VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Chronic Lymphocytic Leukaemia

Chronic lymphocytic leukaemia (CLL; a type of cancer of the white blood cells) is the most common leukaemia in the western world with an incidence of 4:100 000/year. The incidence increases to >30:100 000/year at age >80 years. The median age at diagnosis is 69 years; 14% of CLL patients are younger than 55 years[1]. In the US white population, the incidence rate of CLL varies from 3.35 to 3.69 in men to 1.61-1.92 in women; in Europe, from 2.2 to 3.36 in men to 0.9-1.52 in women[2]. Chronic lymphocytic leukaemia accounts for approximately 30% of adult leukaemias. In the European Union (EU), more than 62,000 people were diagnosed with leukaemia in 2012 and over 41,000 people died from the disease[3].

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL: cancer that begins in a type of white blood cell that normally fights infection) is solid tumour. There were an estimated 356 000 new cases of NHL and 192 000 deaths from NHL worldwide in 2008. NHL is the 8th most commonly diagnosed cancer in men and the 11th in women. The disease accounts for ~5.1% of all cancer cases and 2.7% of all cancer deaths. Areas with highest incidence of NHL include North America, Europe, Oceania, as well as several African countries. The occurrence of NHL is higher in men [worldwide age-standardized rate (ASR) 6.1/100 000] then women (ASR 4.2/100 000)[4]. NHL is the 11th most common cancer in Europe, with around 93,500 new cases diagnosed in 2012 (3% of the total). In Europe (2012), the highest World age-standardised incidence rates for NHL are in Italy for men and the

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Netherlands for women. NHL is the tenth most common cancer worldwide, with nearly 386,000 new cases diagnosed in 2012 (3% of the total)[5].

Multiple Myeloma

Multiple myeloma is a cancer that begins in plasma cells, a type of white blood cell. Worldwide, multiple myeloma accounted for ~0.8% of all cancer diagnoses and ~0.9% of cancer deaths in 2002. Incidence rates were higher among males than females, and highest among African Americans. Incidence rates for white Americans, Canadians and in most European countries were generally similar[6]. Around 39,000 new cases of myeloma were diagnosed in Europe in 2012 (1% of total cancer cases). More than 114,000 new cases of myeloma were diagnosed worldwide in 2012 (0.8% of total cancer cases)[7].

VI.2.2 Summary of Treatment Benefits

As monotherapy, bendamustine was effective in the first-line treatment of adults with chronic lymphocytic leukaemia (CLL; a type of cancer of the white blood cells), significantly prolonging progression-free survival (PFS) and improving the overall response rate after a median duration of follow-up of 35 months compared with chlorambucil (another anticancer medicine) in various studies. Progression-free survival and the overall response rate were at least 2-fold greater with bendamustine than with chlorambucil (another anticancer medicine) when data from the overall patient population.

In the treatment of adults with indolent non-Hodgkin's lymphoma (NHL: cancer that begins in a type of white blood cell that normally fights infection), monotherapy with bendamustine was efficacious, with an overall response achieved by at least three-quarters of patients in two studies.

Front-line combination therapy with bendamustine plus prednisone (corticosteroids) was significantly more effective than combination therapy with melphalan (another anticancer medicine) plus prednisone in prolonging the time to treatment failure, according to a study in adults with multiple myeloma (MM; is a cancer that begins in plasma cells, a type of white blood cell). Moreover, the benefits of bendamustine plus prednisone appeared to be maintained beyond 30 months, with a retrospective calculation of progression-free survival demonstrating a borderline statistical significance in favour of bendamustine plus prednisone over melphalan plus prednisone[8].

VI.2.3 Unknowns relating to treatment benefits

Different people respond differently to medication depending on which ethnic group, genetic they come, from their age or genetic background.

Experience with Bendamustine in the use during Breast-feeding, use in patients with severe renal impairment and use in Paediatric (children) patients is very limited.

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Due to the lack of availability of data Bendamustine should not be used in the pregnancy and lactation. So women of child bearing potential should use contraception.

It is not known whether Bendamustine is excreted in human milk and adverse reactions on the suckling child cannot be excluded. Breast-feeding must be discontinued during Bendamustine therapy.

