Version 4.0, 02/2016

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

/…/ 2.5 mg/ml powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One 26 ml-vial contains 25 mg bendamustine hydrochloride.
One 60 ml-vial contains 100 mg bendamustine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to off-white lyophilisate powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Posology

Monotherapy for chronic lymphocytic leukaemia

100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks up to 6 times.

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 for at least 6 times.

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 for at least 3 times.

Hepatic impairment
On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2 mg/dl). A 30% dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2-3.0 mg/dl).

No data is available in patients with severe hepatic impairment (serum bilirubin values of > 3.0 mg/dl) (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 population
The safety and efficacy of bendamustine hydrochloride in children have not yet been established. Current available data is not sufficient to make a recommendation on posology.

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

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).

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 instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in 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
Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200/µl) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine hydrochloride is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. In case of low CD4-positive T-cell counts (<200/µl) *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis should be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections.

Hepatitis B reactivation
Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received bendamustine hydrochloride. Some cases resulted in acute hepatic failure or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with bendamustine hydrochloride. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B tests (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with bendamustine hydrochloride should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Skin reactions
A number of skin reactions have been reported. These events have included rash, severe cutaneous reactions and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), some fatal, have been reported with the use of bendamustine hydrochloride. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. When skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, bendamustine hydrochloride should be withheld or discontinued. For severe skin reactions with suspected relationship to bendamustine hydrochloride, treatment should be discontinued.

Cardiac disorders
During treatment with bendamustine hydrochloride the concentration of potassium in the blood of patients with cardiac disorders must be closely monitored and potassium supplement must be given when K^+ < 3.5 mEq/l, and ECG measurement must be performed.

Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine hydrochloride treatment. Patients with concurrent or history of cardiac disease should be observed closely.

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

Tumour lysis syndrome
Tumour lysis syndrome (TLS) associated with bendamustine hydrochloride treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of bendamustine hydrochloride and, without intervention, may lead to acute renal failure and death. Preventive measures such as adequate hydration, close monitoring of blood chemistry, particularly potassium and uric acid levels, and the use of hypouricemic agents (allopurinol and rasburicase) should be considered prior to therapy. There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were 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 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 hydrochloride is combined with myelosuppressive agents, the effect of bendamustine hydrochloride 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 hydrochloride.

Combination of bendamustine hydrochloride 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.

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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3). During pregnancy bendamustine hydrochloride should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with bendamustine hydrochloride 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.

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

Men being treated with bendamustine hydrochloride 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 hydrochloride.

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

4.7 Effects on ability to drive and use machines

Bendamustine has major influence on the ability to drive and use machines. Ataxia, peripheral neuropathy and somnolence have been reported during treatment with bendamustine hydrochloride (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.

4.8 Undesirable effects

The most common adverse reactions with bendamustine hydrochloride are haematological 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.

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 kn** **(canno estima from t availa**
Infections and infestations	Infection NOS Including Opportunistic infection e.g. Herpes zoster, cytomegalovirus, hepatitis B		Pneumocystis jirovecii pneumonia	Sepsis	Pneumonia primary atypical	
Neoplasms benign, malignant and unspecified (including cyst and polyp)		Tumour lysis syndrome	Myelodysplastic syndrome, acute myeloid leukemia			
Blood and lymphatic system	Leukopenia NOS, Thrombocytopenia,	Haemorrhage, Anaemia,	Pancytopenia	Bone marrow failure	Haemolysis	

disorders	Lymphopenia	Neutropenia				
Immune system disorders		Hypersensitivity NOS		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Nervous system disorders	Headache	Insomnia, Dizziness		Somnolence, Aphonia	Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders, Ataxia, Encephalitis	
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia	Pericardial effusion, Myocardial infarction, Cardiac failure		Tachycardia	Atrial fibrilla
Vascular disorders		Hypotension, Hypertension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	Pneum Pulmo alveola haemo
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea, Constipation, Stomatitis			Haemorrhagic oesophagitis, Gastrointestinal haemorrhage	
Hepatobiliary disorders						Hepati
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS, Urticaria		Erythema, Dermatitis, Pruritus, Maculopapular Rash, Hyperhidrosis		Steven Johnso syndro Toxic Epider Necrol (TEN) reactio eosino and sy sympt (DRES
Reproductive system and breast disorders		Amenorrhea			Infertility	
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				
Renal and urinary disorders						Renal

NOS = Not otherwise specified
*=combination therapy with rituximab

Description of selected adverse reactions
There have been isolated reports of necrosis after accidental extra-vascular administration and tumour lysis syndrome and anaphylaxis.

