VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Chronic lymphocytic leukaemia:

Chronic lymphocytic leukemia (CLL) is a cancer of a type of white blood cells called lymphocytes and it is the most common cancerin the Western world. It is estimated that4.2 new cases per 100 000 people are reported each year. More than 30 new cases per 100 000 people are reported each year in population with 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.

Whereas CLL is the most frequent form of leukaemia in Western countries, where it accounts for 30% of all leukaemias, it only constitutes 10% of all leukaemias in Asian populations. In most series, CLLis more frequent in males than in females. The cause of CLL is unknown. About one-half of people diagnosed in the early stages of CLL live more than 12 years.

Indolent non-Hodgkin's lymphoma:

Non-Hodgkin lymphoma (NHL) isa cancer of the lymph tissue and is the tenth most common cancer worldwide. An estimated356,000 new cases diagnosed in 2008 (3% of the total). Incidence of NHL varies worldwide, with the highest rates beingreported in the most economically developed regions of the world (e.g. Northern America,Australia/New Zealand, and Northern Europe) and the lowest rates in the least developed regions(e.g. South-Central and Eastern Asia, and the Caribbean). NHL is the fifth most common cancer in the UK (2009), accounting for 4% of all new cases. It isthe fifth most common cancer among men (2009) in the UK and the seventh most commoncancer among women (2009). In most people cause is unknown however it may develop in people with weakened immune systems like in people with organ transplant and HIV infection.

Multiple myeloma (Durie-Salmon stage II with progress or stage III):

In Europe is 6.0 new cases are reported per 100 000 people each year with a common age of diagnosis between 63 and 70 years; 4.1 cases are reported to be fatal per 100 000 people each year.

Multiple myelomas are a less frequent cancer site among both sexes. On a worldwide scale, it is estimated that about 86,000 incident cases occur annually (47,000 males and 39,000 females), accounting for about 0.8% of all new cancer cases. About 63,000 subjects are reported to die from the disease each year (33,000 males and 30,000 females), accounting for 0.9% of all cancer deaths.

Geographically, the industrialized regions of Australia/New Zealand, Europe, and North America have the highest number of new cases. It is estimated that within the population of the USA there is an almost doubled occurrence of multiple myeloma among the blacks compared to the whites, while people of Asian origin, especially Chinese and Japanese, experience a much lower incidence.

VI.2.2 Summary of treatment benefits

Accord has not conducted any studies for bendamustine on expected benefit considering the similarities to the currently marketed product (Ribomustin® Pulver zur Herstellung einer Infusionslösung / Levact Powder for Concentrate for Solution for Infusion 2.5 mg/ml, Astellas Pharma Gmbh). Accord's Bendamustine is expected to be beneficial for:

When used alone (monotherapy) or incombination with other medicines for thetreatment of the following forms of cancer:

— chronic lymphocytic leukaemia incases where fludarabine combination chemotherapy is not appropriate,

— non-Hodgkin's lymphomas, which had not, or only shortly, responded to prior rituximab treatment,

— Multiple myeloma in cases where high dose chemotherapy with autologous stem cell transplantation, thalidomide or bortezomib containing therapy is not appropriate

VI.2.3 Unknowns relating to treatment benefits

Data on exposure of bendamustinein paediatric patients,patients with impaired renal or hepatic function is not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Myelosuppression (severely disturbed bone marrow function)	Patients treated with bendamustine hydrochloride may experience myelosuppression.	The doctor or pharmacist should be informed if the patient is taking or has recently taken other

Risk	What is known	Preventability
	Bendamustine for Infusion when used in combination with medicines which inhibit the formation of blood in the bone marrow, the effect on the bone marrow may be intensified.	medicines, including medicines obtained without a prescription. Bendamustine infusion should not be used in case of severely disturbed bone marrow function (bone marrow depression) and serious changes in your number of white blood cells and platelets in the blood (white blood cells and/or thrombocyte values drop to < 3,000/µl or < 75,000/µl, respectively.). Special care should be taken with bendamustine for infusion in case of reduced capability of the bone marrow to replace blood cells. The number of white blood cells and platelets in the blood should be checked before starting treatment with bendamustine for infusion, before each subsequent course of treatment and in the intervals between courses of

