-Hodgkin's lymphomas
The indication for bendamustine use in indolent NHL relied on two clinical studies. In one study 100 patients with indolent B-cell NHL, for whom rituximab alone or with other medicines did not work, were treated with bendamustine single agent. The overall response rate (*i.e.* the reduction in tumour

size) was 75%. The other study included 77 patients, for whom prior rituximab treatment gave no response, was followed by tumour progression within 6 months, or had given side effects. The overall response rate was 76% with a median duration of response of 5 months[4].

Multiple myeloma
One study supported the use of bendamustine for the treatment of MM. This study included 131 patients with advanced MM. Therapy with bendamustine in combination with prednisone (BP) was compared to treatment with melphalan and prednisone (MP). Patients with BP treatment took longer to get worse than patients with MP (15 *versus* 12 months). The median time to treatment failure was 14 months with BP and 9 months with MP treatment. The duration of remission (period without disease) was 18 months with BP and 12 months with MP treatment[4].

VI.2.3 Unknowns relating to treatment benefits

There is no or limited experience on the use of bendamustine in people from different racial groups, children and adolescents, patients with severe kidney impairment, and pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions (Drug hypersensitivity)	These reactions are rare. They may affect up to 1 in 1,000 people during treatment with bendamustine. Anaphylactic reaction and anaphylactoid reactions are potentially life-threatening types of allergic reactions. Clinically, these two types of reactions are indistinguishable. Symptoms vary from mild, *e.g.* urticaria, to severe, *e.g.* airway obstruction, refractory shock[11].	Not preventable during the first cycle of therapy. However, doctors must ask the patients about symptoms suggestive of infusion reactions (*e.g.* fever, chills, itching and skin rash) after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids, must be considered in subsequent cycles in patients who have previously experienced serious allergic reactions.
Cardiac disorders • Disturbed function (dysfunction) of the heart: palpitations (feelings or sensations that your heart is pounding or racing), angina pectoris (type of chest pain caused by reduced blood flow to the heart muscle) • disturbed heart rhythms (arrhythmia) • accumulation of fluid in the heart sac, escape of fluid into the	Palpitations, angina pectoris and arrhythmia are common side effects that may affect up to 1 in 10 people treated with bendamustine. Pericardial effusion is an uncommon side effect that may affect up to 1 in 100 people. Tachycardia, myocardial infarction and heart failure are very rare side effects that may affect up to 1 in 10,000 people.	Patients must inform their doctor in cases of existing heart disease (e.*g.* heart attack, chest pain, severely disturbed heart rhythms). The doctor should monitor the potassium levels in blood and must give potassium supplement when the level of potassium is lower than 3.5 mEq/L. Furthermore, the doctor must perform electrocardiogram measurement.

Risk	What is known	Preventability
pericardial space (pericardial effusion) • increased heart rate (tachycardia) • heart attack (myocardial infarct) • heart failure		
Infections	Infections such as pneumonia (very rarely, *i.e.* up to 1 in 10,000 people) and sepsis (rarely, *i.e.* up to 1 in 1,000 people) have been reported during treatment with bendamustine. In rare cases, infection has been associated with hospitalization, septic shock and death. Patients with neutropenia and/or lymphopenia following treatment with bendamustine hydrochloride are more susceptible to infections.	Patients with myelosuppression following bendamustine hydrochloride treatment should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms. Signs or symptoms of infection should receive prompt treatment.
Reduced capability of the bone marrow to replace blood cells (white blood cells), red blood cells and platelets (myelosuppression)	Myelosupression is a common side effect. It may affect up to 1 in 10 people. Low blood counts such as low counts of white blood cells (leukocytopenia), low counts of platelets (thrombocytopenia) and decrease in the red pigment cells of the blood (haemoglobin) are very common side effects and may affect more than 1 in 10 people. Low counts of neutrophils (neutropenia) and reduction in red blood cells which can make the skin pale and cause weakness of breathlessness (anaemia) is a common side effect. The impaired bone marrow function usually returns to normal after treatment. Suppressed bone marrow function increases the risk of infection.	The level of haemoglobin, and the number of white blood cells and platelets in the blood should be checked before starting treatment with bendamustine, before each subsequent course of treatment and in intervals between courses of treatment.
Serious skin reactions	Skin reactions occurred in some patients being treated with bendamustine alone or together with anti-cancer medicines. These skin reactions can get worse if treatment is continued. A small number of patients got serious skin reactions (such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) while being treated with bendamustine together with other medicines (*i.e.* allopurinol, allopurinol and rituximab).	If skin reactions get worse, bendamustine should be withheld or discontinued. If the doctor thinks that a serious skin reaction is caused by bendamustine, treatment should be stopped.

