1.8.2 Risk-management System

Enclosed

RISK MANAGEMENT PLAN

For

Bendamustine

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Active substance(s) (INN or common name):	Bendamustine
Pharmaco-therapeutic group (ATC Code):	L01AA09
Name of Marketing Authorisation Holder or Applicant:	Accord Healthcare Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Bendamustine Accord

Data lock point for this RMP	08-March-2013
Version number	1
Date of final sign off	22-March-2013

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse drug event
ADR	Adverse drug reaction
EU	European Union
ICSR	Individual Case Safety Report
MAA	Marketing Authorization Applicant
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
EPAR	European Public Assessment Report
PIL	Patient Information Leaflet
WHO	World Health Organization

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PART I: PRODUCT(S) OVERVIEW

Part	**Module/annex**	**Date last updated for submission (sign off date)**	***Version number of RMP when last submitted**
Part II Safety Specification	SV Post authorisation experience	Not applicable	Not applicable
	SVIII Summary of the safety concerns	22-March-2013	
Part III Pharmacovigilance Plan		22-March-2013	
Part IV Plan for post-authorisation efficacy studies		Not applicable	Not applicable
Part V Risk Minimisation Measures		22-March-2013	
Part VI Summary of RMP		22-March-2013	
Part VII Annexes	ANNEX 2 Proposed SmPC/PIL	22-March-2013	
	ANNEX 3 Worldwide marketing status by country	Not applicable	Not applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Not applicable	Not applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not applicable	Not applicable
	ANNEX 7 Specific adverse event follow-up forms	Not applicable	Not applicable

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Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted
	ANNEX 8 Protocols for studies in Part IV	Not applicable	Not applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not applicable	Not applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	Not applicable	Not applicable
	ANNEX 11 Mock up examples	Not applicable	Not applicable
	ANNEX 12 Other supporting data	22-March-2013	Not applicable

QPPV name	Paresh Dhameliya (Deputy QPPV)
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Overview of versions:

Version number of last agreed RMP:

Version number: Not applicable

Agreed within: Not applicable

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
Not applicable		

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Invented name(s) in the European Economic Area (EEA)	Bendamustine
Authorisation procedure	Decentralised Procedure
Brief description of the product including:	Pharmacotherapeutic group: Antineoplastic agents, alkylating agents. Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. The antitumour effect of bendamustine hydrochloride has been demonstrated by several in vitro studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovary carcinoma and different leukaemia) and in vivo in different experimental tumour models with tumours of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer). (1)
Indication(s) in the EEA Proposed	Bendamustine is indicated as: First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. Front line treatment of multiple myeloma (Durie-Salmon

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	stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment. (1)
Posology and route of administration in the EEA Proposed	Bendamustine is used as intravenous infusion over 30 - 60 minutes. Monotherapy for chronic lymphocytic leukaemia: 100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks. Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab: 120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks. Multiple myeloma 120 - 150 mg/m² body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m² body surface area prednisone i.v. or per os on days 1 to 4; every 4 weeks. (1)
Pharmaceutical form(s) and strengths Proposed	Bendamustine 2.5 mg/ml powder for concentrate for solution for infusion. (1)

Country and date of first authorisation worldwide	Not yet authorized
Country and date of first launch worldwide	Not yet launched

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Country and date of first authorisation in the EEA	Not yet authorised

Is the product subject to additional monitoring in the EU? Yes ☐ No ☑

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PART II: SAFETY SPECIFICATION

Module SV - Post-authorisation experience

SV.1 Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons:

There have been no marketing authorisation restrictions on distribution, clinical trial suspensions, dosage modification, changes in target populations or indications, or formulation changes to bendamustine, for any safety reasons.

SV.2 Non-study post-authorisation exposure

Not applicable

SV.3 Post-authorisation use in special populations

Not applicable

SV.4 Post-authorisation off-label use

Not applicable

SV.5 Epidemiological study exposure (if applicable)

Not applicable.

