VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Leukaemia is a cancer that starts in the blood-forming cells of the bone marrow. Chronic lymphocytic leukaemia (CLL) is a type of cancer that starts from cells that become certain white blood cells (called lymphocytes) in the bone marrow. The cancer (leukaemia) cells start in the bone marrow but then go into the blood.
In CLL, the leukaemia cells often build up slowly over time, and many people don't have any symptoms for at least a few years. In time, the cells can spread to other parts of the body, including the lymph nodes, liver, and spleen.
CLL accounts for about one-quarter of the new cases of leukaemia. 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 mainly affects older adults. The average age at the time of diagnosis is around 71 years. It is rarely seen in people under age 40, and is extremely rare in children

Multiple myeloma is a cancer that forms in a type of white blood cell called a plasma cell. Plasma cells help you fight infections by making antibodies that recognize and attack germ. Myeloma occurred with increased frequency in those exposed to the radiation of nuclear warheads in World War II after a 20-year latency. Myeloma has been seen more commonly than expected among farmers, wood workers, leather workers, and those exposed to petroleum products.
Myeloma increases in incidence with age. The median age at diagnosis is 70 years; it is uncommon under age 40. Males are more commonly affected than females, and blacks have nearly twice the incidence of whites.

Lymphoma is cancer that begins in cells of the lymph system. The lymph system is part of the immune system, which helps the body fight infection and disease. Because lymph tissue is found all through the body, lymphoma can begin almost anywhere. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types. The number of new cases of non-Hodgkin lymphoma was 19.7 per 100,000 men and women per year. The number of deaths was 6.2 per 100,000 men and women per year. These rates are age-adjusted and based on 2008-2012 cases and deaths. Approximately 2.1 percent of men and women will be diagnosed with non-Hodgkin lymphoma at some point during their lifetime.

VI.2.2 Summary of treatment benefits

Bendamustine is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:

– Chronic lymphocytic leukaemia (a cancer of a type of white blood cell called lymphocytes) in patients for whom treatment with fludarabine (another anticancer medicine) is not appropriate,

– Non-Hodgkin lymphomas (a cancer of the lymph tissue, part of the immune system) in patients whose cancer got worse during or following treatment containing rituximab (another anticancer medicine);

– Multiple myeloma (a cancer of the bone marrow), in cases where thalidomide or bortezomib (other anticancer medicines) containing therapy is not appropriate for you and, in combination with prednisone, in patients older than 65 years who are not eligible for stem-cell transplantation.

Bendamustine alone or in combination with other agents has been shown to have clinical efficacy in chronic lymphocytic leukaemia (CLL). The results of a randomized phase III trial of patients with CLL, who were never treated for this disease, demonstrated a significantly higher overall response rate in patients treated with bendamustine compared with chlorambucil (59% versus 26%, P<0.0001). The median period during which the disease did not progress was also found to be longer in the

bendamustine-treated patients (17.6 versus 5.7 months; p<0.0001). In addition, analysis of retrospective studies have also shown that primary therapy with bendamustine and rituximab is very active and well tolerated in patients with CLL who were never treated for this disease, as well as in patients who were previously and intensively treated with other medicines [**Wu M, 2013**]. In patients in whom CLL relapsed, combination treatment of bendamustine with rituximab has demonstrated promising activity in high-risk patients such as those who do not respond to other anticancer medicines, such as fludarabine or alkylating agents [**Van der Jagt R, 2012**].

Available data indicate that bendamustine may be a particularly useful treatment option as monotherapy or in combination with other medicines in patients with Non Hodgkin lymphomas (NHL), when they grow very slowly (indolent), and whose disease progressed during or following rituximab-based therapy. Many of these patients are also refractory to other anticancer medicines. Bendamustine has also been used in combination with other agents in the treatment of patients with relapsed disease following chemotherapy [**Plosker GL, 2008**; **Garnock-Jones KP, 2010**; **Gil L, 2014**].

Bendamustine is currently used as treatment of first choice multiple myeloma and, in combination with prednisone, in patients older than 65 years who are not eligible for stem-cell transplantation and cannot be treated with thalidomide or bortezomib [**Pratt G, 2013**; **Palumbo A, 2015**].

VI.2.3 Unknowns relating to treatment benefits

Data on exposure of bendamustine in paediatric patients (below the age of 18 years) and in pregnant and breast-feeding women are not available.

The effect of race on safety and/or efficacy of bendamustine has not been determined. Although a small number (n=6) of Japanese subjects had an average exposure that was 40% higher than that of non-Japanese subjects (number not specified) receiving the same dose, the significance of this difference is not known.

