VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most common type of leukemia. It occurs in around 2,750 people each year in the United Kingdom (UK). CLL estimates in the United States (US) for 2014 are about 15,720 new cases of CLL and about 4,600 deaths from CLL. CLL accounts for about one-third of the new cases of leukemia (52,380 new cases of leukemia is estimated in 2014). The average person's lifetime risk of getting CLL is about ½ of 1% (about 1 in 200). The risk is slightly higher in men than in women. CLL is most common in Australia. CLL is more common in North America and Europe than in Asia. Factors such as having a family history of CLL may raise this risk. CLL mainly affects older adults. The average age at the time of diagnosis is around 72 years. It is rarely seen in people under age 40, and is extremely rare in children. [1, 2]

Indolent non-Hodgkin's lymphomas

Non-Hodgkin lymphoma (NHL) is estimated to be the tenth most common cancer worldwide. With 356,000 new cases diagnosed in 2008 (3% of the total), it comprises 2 in 5 (41%) haematological cancers. In the UK in 2010, around 12,200 new cases of NHL were registered, and around 4,400 people were recorded as having died from NHL. In the UK, NHL is the sixth most common cancer and the 12th most common cause of cancer death.

While NHL can occur at any age, about half of patients are older than 65, and is slightly more common in men than women, the age and sex profile varying between NHL subtypes. The risk of developing NHL increases throughout life. Death rates from NHL have been decreasing since the late 1990s. Although some types of NHL are among the more common childhood cancers, more than 95% of cases occur in adults. [3, 4, 5]

Multiple myeloma

Multiple myeloma (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. [6] In the US, the median age at diagnosis of MM is 69 years, with age-adjusted incidence of 5.8 cases per 100,000 persons per year. It is estimated that in 2012, approximately 22,000 people were diagnosed and 11,000 people died of MM in the US. The incidence of MM varies widely, ranging from 0.4 to 5 cases per 100,000 persons, with the highest rates in Australia, New Zealand, North America and parts of Europe, and the lowest rates in Asia. [7]

VI.2.2 Summary of treatment benefits

Many types of cancer can be prevented by lifestyle changes to avoid certain risk factors, but there are very few known risk factors for CLL, and most of these cannot be avoided. CLL often grows slowly, not everyone needs to be treated right away. When treatment is needed, the main treatments used are chemotherapy, monoclonal antibodies, targeted therapy, supportive care, or stem cell transplant. Less often, leukapheresis (a way of removing abnormal white blood cells

from the blood), surgery, or radiation therapy may also be used. The major types of chemotherapeutics used to treat CLL include purine analogs (such as fludarabine, pentostatin, or cladribine). These drugs can have major side effects, including an increased risk of infection. Alkylating agents including chlorambucil and cyclophosphamide are often used along with a purine analog, with other chemotherapeutic drugs, with corticosteroids, or with the monoclonal antibody rituximab. [1]

NHL is a cancer of lymphocytes (white blood cells) which is often marked by lymph nodes that are larger than normal, fever and weight loss. Indolent NHL means a slow growing lymphoma. The main types of treatment for NHL are chemotherapy (including bendamustine), radiation, immunotherapy or stem cell transplant. In rare cases, surgery is also used. [3, 8]

MM (multiple myeloma) is a fatal hematological disease caused by malignant transformation of plasma cells. The treatment for MM may include chemotherapy (including bendamustine), bisphosphonates, radiation, surgery, biologic therapy, stem cell transplant or plasmapheresis. [9]

Bendamustine is an alkylating agent with some properties of purine analogs. It consists of an alkylating nitrogen mustard group bound to a purine-like benzimidazole ring and due to this bifunctional structure bendamustine activity profile is different from other alkylators. [10] Bendamustine is indicated as a first line treatment for CLL in patients for whom fludarabine combination chemotherapy is not appropriate. [1] It has been shown an effective drug as a first-line NHL treatment for people who have already had rituximab. Moreover, there were fewer toxic complications after bendamustine-containing therapy compared to other chemotherapeutic regimens. [5, 10, 11]

VI.2.3 Unknowns relating to treatment benefits

Paediatric population

There is no experience in children and adolescents with bendamustine 2.5 mg/ml powder for concentrate for solution for infusion product.