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Module SVIII - Summary of the safety concerns

Table 1 Summary of safety concerns

Important identified risk (s)	Nil
Important potential risk (s)	Nil
Important missing information	• Paediatric population • Patients with severe hepatic impairment • Patients with severe renal impairment • Pregnancy and lactation

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PART III: PHARMACOVIGILANCE PLAN

III.1 Routine pharmacovigilance system at Accord

Accord's global pharmacovigilance activities have been contracted to Lambda, which has its European headquarters in the UK and is owned by Lambda Therapeutics research Ltd. in India. Currently Pharmacovigilance activities of Accord are conducted at both UK and India.

At Lambda, pharmacovigilance procedures and policies are formulated to promote optimum patient safety, product stewardship and regulatory compliance. Routine practices are in accordance with standards set by regional and local health authorities, with global procedures being specifically written to meet the expectations of the authority or authorities with the most comprehensive regulatory requirements.

The following list summarizes Lambda's activities for conducting routine global pharmacovigilance:

- Management ADR Reporting training for MAA employees likely to have an interface with customers and/or regulatory authorities
- Generation of Safety Data Exchange Agreement covering different business arrangements (like co-marketing, co-distribution, out-licensing etc.)
- Handling of Product Quality Complaints Associated with ADE/ADR including lack of efficacy
- Global Case Processing (spontaneous, literature and regulatory authority cases)
- Follow up of safety reports for missing information and for information on the progress and outcome of the cases
- Generation of Aggregate Reports with cumulative analysis of data from all sources
- Management and evaluation of cases with exposure to medicinal products during pregnancy
- Handling of Customer communications/Medical Inquiries
- Periodic Signal Detection activity

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- Conducting Literature Searches on Weekly Basis
- Identification of duplicate individual case safety reports (ICSRs) in pharmacovigilance (ADR) database

Routine processing of ICSRs includes a medical evaluation of ICSRs. Risk benefit assessment for individual products is undertaken as part of Safety Data Review Group meetings held at predetermined periodicity. Appropriate actions as determined during such meetings are addressed in accordance to the strength of evidence.

III.2 Safety concerns and overview of planned pharmacovigilance actions

Table 2: Important missing information: Paediatric population

Safety concern: Paediatric population		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Confirming the nature and incidences of adverse reactions following exposure to medicinal product in paediatric population.	Routine pharmacovigilance activities will be carried out as stated in section III.1.	To investigate the possibility of a risk or to provide reassurance about the absence of a risk

Table 3: Important missing information: Patients with severe hepatic impairment

Safety concern: Patients with severe hepatic impairment		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Confirming the incidences and nature of adverse reactions following exposure to medicinal	Routine pharmacovigilance activities as stated in section III (Routine	To investigate the possibility of a risk or to provide reassurance about the absence

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Safety concern: Patients with severe hepatic impairment		
product in patients with severe hepatic impairment	pharmacovigilance system at Accord) will be carried out.	of a risk

Table 4: Important missing information: Patients with severe renal impairment

Safety concern: Patients with severe renal impairment		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Confirming the incidences and nature of adverse reactions following exposure to medicinal product in Patients with severe renal impairment	Routine pharmacovigilance activities as stated in section III (Routine pharmacovigilance system at Accord) will be carried out.	To investigate the possibility of a risk or to provide reassurance about the absence of a risk

Table 5: Important missing information: Pregnancy and Lactation

Safety concern: Pregnancy and Lactation		
Areas requiring confirmation or further investigation	**Proposed routine and additional PhV activities**	**Objectives**
Confirming the incidences and nature of adverse reactions following exposure to medicinal product in pregnant and lactating mothers	Routine pharmacovigilance activities will be carried out as stated in section III.1.	To investigate the possibility of a risk or to provide reassurance about the absence of a risk

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III.3 Additional pharmacovigilance activities to assess effectiveness of risk minimisation measures

No Additional pharmacovigilance activities are recommended in EU.