The risk of myelodysplastic syndrome and acute myeloid leukaemias is increased in patients treated with alkylating agents (including bendamustine). The secondary malignancy may develop several years after chemotherapy has been discontinued.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

After application of a 30 min infusion of bendamustine hydrochloride 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 hydrochloride at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m². 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 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, ovarian 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 0.8 mg/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 biological 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). 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 had 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). Tolerability in both treatment arms was in line with the known safety profile of the respective medicinal products with significantly more dose reductions in the BP arm. 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 cycles in the BP and 8.7 cycles in the MP group.

Patients with BP treatment had a longer median progression free survival than patients with MP (15 [95% CI 12-21] versus 12 [95% CI 10-14] months) ($p = 0.0566$). The median time to treatment failure was 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 known 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/m² area to 12 subjects was 28.2 minutes.

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).

Biotransformation
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 or 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
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

Before opening: 3 years

Reconstituted concentrate
The powder should be reconstituted immediately after opening of the vial.
The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution (see section 6.6).

Solution for infusion
After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 ºC/ 60% RH, in normal light conditions and 2 days at 2 ºC to 8 ºC, protected from light, 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 and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened: This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I amber glass vials of 26 ml or 60 ml with type I rubber (bromobutyl) lyo-stopper and an aluminium cap with polypropylene disk. <Vials are sheathed in protective sleeve.>

26 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 and 20 vials.
60 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When handling /.../, 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 eyes should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbent 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 26 ml-vial containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking;

Reconstitute each 60 ml-vial 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 /.../ immediately with 0.9% NaCl solution to produce a final volume of about 500 ml.
/.../ must be diluted with 0.9% NaCl solution and not with any other injectable solution. /.../ must not be mixed in an infusion with other substances.

3. Administration
The solution is administered by intravenous infusion over 30-60 min.
The vials are for single use only.

The medicinal product should not be used if any visible signs of deterioration or damages to the vials are detected. Following reconstitution and dilution, the product should be inspected visually for particulate matter or discolouration. The solution should only be used if the solution is clear and free from particles.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Vial carton

1. NAME OF THE MEDICINAL PRODUCT

/…/ 2.5 mg/ml powder for concentrate for solution for infusion

bendamustine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 ml of concentrate contains 2.5 mg bendamustine hydrochloride.

One 26 ml-vial contains 25 mg bendamustine hydrochloride.
One 60 ml-vial contains 100 mg bendamustine hydrochloride.

3. LIST OF EXCIPIENTS

Contains mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.

[26 ml vials – 25 mg bendamustine:]
1 x 25 mg vial
5 x 25 mg vials
10 x 25 mg vials
20 x 25 mg vials

[60 ml vials – 100 mg bendamustine:]
1 x 100 mg vial
5 x 100 mg vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use as infusion, after reconstitution and dilution.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Read the leaflet for shelf-life of the reconstituted and diluted product.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial label

1. NAME OF THE MEDICINAL PRODUCT

/…/ 2.5 mg/ml powder for concentrate for solution for infusion

bendamustine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml concentrate=2.5 mg bendamustine hydrochloride.

One 26 ml-vial contains 25 mg bendamustine hydrochloride.
One 60 ml-vial contains 100 mg bendamustine hydrochloride.

3. LIST OF EXCIPIENTS

Contains mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.

[26 ml vials – 25 mg bendamustine:]
25 mg

[60 ml vials – 100 mg bendamustine:]
100 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

i.v.

Must be reconstituted and diluted.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Read the leaflet for shelf-life of the reconstituted and diluted product.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PACKAGE LEAFLET

Package leaflet: Information for the user

/…/ 2.5 mg/ml powder for concentrate for solution for infusion

Bendamustine hydrochloride

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What /…/ is and what it is used for

/.../ is a medicine which is used for the treatment of certain types of cancer (cytotoxic medicine).

/.../ is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:
- chronic lymphocytic leukaemia in cases where fludarabine combination chemotherapy is not appropriate for you.
- non-Hodgkin's lymphomas, which had not, or only shortly, responded to prior rituximab treatment.
- multiple myeloma in cases where thalidomide or bortezomib containing therapy is not appropriate for you.