Pregnancy

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 2.5 mg/ml powder for concentrate for solution for infusion product should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with bendamustine 2.5 mg/ml powder for concentrate for solution for infusion product 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.

Breast-feeding

It is not known whether bendamustine hydrochloride passes into the breast milk, therefore, bendamustine 2.5 mg/ml powder for concentrate for solution for infusion product is

contraindicated during breast-feeding. Breast-feeding must be discontinued during treatment with bendamustine 2.5 mg/ml powder for concentrate for solution for infusion product.

VI.2.4 Summary of safety concerns

Table 32 Part VI - Summary table of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Decreased bone marrow activity resulting in reduced production of red and white blood cells, and platelets (Myelosuppression)	Myelosuppression may occur in patients while on treatment with anticancer agents, including bendamustine. It is a serious side effect in which the bone marrow activity is decreased, resulting in symptoms such as decreased red pigment in the blood (heamoglobin) and white blood cells (leukocytopenia), and low count of platelets (thrombocytopenia). Due to the reduced blood components, patients are at higher risk of infections, even life-threatening.	This medicine should not be used in patients with severely disturbed bone marrow function and severe blood count alterations (in case of white blood cells and platelets levels below 3,000/ µl or < 75,000/µl, respectively). Prior to the initiation of the treatment cycle, before each subsequent course and in the intervals between the courses of treatment, the number of white blood cells and platelets levels should be assessed and the treatment provide only if above specific levels. In the event of myelosuppression, blood components [white blood cells, platelets, haemoglobin, and neutrophils (type of white blood cells)] must be monitored at least weekly. Patients with myelosuppression following bendamustine treatment should contact their doctor in case of any symptoms/signs of infection.
Infections	Infections can be very serious in people getting chemotherapy (including bendamustine).	This medicine should not be used in patients having an infection, especially one accompanied by a reduction in

Risk	What is known	Preventability
	Infections are very common in patients receiving bendamustine treatment. Infections of the blood (sepsis) can occur rarely in these patients. Due to the reduced blood components resulting from bendamustine treatment, patients are at higher risk of infections which can be even life-threatening (septic shock and death). Symptoms of infection include fever and lung problems.	white blood cells. Patients are advices to contact their doctor in case of any symptoms/signs of infection. Drugs known as growth factors (G-CSF or GM-CSF, for example) are sometimes given to help the white blood cells recover from the effects of chemotherapeutics and thus reduce the chance of infection. Antibiotics may also be given at the earliest sign of an infection, such as a fever. [3]
Severe skin reactions	Skin reactions including rash, toxic skin reactions and bullous exanthema have been reported with bendamustine. Some events occurred when bendamustine was given in combination with other anticancer agents, so the precise relationship is not certain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. A small number of cases of severe skin reactions (Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) have been reported.	This medicine should not be used in patients having reactions on their skin during bendamustine treatment. The reactions may increase in severity. If skin reactions are severe or progressive and the relationship with bendamustine cannot be excluded, bendamustine must be withdrawn or discontinued.
Heart disorders (Cardiac disorders)	Heart related problems is a possible side effect of chemotherapeutic drugs. Various cardiac disorders including disturbed heart function such as feeling your heartbeat (palpitations) or chest pain (angina pectoris), disturbed heart rhythms (arrhythmia), increased heart rate (tachycardia) or heart failure have	Patients with heart disorders must be closely monitored for potassium levels in the blood and in case of potassium levels below 35 mEq/L, potassium supplement must be given. ECG measurement must be performed in these patients. Patients with existing heart problems should tell their doctor