Risk	What is known	Preventability
	Sometimes it is not clear whether these reactions are caused by bendamustine itself or by other drugs that the patient is taking.	
Complication due to the breaking down of dying cancer cells in the blood stream (tumour lysis syndrome)	When the patient's tumour is very severe, the body may not be able to clear all the waste products from the dying cancer cells. This complication is called tumour lysis syndrome, and is common. It might affect up to 1 in 10 people during treatment with bendamustine. Without treatment, this syndrome can cause kidney failure and heart problems within 48 hours of the first dose of bendamustine. It can be fatal.	The patient should inform the doctor in case of pain in the side, blood in the urine or reduced amount of urine. Preventive measures include drinking plenty of fluids and close monitoring of blood chemistry, particularly potassium and uric acid levels. The doctor may consider prescribing allopurinol during the first one to two weeks of bendamustine therapy, but this is not necessarily a standard treatment, since there have been a few cases of severe skin reactions when bendamustine and allopurinol were taken together.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Damage to the kidneys (renal toxicity)	Patients using bendamustine who get tumour lysis syndrome (see table of Important identified risks), and are not treated, might get kidney failure. Also, studies in laboratory animals showed possible renal toxicity of bendamustine.
New cancers (secondary malignancies)	Some patients have experienced new cancers after treatment with bendamustine. Because bendamustine damages DNA, there is a potential for treatment-induced development of secondary tumours. Secondary tumours have been reported in up to 4% of patients[7] receiving bendamustine, and include myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma. However, the association with bendamustine has not been determined.
Serious liver problems (hepatic failure)	Liver problems have been reported in some people taking bendamustine. Increases in some blood values, such as liver enzymes AST/ALT, the enzyme alkaline phosphatase, or the bile pigment, indicate damage to the liver. These changes in lab values may affect up to 1 in 10 people taking bendamustine.

Missing information

Risk	What is known
Effect on people from different racial groups	It is useful to collect more information on bendamustine in people from different ethnic groups, since they may react differently to medicines.
Patients below age 18 years	Bendamustine has not been studied in children and adolescents.
Exposure during pregnancy and lactation	<u>Pregnancy</u> Bendamustine has not been studied in pregnant women. However, bendamustine can cause genetic damage and has caused malformations in animal studies. Bendamustine should not be used during pregnancy unless the doctor thinks it is strictly necessary.

Risk	What is known
	Women in reproductive age must use an effective method of contraception both before and during treatment with bendamustine. If pregnancy occurs during treatment with bendamustine the doctor must be informed immediately and genetic consultation should be sought. Breast-feeding Bendamustine has not been studied in breast-feeding women. It is not known if bendamustine passes into the breast milk. Therefore, bendamustine must not be administered during breast-feeding. If treatment with bendamustine is necessary during lactation, the patient must stop breast-feeding.

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 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 no additional risk minimisation measures.

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

No post-authorization studies have been planned.

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

The following changes to the safety concerns were made as provided in the below table.

Version	Date	Safety Concerns	Comments
V1.1	26 August 2016	**The following safety concerns were removed:** Important identified risks • Extravasation Missing information • Use in patients with severe hepatic impairment (serum bilirubin> 3.0 mg/dl) • Use in patients with severe renal impairment **The following safety concerns were modified:** Important identified risks • 'Anaphylaxis' changed to 'Drug hypersensitivity' • 'Infection (including pneumonia and sepsis)' changed to 'Infections' Important potential risks	Update to the safety concerns were made according to the RMS (DK) Day 0 Assessment report. Information in Part II: Module SV – Post-authorisation experience is updated.

		• Safety concern of 'Hepatic failure' moved from Important identified risk to Important potential risk • 'Secondary tumours (including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma)' changed to 'Secondary malignancies' <u>Missing information</u> • 'Use in paediatric patients' changed to 'Patients below age 18 years' • 'Use in paediatric patients' changed to 'Exposure during pregnancy and lactation'	