III.4 Studies and other activities completed since last update of Pharmacovigilance Plan

None

III.5 Details of outstanding additional pharmacovigilance activities

There are no outstanding additional pharmacovigilance activities in EU.

III.6 Summary table of Pharmacovigilance activities

Not applicable

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PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

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PART V: RISK MINIMISATION MEASURES

V.1 Risk minimisation measures by safety concern

Table 6: Important missing information: Paediatric population

Safety concern	**Paediatric population**
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	None proposed
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	

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Table 7: Important missing information: Patients with severe hepatic impairment

Safety concern	**Patients with severe hepatic impairment**
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	None proposed
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	-

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Table 8: Important missing information: Patients with severe renal impairment

Safety concern	**Patients with severe renal impairment**
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	None proposed
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	

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Table 9: Important missing information: Pregnancy and Lactation

Safety concern	**Pregnancy and lactation**
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	None proposed
Additional risk minimisation measure(s)	None proposed.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	

V.2 Risk minimisation measure failure (if applicable)

Not applicable.

V.3 Summary table of risk minimisation measures

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Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Missing information: Paediatric population	None proposed.	None
Missing information: Patients with severe hepatic impairment	None proposed.	None
Missing information: Patients with severe renal impairment	None proposed.	None
Missing information: Pregnancy and lactation	None proposed.	None

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PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risks (s)	Nil
Important potential risks	Nil
Important missing information	• Paediatric population • Patients with severe hepatic impairment • Patients with severe renal impairment • Pregnancy and lactation

VI.1.2 Table of on-going and planned additional Pharmacovigilance studies/activities in the Pharmacovigilance Plan (if applicable)

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan (if applicable)

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information:	None proposed.	None

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Paediatric population		
Missing information: Patients with severe hepatic impairment	None proposed.	None
Missing information: Patients with severe renal impairment	None proposed.	None
Missing information: Pregnancy and lactation	None proposed.	None

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Chronic lymphocytic leukaemia: Chronic lymphocytic leukemia (CLL) is the most common leukemia 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. (2)

The incidence of CLL is about 5 cases per 100 000 people per year, increasing with age. 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, CLL is more frequent in males than in females. (3)

Indolent non-Hodgkin's lymphoma: Non-Hodgkin lymphoma (NHL) is the tenth most common cancer worldwide. With an estimated 356,000 new cases diagnosed in 2008 (3% of the total), it comprises two out of five (41%) haematological cancers. Incidence of NHL varies worldwide, with the highest rates being reported in the most economically developed regions of the world (e.g. Northern America, Australia/New Zealand, and Northern Europe) and the lowest

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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 is the fifth most common cancer among men (2009) in the UK and the seventh most common cancer among women (2009). [4]

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

The incidence of multiple myeloma (MM) in Europe is 6.0/100 000/year with a median age at diagnosis of between 63 and 70 years; the mortality is 4.1/100 000/year. [5]

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. [6]

Geographically, the frequency is very unevenly distributed in the world with the highest incidence in the industrialized regions of Australia/New Zealand, Europe, and North America. The ethnic comparison within the population of the USA shows 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. [6]

VI.2.2 Summary of treatment benefits

Chronic lymphocytic leukaemia:

The goal of treatment in Chronic lymphocytic leukaemia is to maximize response while minimizing toxicities and improving quality of life. Preferred standard first-line treatment options for cll include fludarabine–cyclophosphamide–rituximab (fcr), and fludarabine–rituximab (fr). Although some patients can tolerate aggressive treatment, most patients with chronic lymphocytic leukaemia are elderly and have pre-existing comorbidities. Patients unable to tolerate aggressive therapy because of significant comorbidities or frailty are often treated with chlorambucil with or without rituximab—a regimen that offers more modest efficacy than either fludarabine–cyclophosphamide–rituximab (fcr), or fludarabine–rituximab (fr). [7]