Risk	What is known	Preventability
	been reported in patients treated with bendamustine.	about this condition prior to treatment with bendamustine.
Disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream (Tumour lysis syndrome)	Tumour lysis syndrome is a possible side effect of chemotherapeutics in patients who had large numbers of lymphoma cells in the body before treatment. It occurs most often with the first cycle of chemotherapeutics, usually within 48 hour after first bendamustine dose. When the cancer cells are killed, they break open and release their contents into the bloodstream. This can overwhelm the kidneys, which cannot get rid of all of these substances at once. This can lead to the build-up of excess amounts of certain minerals in the blood and without intervention, it may lead to kidney failure and death. The excess minerals can lead to problems with the heart and nervous system.	Doctors work to prevent these problems by giving the patient extra fluids and certain drugs, such as sodium bicarbonate, allopurinol, and rasburicase. Patients must be closely monitored of blood chemistry, particularly potassium and uric acid levels.
Drug hypersensitivity	Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms are usually very mild and include fever, chills, itching or rash. In rare cases, severe allergic reactions to bendamustine have been reported.	Bendamustine product should not be used in patients who are allergic to the active substance. Patients must be asked about symptoms after their first cycle of therapy. Use of drugs (such as antihistamines, antipyretics and corticosteroids) to prevent severe reactions can be considered in subsequent cycles in patients who have previously experienced infusion reactions. Doctors should monitor patients for any signs of allergy.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Tumours resulting in treatment with chemotherapy (Secondary malignancies)	Secondary tumours may occur in patients on chemotherapeutic therapy. Side effects such as myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma have been reported in patients receiving bendamustine. However, the relationship to bendamustine is uncertain.
Kidney toxicity (Renal toxicity)	Kidney toxicity may occur in patients while on treatment with bendamustine. Side effects such as creatinine increase, urea increase have been reported very commonly with this drug. No dose adjustments is necessary in patients with creatinine clearance above 10 ml/min. Experience in patients with severe kidney disorders is limited. The prescriber should be aware that kidney toxicity may occur during treatment. Doctors should monitor patients for any signs of kidney toxicity. The patients are advised to inform their doctor or pharmacist as soon as possible.
Liver failure (Hepatic failure)	Liver toxicity may occur in patients while on treatment with bendamustine. Side effects such as elevated liver enzymes (AST and ALT) and alkaline phosphatase and liver failure have been reported commonly with the use of bendamustine. Patients are advised not to use bendamustine should they have severe liver dysfunction (damage to the functional cells of the liver), or if they have yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice). Depending on the degree of liver impairment a bendamustine dose may be adjusted or completely withdrawn. The prescriber should be aware that liver toxicity may occur during treatment.

Missing information

Risk	What is known
Patients below age 18 years	There is insufficient information of bendamustine use in children and adolescents below 18 years of age as no studies have been performed in this population.
Exposure during pregnancy and lactation	Bendamustine is known to cause genetic damage and malformations as shown in animal studies.

Risk	What is known
	Therefore, bendamustine should not be used during breastfeeding, pregnancy, in case of possible pregnancy or planning pregnancy. Women in childbearing potential must use an effective method of contraception both before and during the treatment with bendamustine. If pregnancy occurs during the treatment, patients should immediately consult their doctor. Patients should be warned about the risk of potential adverse effects for the unborn baby and genetic consultation is recommended.
Effect on different races	There is limited information regarding bendamustine use in different races or ethnicity.

VI.2.5 Summary of 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 (PIL). 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

No post-authorisation development has been planned as this is a generic drug application.

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

Version	Date	Safety Concerns	Comment
3.0	01-Aug-2016	Important Potential Risk 'Hepatotoxicity' was deleted and replaced by 'Hepatic failure'. Important Potential Risk 'Central	RMP update in line with Day 50 AR comments for DK/H/2406/001/E01 (Line extension) from CMS (BfArM), dated 15-

Version	Date	Safety Concerns	Comment
		neurotoxicity' was removed as a safety concern.	Apr-2016 to ensure the Mylan's RMP is in line with the summary of safety concerns from the innovator product.