2. What you need to know before you use /…/

Do not use /…/:
- if you are allergic to bendamustine hydrochloride or any of the other ingredients of this medicine (listed in section 6)
- while breast-feeding; if treatment with /…/ is necessary during lactation you must discontinue breast-feeding
- if you have severe liver dysfunction (damage to the functional cells of the liver)
- if you have yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)
- if you have severely disturbed bone marrow function (bone marrow depression) and serious changes in your number of white blood cells and platelets in the blood .
- if you have had major surgical operations less than 30 days before starting treatment
- if you have an infection, especially one accompanied by a reduction in white blood cells (leucocytopenia)
- in combination with yellow fever vaccines.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before or during treatment with /…/:

- in case of reduced capability of the bone marrow to replace blood cells. You should have your number of white blood cells and platelets in the blood checked before starting treatment with /.../, before each subsequent course of treatment and in the intervals between courses of treatment.
- in case of infections. You should contact your doctor if you have signs of infection, including fever or lung symptoms.
- in case of reactions on your skin during treatment with /.../. The skin reactions may increase in severity.
- in case of painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips), in particular if you had before light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever.
- in cases of existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms).
- in case you notice any pain in your side, blood in your urine or reduced amount of urine. When your disease is very severe, your 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 /.../. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it.
- in case of severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.

Other medicines and /…/
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If /.../ is used in combination with medicines which inhibit the formation of blood in the bone marrow, the effect on the bone marrow may be intensified.

If /.../ is used in combination with medicines which alter your immune response e.g. ciclosporin and tacrolimus, this effect may be intensified.

Medicines such as bendamustine (cytostatic medicines) may diminish the effectiveness of live-virus vaccination. Additionally cytostatic medicines increase the risk of an infection after vaccination with live vaccines (e.g. viral vaccination).

If /…/ is used in combination with medicines which inhibit a special liver enzyme (CYP1A2), such as fluvoxamine (antidepressant), ciprofloxacin (used to treat bacterial infections), acyclovir (used to treat virus infections) and cimetidine (used to treat heartburn and stomach ulcers), these medicines can interfere with each other.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Pregnancy
/.../ can cause genetic damage and has caused malformations in animal studies. You should not use /.../ during pregnancy unless certainly indicated by your doctor. In case of treatment you should seek medical consultation about the risk of potential adverse effects of your therapy for the unborn child and genetic consultation is recommended.

Fertility
If you are a woman of childbearing potential you must use an effective method of contraception both before and during treatment with /.../. If pregnancy occurs during your treatment with /.../ you must immediately inform your doctor and seek genetic consultation.

If you are a man, you should avoid fathering a child during treatment with /.../ and for up to 6 months after treatment has stopped. There is a risk that treatment with /.../ will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

Breastfeeding
/.../ must not be administered during breastfeeding. If treatment with /.../ is necessary during lactation you must discontinue breastfeeding.

Driving and using machines
/…/ has major influence on the ability to drive and to use machines. Do not drive or operate machines if you experience side effects, such as dizziness or lack of coordination.

3. How to use /…/

/.../ is administered into a vein over 30-60 minutes in various dosages, either alone (monotherapy) or in combination with other medicines.

Treatment should not be started if your white blood cell (leukocytes) and /or your blood platelets have fallen to counts below determined levels. Your doctor will determine these values at regular intervals.

Chronic lymphocytic leukaemia

/.../ 100 mg per square meter of your body surface area (based on your height and weight)	on Days 1 + 2
Repeat the cycle after 4 weeks up to 6 times	

Non-Hodgkin's lymphomas

/.../ 120 mg per square meter of your body surface area (based on your height and weight)	on Days 1 + 2
Repeat the cycle after 3 weeks at least 6 times	

Multiple myeloma

/.../ 120 – 150 mg per square meter of your body surface area (based on your height and weight)	on Days 1 + 2
Prednisone 60 mg per square meter of your body surface area (based on your height and weight) by injection or orally	on Days 1 – 4
Repeat the cycle after 4 weeks at least 3 times	

Treatment should be terminated if white blood cell (leukocyte) and/or platelet values dropped to determined levels. Treatment can be continued after white blood cell and platelet values have increased.

Impaired liver or kidney function
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). No dose adjustment is necessary in case of impairment of kidney function. Your attending doctor will decide whether a dosage adjustment is necessary.

How it is administered
Treatment with /.../ should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of /.../ and use the necessary precautions.

Your attending doctor will administer the solution for infusion after preparation as prescribed. The solution is administered into a vein as a short-term infusion over 30-60 minutes.

Duration of use
There is no time limit laid down as a general rule for treatment with /.../. Duration of treatment depends on disease and response to treatment.

If you are at all worried or have any questions regarding treatment with /.../, please speak to your doctor or nurse.

If you forget to use /…/
If a dose of /.../ has been forgotten, your doctor will usually retain the normal dosage schedule.