Risk	What is known	Preventability
		treatment.
Infection (including pneumonia and sepsis)	Possible side effects: Suppressed bone marrow function increases the risk of infection. Very common: Infections Rare: Infection of the blood (sepsis) Very rare: Primary atypical inflammation of the lungs (pneumonia)	Special care should be taken in case of infections when using with bendamustine for infusion. Doctor should be informed if there are any signs of infection, including fever or lung symptoms.
Tumor lysis syndrome	Special care with taking bendamustine for infusion should be taken in case of any pain in side, blood in urine or reduced 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 called tumour lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of bendamustine	Inform the doctor in case of any pain in side, blood in urine or reduced amount of urine. The doctor may give other medicines to help prevent it.

Risk	**What is known**	**Preventability**
	for infusion.	
Anaphylaxis (allergic hypersensitivity reactions)	Possible side effects: Rare: Severe allergic hypersensitivity reactions (anaphylactic reactions) Signs similar to anaphylactic reactions (anaphylactoid reactions) Bendamustine should not be used in case of hypersensitivity (allergic) to the active substance bendamustine hydrochloride or any of the other ingredients of bendamustine for infusion.	Inform the doctor in case of previous history of any allergic reaction to bendamustine or similar compound.
Extravasation (unintentional injection into the tissue outside blood vessels)	Possible side effects: Tissue changes (necrosis) have been observed very rarely following unintentional injection into the tissue outside blood vessels (extravascular). A burning sensation where the infusion needle is inserted may be a sign for administration outside the blood vessels. The consequence of administration	Unintentional injection into the tissue outside blood vessels (extravasal injection) should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of

Risk	What is known	Preventability
	in this way can be pain and poorly healing skin defects.	corticosteroids are not of clear benefit.
Cardiac disorders	Abnormality of heartbeat (palpitations), chest pain (angina pectoris), disturbed heart rhythms (arrhythmia) has been reported commonly. Accumulation of fluid in the heart sac (Pericardial effusion) has been reported uncommonly. Increased heart rate (tachycardia), Heart attack (myocardial infarct), and heart failure (cardiac failure) has been rarely reported	Patient should take special care with bendamustine for infusion in cases of existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms).
Severe skin reactions	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	Patient should take special care in case of reactions on skin during treatment with bendamustine for Infusion. The reactions may increase in severity.

Risk	**What is known**	**Preventability**
Hepatic failure	Possible side effects: Common: A rise in liver enzymes AST (Aspartate transaminase)/ALT(Alanine transaminase) affecting liver function Not Known (frequency cannot be estimated from the available data):Liver failure	Inform the doctor in case of previous liver impairment to bendamustine or similar compound.Patient should take special care of liver during treatment with bendamustine for Infusion.
Drug interaction with immunosuppressive or myelosuppressive agents	Combination of Bendamustine with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation When Bendamustine is combined with myelosuppressive agents, the effect of Bendamustine and/or the co administered medicinal products on the bone marrow may be potentiated.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicineswhich alter you immuneresponse.
Nausea and vomiting	The most common adverse reactions with bendamustine hydrochloride is gastrointestinal symptoms	An antiemetic may be given for the symptomatic treatment of nausea and vomiting. Inform the doctor in case of

Risk	What is known	Preventability
	(nausea, vomiting). Possible side effects: Very common: Feeling sick (nausea) and vomiting.	previous nausea and vomiting to bendamustine or similar compound.

Important potential risks

Risk	What is known
Secondary tumours (including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma)	Possible side effects: There have been reports of secondary tumours (myelodysplastic syndrome, AML, bronchial carcinoma) following treatment with Bendamustine for Infusion. No clear relationship with Bendamustine for Infusion could be determined.
Kidney toxicity (Renal toxicity)	The doctor must be informed in case the patient notices any pain in side, blood in urine or reduced 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 called tumour lysis syndrome and can cause kidney failure within 48 hours of the first dose of Bendamustine for Infusion. The doctor may give other medicines to help prevent it.
An agent that can disturb the development of the embryo or fetus and an agent cause cancerous effect (Teratogenic and mutagenic effects)	Bendamustine hydrochloride is teratogenic and mutagenic. Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with bendamustine

Risk	What is known
	hydrochloride because of possible irreversible infertility. There are insufficient data from the use of Bendamustine in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic. Animal studies showed that bendamustine is embryotoxic and teratogenic. Bendamustine induces aberrations of the chromosomes and is mutagenic in vivo as well as in vitro. In long-term studies in female mice bendamustine is carcinogenic.