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An increasing number of subjects with CLL are being offered stem-cell transplants. chlorambucil has used as first-line in elderly, fragile populations Purine analogues, particularly fludarabine, are the most effective agents for treating CLL. Treatment with fludarabine results in a much higher CR rate than chlorambucil or alkylating based chemotherapies. (3)

Indolent non-Hodgkin's lymphoma: With recent improvements in the treatment of non-Hodgkin's lymphoma , patients are now surviving longer than they did at the end of the 1990s 20. Despite a multitude of treatment options, indolent non-Hodgkin's lymphoma and mantel cell carcinoma remain incurable with standard therapies. The overall goal of treatment is to achieve effective and durable disease control using agents that minimize toxicity, with the aim of improving pfs , os , and quality of life. The standard initial treatment for patients with indolent non-Hodgkin's lymphoma varies across North America, with both rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone (r - chop) and rituximab–cyclophosphamide–vincristine–prednisone (r - cvp) being widely accepted options. With the success of bendamustine combination regimens such as bendamustine (60 mg/m2)–vincristine–prednisone (bop) and bendamustine dose: 90 mg/m2 (br) for the treatment of non-Hodgkin's lymphoma , ongoing studies are examining novel bendamustine combinations with drugs including lenalidomide, bortezomib, mitoxantrone, obinutuzumab, or ofatumumab. A randomized trial performed in previously untreated patients with indolent non-Hodgkin's lymphoma and mantel cell carcinoma demonstrated significantly longer pfs with bendamustine than with r - chop, and lesser associated toxicity. In light of those results, bendamustine is routinely used in the first-line treatment of non-Hodgkin's lymphoma in many countries across the world. In the relapsed setting, bendamustine has achieved promising response rates of approximately 75%, with significant activity in patients who are refractory to rituximab and prior chemotherapy. (7)

Multiple myeloma (Durie-Salmon stage II with progress or stage III): Oral combination of melphalan plus prednisone (9 mg/m2/day for 4 days) and prednisone (30 mg/m2/day for 4 days) has been the standard treatment for patients ineligible for high-dose chemotherapy with stem-cell support [I, A]. Cycles are repeated every 4–6 weeks until a stable response is achieved. However, two recent randomized studies have shown that the combination of melphalan–prednisone with thalidomide (100 mg/day) is superior to melphalan–prednisone. Other novel agents (bortezomib, lenalidomide) are currently being tested in combination with melphalan–

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prednisone in patients >65 years of age. For patients in good clinical condition high-dose therapy with autologous stem-cell transplantation (ASCT) is the standard treatment [II, B]. Melphalan 200 mg/m2 i.v. is the preparative regimen before autologous transplantation [II, B]. Thalidomide is mostly used in combination with dexamethasone and/or chemotherapy (initial dose 100–200 mg/day) and results in an increased risk of deep vein thrombosis; therefore, at least in patients with increased risk (high tumor burden, history of thrombosis) anticoagulation prophylaxis should be administered. Bortezomib is used either alone or in combination with dexamethasone or with chemotherapy. A recently completed randomized trial shows that bortezomib in combination with pegylated liposomal doxorubicin is superior to bortezomib alone. Lenalidomide has just been approved in Europe for the treatment of relapsed Multiple Myeloma (in combination with dexamethasone). (5)

Bendamustine is a bifunctional alkylating agent with a purine-like benzimidazole ring that has been administered successfully to patients with Multiple Myeloma. It causes only partial cross-resistance to other alkylating agents and anthracyclines. These properties turn bendamustine into an important agent that qualifies for front-line treatments as well as for salvage therapy after failure of other drugs. Based on the findings of a randomized phase III study of the East German Study Group of Hematology and Oncology, the current findings provide evidence that bendamustine is an important advance over melphalan in patients with previously untreated MM. In particular, bendamustine and prednisone (BP) offers significant benefits in terms of CR rates, required duration of treatment, TTF, and quality of life when compared to melphalan and prednisone (MP). Therefore, BP should be considered the new standard in the first-line treatment of patients with MM who are not eligible for transplantation. (8)