VI.2.4 Summary of safety concerns

Important identified risk

Risk	What is known	Preventability
1. A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets (Myelosuppression).	Myelosuppression is a side effect of some cancer treatments, including bendamustine. Low counts of white blood cells (leukocytopenia), red blood cells (anaemia) and low counts of platelets (thrombocytopenia) are very common during treatment with bendamustine. There is an increased risk of getting an infection from a drop in white blood cells. It is harder to fight infections and you can become very ill. You may have headaches, aching muscles, a cough, a sore throat, pain-passing urine, or you may feel cold and shivery. If you have a severe infection this can be life threatening. You may experience tiredness and breathlessness due to a drop in red blood cells (anaemia). You may bruise more easily due to a drop in platelets – this can cause nosebleeds, bleeding gums after brushing your teeth, or lots of tiny red spots or bruises on your arms or legs (known as petechia).	You should have your number of white blood cells and platelets in the blood checked before starting treatment with bendamustine, before each subsequent course of treatment and in the intervals between courses of treatment. This because of a possible reduced capability of the bone marrow to replace blood cells.
2. Infections.	There is an increased risk of getting an infection from a drop in white blood cells. It is harder to fight infections and you can become very ill. You may commonly have headaches, aching muscles, a cough, a sore throat, pain-passing urine, or you may feel cold and shivery. If you have a severe infection this can be life threatening. Finally, reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received bendamustine hydrochloride.	You should contact your doctor if you have signs of infection, including fever or lung symptoms. In addition, the following signs indicate you may have an infection: - your temperature goes over 37.5°C (99.5°F) or over 38°C (100.4°F), depending on the advice given by your chemotherapy team; - you suddenly feel unwell, even with a normal temperature - you have symptoms of an infection – this can include feeling shaky, a sore throat, a cough, diarrhoea or needing to

		pass urine a lot.
Risk	**What is known**	**Preventability**
3. Severe skin reactions.	Bendamustine may cause reactions on your skin during treatment. The reactions may increase in severity. Alopecia and other skin disorders are reported commonly. Reddening of The skin (erythema), inflammation of the skin (dermatitis), Itching (pruritus), skin rash (macular- papular rash) and excessive sweating (hyperhidrosis) were rarely reported. A small number of cases of severe skin reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) have been reported. The relationship with bendamustine is unclear	You should tell your doctor if skin reactions appear during therapy with bendamustine.
4. Cardiac disorders.	In cases of existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms), high doses of bendamustine may aggravate these conditions.	You should tell your doctor of any existing heart disease before starting bendamustine.
5. Tumour lysis syndrome is caused by the abrupt release of large quantities of cellular components into the blood following the rapid lysis of malignant cells.	You may experience pain in side, blood in urine or reduce amount of urine. When the disease is very severe, body may not be able to clear all the waste products from the dying cancer cells. This is condition and can cause kidney failure and heart problems within 48 hours of the first dose of bendamustine.	Your doctor will be aware of this and may give you other medicines to help prevent it.

Risk	What is known	Preventability
6. Severe allergic or hypersensitivity reactions (Anaphylaxis).	Bendamustine may cause hypersensitivity reactions. This nearly always happens in the first 10 minutes. If you are going to have a reaction, it is most likely the first or second time you have the drug. These reactions commonly manifest as allergic inflammation of the skin (dermatitis), or nettle rash (urticaria). Other signs of a reaction can include: a rash; feeling itchy, flushed or short of breath; swelling of your face or lips; feeling dizzy; having pain in your tummy, back or chest; or feeling unwell. Rarely, you may experience severe allergic hypersensitivity reactions (anaphylactic reactions) or signs similar to anaphylactic reactions (anaphylactoid reactions), with low blood pressure, chills, drowsiness and excessive sweating.	Your chemotherapy nurse will monitor you closely. Tell your nurse straight away if you have any of these symptoms. In particular, the following are very common signs of hypersensitivity to bendamustine when the medicine is injected into a vein: hives; difficulty breathing; swelling of your face, lips, tongue, or throat. If you have a reaction, they will treat it quickly.

Important potential risk

Risk	What is known
7. Secondary tumours (malignancies)**.**	There have been reports of secondary tumours (myelodysplastic syndrome, AML, bronchial carcinoma) following treatment with bendamustine. No clear relationship with bendamustine could be determined.
8. Kidney damage (renal toxicity).	No dose adjustment is necessary in case of impairment of kidney function. Your attending doctor will decide whether a dosage adjustment is necessary. There is no experience with bendamustine in severe renal failure.
9. Liver damage (hepatic failure).	Dependent on the degree of impairment of your liver function it may be necessary to adjust your dose (by 30% in case of moderate liver dysfunction). You should not use bendamustine if you have severe liver dysfunction (damage to the functional cells of the liver).

Missing information

Risk	What is known
10. Limited information on use in children (patients below the age of 18 years).	There is no experience in children and adolescents with bendamustine.
11. Limited information on use during pregnancy and breast-feeding.	Bendamustine can cause genetic damage and has caused malformations in animal studies. You should not use bendamustine during pregnancy unless certainly indicated by your doctor. In case of treatment, you should use medical consultation about the risk of potential adverse effects of your therapy for the unborn child and genetic consultation is recommended. If you are a woman of childbearing potential, you must use an effective method of contraception both before and during treatment with bendamustine. If pregnancy occurs during your treatment with bendamustine, you must immediately inform your doctor and should use genetic consultation. Bendamustine must not be administered during breast-feeding. If treatment with bendamustine is necessary during lactation, you must discontinue breast-feeding.
12. Effect on different races	Although a small number of Japanese subjects had an average exposure that was 40% higher than that of non-Japanese subjects receiving the same dose, the significance of this difference is not known**.**

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 (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

Not Applicable.

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

Not Applicable.