Missing information

Risk	What is known
Limited information on the use in paediatric population	There is no experience in children and adolescents with bendamustine.
Limited information on the usein patients with severe liver impairment	Do not use bendamustine in case of severe liver dysfunction (damage to the functional cells of the liver).
Limited information on the use in patients with severe kidney impairment	Experience in patients with severe kidneyimpairment is limited.
Limited information on the use in different races	None proposed

Risk	**What is known**
Limited information on the use in pregnant and breastfeeding women	Pregnancy: Bendamustine can cause genetic damage and has caused malformations in animal studies. Bendamustine should not be used during pregnancy unless certainly indicated by doctor. In case of treatment medical consultation about the risk of potential adverse effects of the therapy for the unborn child and genetic consultation is recommended. A woman of childbearing 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 immediately informed and genetic consultation be done. Avoid fathering a child during treatment with bendamustine for Infusion and for up to 6 months after treatment has stopped. There is a risk that treatment with Bendamustine will lead to infertility. Advice on conservation of sperm before treatment starts can be seeked. Bendamustine must not be administered during breast feeding. If treatment with bendamustine is necessary during lactation, breast-feeding must be discontinued.

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 minimizing 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 special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions can be found in Annex 10 and 11 of this RMP; how they are implemented in each country however will depend upon agreement between the MAH and the national authorities. This additional risk minimisation measures is forfatal opportunisticinfection.

DHPC (Direct Healthcare Professional Communications)
Objective and Rationale: The key aim of direct healthcare professional communications based on increased mortality observed in recent clinical studies when Levact® (bendamustine) was used in non-approved combination treatments or outside the approved indications. Fatal toxicities were mainly due to (opportunistic) infections, but also some fatal cardiac, neurological, and respiratory toxicities were reported.
Propose Action: Each National agency will be contacted for local requirements on the circulation and local agency advice will be followed for distribution.

VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concern	Comment
2.0	16-September-2013	Following safety concerns are added:	-

		Important identified risk: • Myelosuppression • Infections • Tumor lysis syndrome • Anaphylaxis • Extravasation **Important potential risk:** • Secondary malignancies	
3.0	20-January-2014	Following safety concerns are added: **Important identified risk**: • Cardiac disorders • Severe skin reactions • Hepatic failure Risk of "Pregnancy and lactation" as missing information is migrated as important potential risk as "Pregnancy (teratogenic and genotoxic effect in non-clinical studies) and lactation". "Important missing information" is changed as "missing information"	

		In the RMP Part V "Risk minimisation measures", information from SmPC was included for the missing information "Paediatric population", "Patients with severe hepatic impairment" and "Patients with severe renal impairment".	
4.0	27-May-2014	Following safety concern is added: Important potential risk: Renal toxicity	-
5.0	12-October-2015	• An additional safety concern "Effect on different races" has been added to Missing information. • Previously considered Important potential risk "Pregnancy (teratogenic and genotoxic effect in non-clinical studies) and lactation" has been moved to missing information as "Use in pregnant and breastfeeding women".	The RMP has been revised as per CMS Day-50 and Day-55 assessment reports.

6.0	14 June 2017	Following safety concernswere added in this RMP. Important identified risks: • Drug interaction with immunosuppressive or myelosuppressive agents • Nausea and vomiting Important potential risk: • Teratogenic and mutagenic effects	The RMP has been updated as per Preliminary Variation Assessment Report of bendamustine (AT/H/0497/001/II/007- Type II variation)), dated 11 Sep 2016. DHCP letter (published by Astellas for Levact®) has been added as suggested by AEMPS and ANSM national health authority.