VI.2.3 Unknowns relating to treatment benefits

Not applicable

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VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known
None	None

Important potential risks

Risk	What is known
None	None

Important missing information

Risk	What is known
Limited information on the use in paediatric population	There is no experience in children and adolescents with bendamustine. (1)
Limited information on the use in patients with severe hepatic impairment	On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2mg/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) (1)
Limited information on the use in patients with severe renal impairment	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. (1)
Limited information on the	Pregnancy: There are insufficient data from the use of

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use in pregnant and lactating mothers	Bendamustine in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic (see section 5.3). 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. Breast-feeding: It is not known whether bendamustine passes into the breast milk, therefore, bendamustine is contraindicated during breast-feeding (see section 4.3). Breast-feeding must be discontinued during treatment with bendamustine. (1)

VI.2.5 Summary of additional risk minimisation measures by safety concern

Currently available information does not support the need for additional risk minimisation activities.

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

No studies planned.

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

Not applicable.

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PART VII: ANNEXES

Annex 1 – EudraVigilance Interface

Not applicable

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Annex 2 - SmPC & Package Leaflet

SPC of Accord SPC Bendamustine Accord 2.5 mg/ml powder for concentrate for solution for infusion

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1.3.1 SPC, Labelling and Package Leaflet

1.3.1.1 Summary of the Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Bendamustine Accord 2.5 mg/ml powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 25 mg bendamustine hydrochloride.

One vial contains 100 mg bendamustine hydrochloride.

1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride when reconstituted according to section 6.6.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White, microcrystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.

Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

4.2 Posology and method of administration

For intravenous infusion over 30 - 60 minutes (see section 6.6).

Infusion must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity. Treatment should not be started if leukocyte and/or platelet values dropped to < 3,000/µl or < 75,000/µl, respectively (see section 4.3).

Monotherapy for chronic lymphocytic leukaemia

100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab

120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks.

Multiple myeloma

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120 - 150 mg/m² body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m² body surface area prednisone i.v. or per os on days 1 to 4; every 4 weeks.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to < 3,000/µl or < 75,000/µl, respectively. Treatment can be continued after leukocyte values have increased to > 4,000/µl and platelet values to > 100,000/µl.

The leukocyte and platelet Nadir is reached after 14-20 days with regeneration after 3-5 weeks. During therapy free intervals strict monitoring of the blood count is recommended (see section 4.4).

In case of non-haematological toxicity dose reductions have to be based on the worst CTC grades in the preceding cycle. A 50% dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity.

If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

For preparation and administration instructions see section 6.6.

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2mg/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) (see section 4.3).

Renal impairment

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.

Paediatric patients

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There is no experience in children and adolescents with Bendamustine.

Elderly patients

There is no evidence that dose adjustments are necessary in elderly patients (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1)

During breast-feeding

Severe hepatic impairment (serum bilirubin > 3.0 mg/dl)

Jaundice

Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3,000/µl or < 75,000/µl, respectively)

Major surgery less than 30 days before start of treatment

Infections, especially involving leukocytopenia

Yellow fever vaccination

4.4 Special warnings and precautions for use

Myelosuppression

Patients treated with bendamustine hydrochloride may experience myelosuppression. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4,000/µl or > 100,000/µl, respectively.

Infections

Infection, including pneumonia and sepsis, has been reported. In rare cases, infection has been associated with hospitalization, septic shock and death. Patients with neutropenia and/or lymphopenia following

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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.

Skin reactions

A number of skin reactions have been reported. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, Bendamustine should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued.

Patients with cardiac disorders

During treatment with bendamustine hydrochloride the concentration of potassium in the blood must be closely monitored and potassium supplement must be given when K^+ <35 mEq/l, and ECG measurement must be performed.

Nausea, vomiting

An antiemetic may be given for the symptomatic treatment of nausea and vomiting.