If you stop using /…/
The doctor treating you will decide whether to interrupt the treatment or to change over to a different preparation.

If you have any further questions on the use of this this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Some of the findings listed below may be found after tests are performed by your doctor.

Tissue decay (necrosis) has been observed very rarely following leakage of /…/ into the tissue outside the blood vessels (extravascular). A burning sensation where the infusion needle is inserted may be a sign of leakage outside the blood vessels. The consequence can be pain and poorly healing skin defects.

The dose-limiting side-effect of /.../ is impaired bone-marrow function, which usually returns to normal after treatment. Suppressed bone marrow function may lead to low counts of blood cells, which in turn may lead to an increased risk of infection, anemia or a heightened risk of bleeding.

Very common *(may affect more than 1 in 10 people):*
- Low counts of white blood cells (disease-fighting cells in your blood)
- Decrease in the red pigment of the blood (haemoglobin: a protein in red blood cells that carries oxygen throughout the body)
- Low counts of platelets (colorless blood cells that help blood clot)
- Infections
- Feeling sick (nausea)
- Vomiting
- Mucosal inflammation
- Headache
- Increased blood level of creatinine (a chemical waste product that is produced by your muscle)
- Increased blood level of urea (a chemical waste product)
- Fever
- Fatigue

Common *(may affect up to 1 in 10 people):*
- Bleeding (haemorrhage)
- Disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- Low counts of neutrophils (a common type of white blood cells important to fighting off infections
- Hypersensitivity reactions such as allergic inflammation of the skin (dermatitis), nettle rash (urticaria)
- A rise in liver enzymes AST/ALT (which may indicate inflammation or damage to cells in the liver
- A rise in the enzyme alkaline phosphatase (an enzyme made mostly in the liver and bones)
- A rise in bile pigment (a substance made during the normal breakdown of red blood cells)

- Low potassium blood levels (a nutrient that is necessary for the function of nerve and muscle cells, including those in your heart)
- Disturbed function (dysfunction) of the heart
- Disturbed heart rhythms (arrhythmia)
- Low or high blood pressure (hypotension or hypertension)
- Disturbed lung function
- Diarrhoea
- Constipation
- Sore mouth (stomatitis)
- Loss of appetite
- Hair loss
- Skin changes
- Missed periods (amenorrhoea)
- Pain
- Insomnia
- Chills
- Dehydration
- Dizziness
- Itchy rash (urticaria)

Uncommon *(may affect up to 1 in 100 people):*
- inflammation of the lungs (pneumocystis jirovecii pneumonia)
- Accumulation of fluid in the heart sac (escape of fluid into the pericardial space)
- Ineffective production of all blood cells in the bone marrow (the spongy material inside your bones where blood cells are made)
- Acute leukemia
- Heart attack, chest pain (myocardial infarction)
- Heart failure

Rare *(may affect up to 1 in 1,000 people):*
- Infection of the blood (sepsis)
- Reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests
- Severe allergic hypersensitivity reactions (anaphylactic reactions)
- Signs similar to anaphylactic reactions (anaphylactoid reactions)
- Drowsiness
- Loss of voice (aphonia)
- Acute circulatory collapse (failure of blood circulation mainly from a cardiac origin with failure to maintain the supply of oxygen and other nutrients to the tissues and removing toxins)
- Reddening of the skin (erythema)
- Inflammation of the skin (dermatitis)
- Itching (pruritus)
- Skin rash (macular exanthema)
- Excessive sweating (hyperhidrosis)

Very rare *(may affect up to 1 in 10,000 people):*
- Primary atypical inflammation of the lungs (pneumonia)
- Break-down of red blood cells
- Rapid decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock)
- Disturbed sense of taste
- Altered sensations (paraesthesia)
- Malaise and pain in the limbs (peripheral neuropathy)
- Serious condition resulting in the blockade of specific receptor in the nervous systems
- Disorders of the nervous system
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)

- Increased heart rate (tachycardia)
- Inflammation of the veins (phlebitis)
- Formation of tissue in the lungs (fibrosis of the lungs)
- Bleeding and inflammation of the gullet (haemorrhagic oesophagitis)
- Bleeding of stomach or gut
- Infertility
- Multiple organ failure

Not know *(frequency cannot be estimated from the available data):*
- Liver failure
- Renal failure
- Irregular and often rapid heart rate (atrial fibrillation)
- Painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips), in particular if you had before light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever.
- Drug rash in combination therapy with rituximab
- Pneumonitis
- Bleeding from the lungs

There have been reports of tumours (myelodysplastic syndrome, acute myeloid leukaemia (AML), bronchial carcinoma) following treatment with bendamustine. No clear relationship with bendamustine could be determined.