VI.2.4 Summary of safety concerns

Safety Concern	What is known	Preventability
Important Identified Risks		
Myelosuppression (decrease in the ability of the bone marrow to produce blood cells)	Reduction in the number of white blood cells may or may not associate with fever (symptoms included frequent infections such as fever, severe chills, sore throat or mouth ulcers) and red blood cells (symptoms included tiredness, headaches, being short of breath when exercising, dizziness and looking pale) have been reported with the use of Bendamustine therapy.	Yes by monitoring of early symptoms. You should inform your doctor immediately if you feel tiredness, headache, chill, fever or any infection. Routine monitoring of blood cell counts is recommended. Your doctor may reduce the dose of Bendamustine if your blood cell count is low. Do not take Bendamustine if you suffer from severe suppression of bone marrow functionality, symptoms may be: extreme tiredness, easy bruising or bleeding, occurrence of infections.
Infections	Your **white blood cells** may decrease 2 to 3 weeks after your treatment. They usually return to normal before your next treatment. White blood cells protect your body by fighting bacteria (germs) that cause infection. When they are low, **you are at greater risk of having an infection.**	Wash your hands often and always after using the bathroom. Avoid crowds and people who are sick. Call your doctor ***immediately*** at the first sign of an infection such as fever (over 100°F or 38°C by an oral thermometer), chills, cough, or burning when you pass urine.

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Safety Concern	What is known	Preventability
Serious skin reactions	A number of skin reactions have been reported. These events have included rash, toxic skin reactions and bullous exanthema.	If rash is accompanied by signs of an allergic reaction such as flushing, dizziness, swelling, or breathing problems, call your doctor immediately. If rash gets worse or itching is very irritating, call your doctor. Otherwise, be sure to mention it at your next visit.
Cardiac disorders (Heart related Problems)	Cardiac dysfunction such as Palpitations (feeling that your heart is beating too hard or too fast), angina pectoris (chest pain), Arrhythmia (irregular heartbeat), Pericardial effusion (accumulation fluid around the heart), Tachycardia (heart rate that exceeds the normal range), Myocardial infarction (heart attack) may occurs.	Yes by monitoring of early symptoms. You should inform your doctor immediately if you feeling that your heart is beating too hard or too fast, chest pain etc. The concentration of potassium in the blood must be closely monitored and potassium supplement must be given when K+ <3.5 mEq/l. ECG measurement must be performed.
Tumour lysis syndrome (oncologic emergency that is caused by massive tumor cell lysis with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation)	Bendamustine treatment may cause the rapid breakdown of lymphoma cells, which may lead to abnormalities in the blood. The onset tends to be within 48 hours of the first dose of Bendamustine and, without intervention, may lead to acute renal (Kidney) failure and death.	Your doctor will tell you if you are at risk. You should be given a kidney-protective medicine called allopurinol for the first cycle of treatment, and your doctor may do additional blood tests to monitor this side effect. Adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels is recommended.
Drug Hypersensitivity	Anaphylactic reaction, Anaphylactoid reaction and Anaphylactic shock may occur with Bendamustine therapy.	Yes by monitoring of early symptoms. Tell doctor immediately if you notice signs of allergic reaction or hypersensitivity.

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Safety Concern	What is known	Preventability
		Do not take Bendamustine if you are allergic to Bendamustine or any of the other ingredients of this medicine.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Renal toxicity	On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 ml/min. Experience in patients with severe renal impairment is limited.
Hepatic failure	On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2 mg/dl). A 30% dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2 - 3.0 mg/dl). No data is available in patients with severe hepatic impairment (serum bilirubin values of > 3.0 mg/dl).
Secondary malignancies	There are reports of secondary tumours, including myelodysplastic syndrome (a group of diseases that affect normal blood cell production in the bone marrow), myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma. The association with bendamustine hydrochloride therapy has not been determined.

Missing information

Risk	What is known
Limited information on Exposure during pregnancy and lactation	There are insufficient data from the use of bendamustine hydrochloride in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic. During pregnancy bendamustine should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with bendamustine is absolutely necessary during pregnancy or if pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered. It is not known whether bendamustine passes into the breast milk, therefore, bendamustine is contraindicated during breast feeding. Breast feeding must be discontinued during treatment with

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Risk	What is known
	bendamustine
Effect on different races	No information is avaialble.
Patients below age 18 years	There is no experience in children and adolescents with Bendamustine Hydrochloride.

VI.2.5 Summary of risk minimisation measures by safety concern

The Summary of Product Characteristics and the Package Leaflet for Bendamustine 2.5 mg/ml powder for concentrate for solution for infusion contain information about routine risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Not applicable.