Tumour lysis syndrome

Tumour lysis syndrome associated with Bendamustine treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of Bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. The use of allopurinol during the first one to two weeks of Bendamustine therapy can be considered but not necessarily as standard. However, there have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion

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reactions 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 infusion reactions.

Patients who experienced Grade 3 or worse allergic-type reactions were typically not re-challenged.

Contraception

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 hydrochloride because of possible irreversible infertility.

Extravasation

An 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 corticosteroids are not of clear benefit.

4.5 Interaction with other medicinal products and other forms of interaction

No *in-vivo* interaction studies have been performed.

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. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of Bendamustine.

Combination of Bendamustine with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

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Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme (see section 5.2). Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.

4.6 Pregnancy and lactation

Pregnancy

There are insufficient data from the use of Bendamustine in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic (see section 5.3). 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.

Women of childbearing potential/contraception

Women of childbearing potential must use effective methods of contraception both before and during Bendamustine therapy.

Men being treated with Bendamustine are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Bendamustine.

Breast-feeding

It is not known whether bendamustine passes into the breast milk, therefore, Bendamustine is contraindicated during breast-feeding (see section 4.3). Breast-feeding must be discontinued during treatment with Bendamustine.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, ataxia, peripheral neuropathy and somnolence have been reported during treatment with Bendamustine (see section 4.8). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

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4.8 Undesirable effects

The most common adverse reactions with bendamustine hydrochloride are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

The table below reflects the data obtained with bendamustine hydrochloride in clinical trials.

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1, 000**	**Very rare <1/10, 000**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Infection NOS*			Sepsis	Pneumonia primary atypical	
Neoplasma benign, malignant		Tumour lysis syndrome				
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombocytopenia	Haemorrhage, Anaemia, Neutropenia			Haemolysis	
Immune system disorders		Hypersensitivity NOS*		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Nervous system disorders		Insomnia		Somnolence, Aphonia	Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinerg	

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MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1, 000**	**Very rare <1/10, 000**	**Not known (cannot be estimated from the available data)**
					ic syndrome, Neurological disorders, Ataxia, Encephalitis	
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia	Pericardial effusion		Tachycardia, Myocardial infarction, Cardiac failure	
Vascular disorders		Hypotension, Hypertension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea, Constipation, Stomatitis			haemorrhagic oesophagitis, Gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS*		Erythema, Dermatitis, Pruritus, Macular-papular rash, Hyperhidrosis		
Reproductive system and		Amenorrhea			Infertility	

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MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1, 000**	**Very rare <1/10, 000**	**Not known (cannot be estimated from the available data)**
breast disorders						
General disorders and administration site conditions	Mucosal inflammation, Fatigue, Pyrexia	Pain, Chills, Dehydration, Anorexia			Multi organ failure	
Investigations	Haemoglobin decrease, Creatinine increase, Urea increase	AST increase, ALT increase, Alkaline phosphatase increase, Bilirubin increase, Hypokalemia				

NOS = Not otherwise specified

A small number of cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported in patients using bendamustine in combination with allopurinol or in combination with allopurinol and rituximab.

The CD4/CD8 ratio may be reduced. A reduction of the lymphocyte count was seen. In immuno-suppressed patients, the risk of infection (e.g. with herpes zoster) may be increased.

There have been isolated reports of necrosis after accidental extra-vascular administration and toxic epidermal necrosis, tumour lysis syndrome, and anaphylaxis.

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There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma. The association with Bendamustine therapy has not been determined.

4.9 Overdose

After application of a 30 min infusion of Bendamustine once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m². Cardiac events of CTC grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of Bendamustine at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m^2. The dose limiting toxicity was grade 4 thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Counter measures

There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be made or haematological growth factors may be given as effective countermeasures to control haematological side-effects.

Bendamustine hydrochloride and its metabolites are dialyzable to a small extent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents,

ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross-linking of DNA single

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and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. The antitumour effect of bendamustine hydrochloride has been demonstrated by several *in vitro* studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovary carcinoma and different leukaemia) and *in vivo* in different experimental tumour models with tumours of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer).