Contact your doctor or seek medical attention immediately if you notice any of the following side effects (frequency not known):
- Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms.
- Widespread rash, high body temperature, enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store /…/

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month..

Unopened
This medicinal product does not require any special storage conditions.

Reconstituted concentrate
The powder should be reconstituted immediately after opening of the vial.
The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution (see instructions at the end of this leaflet).

Solution for infusion

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 ºC/ 60% RH, in normal light conditions and 2 days at 2 ºC to 8 ºC, protected from light, 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 and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6. Contents of the pack and other information

What /…/ contains

- The active substance is bendamustine hydrochloride. After reconstitution, 1 ml of concentrate contains 2.5 mg bendamustine hydrochloride. One 26 ml-vial contains 25 mg bendamustine hydrochloride. One 60 ml-vial contains 100 mg bendamustine hydrochloride.
- The other ingredient is mannitol.

What /…/ looks like and contents of the pack.

White to off-white lyophilisate powder.

Type I amber glass vials of 26 ml or 60 ml with type I rubber (bromobutyl) lyo-stopper and an aluminium cap with polypropylene disk. <Vials are sheathed in protective sleeve.>

26 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 and 20 vials.
60 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
[To be completed nationally]

Manufacturer
[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Bendamustin 2,5 mg/ml Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Bulgaria	Bendamustine Actavis
Croatia	Bendamustin Actavis 2,5 mg/ml prašak za koncentrat za otopinu za infuziju
Denmark	Bendamustin Actavis
Estonia	Bendamustine Actavis
Greece	Bendamustine/ Actavis
Hungary	Bendamustin Teva 2,5 mg/ml por oldatos infúzióhoz való koncentrátumhoz
Ireland	Bendamustine 2.5 mg/ml Powder for Concentrate for Solution for Infusion
Malta	Bendistin
Netherlands	Bendamustine HCl Teva 2,5 mg/ml, poeder voor concentraat voor oplossing voor infusie
Norway	Bendamustin Actavis
Romania	Bendamustina Actavis 2,5 mg/ml Pulbere pentru concentrat pentru soluție perfuzabilă
Slovenia	Bendamustin Actavis 2.5 mg/ml prašek za koncentrat za raztopino za

	infundiranje
Sweden	Bendamustin Actavis
United Kingdom	Bendamustine hydrochloride 2.5mg/ml Powder for Concentrate for Solution for Infusion

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

[To be completed nationally]

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The following information is intended for healthcare professionals only:

As with all similar cytotoxic substances, stricter safety precautions apply as far as nursing staff and doctors are concerned, due to the potentially genome-damaging and cancer-causing effect of the preparation. Avoid inhalation (breathing in) and contact with the skin and mucous membranes when handling /.../ (wear gloves, protective clothing, and possibly a face mask!). If any parts of the body become contaminated, clean them carefully with soap and water, and flush the eyes with 0.9 % (isotonic) saline solution. If possible, it is advisable to work on a special safety work bench (laminar flow) with a disposable absorbing sheet that is impermeable to liquids. Contaminated articles are cytostatic waste. Please comply with national guidelines on the disposal of cytostatic material! Pregnant staff must be excluded from working with cytostatics.

The solution ready for use must be prepared by dissolving the contents of a vial of /…/ exclusively in water for injections as follows:

1. Preparation of the concentrate
- One 26 ml-vial of /.../ containing 25 mg of bendamustine hydrochloride is first dissolved in 10 ml of water for injections by shaking.
- One 60 ml-vial of /.../ containing 100 mg of bendamustine hydrochloride is first dissolved in 40 ml of water for injections by shaking.

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

2. Preparation of the solution for infusion
As soon as a clear solution is obtained (generally after 5-10 minutes), the total recommended dose of /.../ is immediately diluted with 0.9 % (isotonic) saline solution to obtain a final volume of approximately 500 ml. /.../ must not be diluted with other solutions for infusion or injection. /.../ must not be mixed in an infusion with other substances.

3. Administration
The solution is administered by intravenous infusion over 30-60 min.
The vials are for single use only.

Do not use this medicine if you notice any visible signs of deterioration or damage to the vials. Following reconstitution and dilution, the product should be inspected visually for particulate matter or discolouration. The solution should only be used if the solution is clear and free from particles.

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 corticosteroids are not of clear benefit (see section 4).

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