Bendamustine hydrochloride showed an activity profile in human tumour cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab. However, the number of assessed patients is small.

Chronic lymphocytic leukaemia

The indication for use in chronic lymphocytic leukaemia is supported by a single open label study comparing bendamustine with chlorambucil. In the prospective, multi-centre, randomised, study, 319 previously untreated patients with chronic lymphocytic leukaemia stage Binet B or C requiring therapy were included. The first line therapy with bendamustine hydrochloride 100 mg/m² i.v. on days 1 and 2 (BEN) was compared to treatment with chlorambucil 0.8mg/kg days 1 and 15 (CLB) for 6 cycles in both arms. Patients received allopurinol in order to prevent tumour lysis syndrome.

Patients with BEN had a significantly longer median progression free survival than patients with CLB treatment (21.5 versus 8.3 months, $p < 0.0001$ in the latest follow-up). Overall survival was not statistically significantly different (median not reached). The median duration of remission was 19 months with BEN and 6 months with CLB treatment ($p < 0.0001$). The safety evaluation in both treatment arms did not reveal any unexpected undesirable effects in nature and frequency. The dose of BEN was reduced in 34% of the patients. Treatment with BEN was discontinued in 3.9% of patients due to allergic reactions.

Indolent non-Hodgkin’s lymphomas

The indication for indolent non-Hodgkin’s lymphomas relied on two uncontrolled phase II trials.

In the pivotal prospective, multi-centre, open study 100 patients with indolent B-cell non-Hodgkin´s lymphomas refractory to rituximab mono- or combination therapy were treated with BEN single agent. Patients had received a median of 3 previous chemotherapy or biologic therapy courses. The median number of previous rituximab-containing courses was 2. The patients had had no response or there had been progression within 6 months after rituximab treatment. The dose of BEN was 120 mg/m² i.v. on days 1 and 2 planned for at least 6 cycles. Duration of treatment depended on response (6 cycles planned).

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The overall response rate was 75% including 17% complete (CR and CRu) and 58% partial response as assessed by independent review committee. The median duration of remission was 40 weeks. BEN was generally well tolerated when given in this dose and schedule.

The indication is further supported by another prospective, multi-centre, open study including 77 patients. The patient population was more heterogeneous including: indolent or transformed B-cell non-Hodgkin's lymphomas refractory to rituximab mono- or combination therapy. The patients had no response or there had been progression within 6 months or had had an untoward reaction to prior rituximab treatment. Patients received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses had been 2. The overall response rate was 76% with a median duration of response of 5 months (29 [95% CI 22.1, 43.1] weeks).

Multiple myeloma

In a prospective, multi-centre, randomised, open study 131 patients with advanced multiple myeloma (Durie-Salmon stage II with progression or stage III) were included. The first line therapy with bendamustine hydrochloride in combination with prednisone (BP) was compared to treatment with melphalan and prednisone (MP). Neither transplant-eligibility nor the presence of specific co-morbidities played a role for inclusion into the trial. The dose was bendamustine hydrochloride 150 mg/m² i.v. on days 1 and 2 or melphalan 15 mg/m² i.v. on day 1 each in combination with prednisone. Duration of treatment depended on response and averaged 6.8 in the BP and 8.7 cycles in the MP group.

Patients with BP treatment have a longer median progression free survival than patients with MP (15 [95%Cl 12-21] versus 12 [95%Cl 10-14] months) (p=0.0566). The median time to treatment failure is 14 months with BP and 9 months with MP treatment. The duration of remission was 18 months with BP and 12 months with MP treatment. The difference in overall survival was not significantly different (35 months BP versus 33 months MP). Tolerability in both treatment arms was in line with the know safety profile of the respective medicinal products with significantly more dose reductions in the BP arm.

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2ß}$ after 30 min i.v. infusion of 120 mg/m^2 area to 12 subjects was 28.2 minutes.

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Following 30 min i.v. infusion the central volume of distribution was 19.3 l. Under steady-state conditions following i.v. bolus injection the volume of distribution was 15.8-20.5 l.

More than 95% of the substance is bound to plasma proteins (primarily albumin).

Metabolism

A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and dihydroxy-bendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy-bendamustine by hepatic metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Another major route of bendamustine metabolism involves conjugation with glutathione.

In-vitro bendamustine does not inhibit CYP 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 and CYP 3A4.

Elimination

The mean total clearance after 30 min i.v. infusion of 120 mg/m^2 body surface area to 12 subjects was 639.4 ml/minute. About 20% of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment

In patients with 30 - 70% tumour infestation of the liver and mild hepatic impairment (serum bilirubin < 1.2 mg/dl) the pharmacokinetic behaviour was not changed. There was no significant difference to patients with normal liver and kidney function with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment

In patients with creatinine clearance >10 ml/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance.

Elderly subjects

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Subjects up to 84 years of age were included in pharmacokinetic studies. Higher age does not influence the pharmacokinetics of bendamustine.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Histological investigations in dogs showed macroscopic visible hyperaemia of the mucosa and haemorrhagia in the gastrointestinal tract. Microscopic investigations showed extensive changes of the lymphatic tissue indicating an immunosuppression and tubular changes of kidneys and testis, as well as atrophic, necrotic changes of the prostate epithelium.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

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2 years.

The powder should be reconstituted immediately after opening of the vial.

The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution.

Solution for infusion

After reconstitution and dilution, chemical and physical stability has been demonstrated for 5 hours at 25 ºC/ 60%RH and 5 days at 2 ºC to 8 ºC in polyethylene bags.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted or diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I brown glass vials of 10 ml or 50 ml with rubber stopper and an aluminium flip-off cap.

10 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 5, 10 and 20 vials.

50 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in pack of 1 and 5 vials.

Not all pack sizes may be marketed.

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6.6 Special precautions for disposal <and other handling>

When handling Bendamustine, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes!). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbing disposable foil. Pregnant personnel should be excluded from handling cytostatics.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution

Reconstitute each vial of Bendamustine hydrochloride 2.5 mg/mL powder for concentrate for solution for infusion containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking;

Reconstitute each vial of Bendamustine hydrochloride 2.5 mg/mL powder for concentrate for solution for infusion containing 100 mg bendamustine hydrochloride in 40 ml water for injection by shaking.

The reconstituted concentrate contains 2.5 mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

2. Dilution

As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of Bendamustine hydrochloride 2.5 mg/mL powder for concentrate for solution for infusion immediately with 0.9% NaCl solution to produce a final volume of about 500 ml.

Bendamustine hydrochloride 2.5 mg/mL powder for concentrate for solution for infusion must be diluted with 0.9% NaCl solution and not with any other injectable solution.

3. Administration

The solution is administered by intravenous infusion over 30-60 min.

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The vials are for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<to completed nationally>

8. MARKETING AUTHORISATION NUMBER(s)

<to completed nationally>

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

<to completed nationally>

10. DATE OF REVISION OF THE TEXT

<to completed nationally>

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Annex 3 - Worldwide marketing authorisation by country (including EEA)

A3.1 Licensing status in the EEA

Country	Current licence status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Not applicable					

A3.2 Licensing status in the rest of the world

Country	Current licence status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Not applicable					

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Annex 4 - Synopsis of on-going and completed clinical trial programme

None

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Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

None

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Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

None

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Annex 7 - Specific adverse event follow-up forms

None

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Annex 8 - Protocols for proposed and on-going studies in RMP part IV

None

The data and conclusions included in this report are confidential and proprietary information of Accord Healthcare Limited

Annex 9 - Newly available study reports for RMP parts III & IV

None

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Annex 10 - Details of proposed additional risk minimisation measures (if applicable)

None

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Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)

None

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Annex 12 - Other supporting data (including referenced material)

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