PROFESSIONAL INFORMATION FOR HUMAN MEDICINE

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

BENDAMUSTINE 25 mg FRESENIUS Powder for concentrate for solution for infusion

BENDAMUSTINE 100 mg FRESENIUS Powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of the concentrate contains 2,5 mg bendamustine hydrochloride when reconstituted according to section 6.6.

BENDAMUSTINE 25 mg FRESENIUS: One vial contains 25 mg bendamustine hydrochloride.

BENDAMUSTINE 100 mg FRESENIUS: One vial contains 100 mg bendamustine hydrochloride.

Contains sugar:

BENDAMUSTINE 25 mg FRESENIUS: Mannitol*:* 30,0 mg/vial

BENDAMUSTINE 100 mg FRESENIUS: Mannitol: 120,0 mg/vial

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to off-white lyophilised powder or cake.

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.
- First-line treatment of indolent CD 20 positive non-Hodgkin's lymphoma in combination with rituximab.
- 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/m^2 body surface area BENDAMUSTINE FRESENIUS on days 1 and 2; every 4 weeks.

Combination treatment for first-line indolent non-Hodgkin's lymphoma

90 mg/m^2 body surface area BENDAMUSTINE FRESENIUS on days 1 and 2 in combination with 375 mg/m^2 body surface area rituximab as a slow I.V. infusion on day 1; every 4 weeks.

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

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

Multiple Myeloma

120-150 mg/m² body surface area BENDAMUSTINE FRESENIUS on days 1 and 2, 60 mg/m² body surface area prednisone I.V. or orally on days 1 to 4; every 4 weeks.

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment [serum bilirubin < 34,2 µmol/L (2,0 mg/dL)].

A 30 % dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin [34,2 µmol/L – 51,3 µmol/L (2 – 3,0 mg/dL)].

No data is available in patients with severe hepatic impairment [serum bilirubin values of > 51,3 µmol/L (3,0 mg/dL)].

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

There is no experience in children and adolescents with BENDAMUSTINE FRESENIUS.

Elderly patients

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

Method of Administration

Precaution to be taken before manipulating or administering the product. When handling BENDAMUSTINE FRESENIUS, 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 (see section 6.6).

For intravenous infusion over 30 to 60 minutes. Infusion must be administered under the supervision of

a medical physician qualified and experienced in the use of chemotherapeutic medicines.

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity.

Treatment should not be started if leukocyte and/or platelet values have dropped to < 3 x 10^9/L or < 75 x 10^9/L, respectively (see section 4.3).

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to ≤ 3 x 10^9/L or ≤ 75 x 10^9/L, respectively. Treatment can be continued after leukocyte values have increased to > 4 x 10^9/L and platelet values to > 100 x 10^9/L.

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 the 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 medicine , see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Pregnancy and lactation (See section 4.6)
- Severe hepatic impairment [serum bilirubin > 34,2 µmol/L (2,0 mg/dL)]
- Jaundice

- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 x 10^9/L or < 75 x 10^9/L, respectively)
- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopenia
- Yellow fever vaccination or any other live (attenuated) vaccination
- Congenital QT prolongation
- Concomitant medicines causing QT prolongation

4.4 Special warnings and precautions for use

Myelosuppression

Patients treated with BENDAMUSTINE FRESENIUS may experience myelosuppression. 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 x 10/µL or > 100 x 10/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 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. Cases of tuberculosis have been less frequently reported compared to other infections. Latent or dormant tuberculosis may become active. (see section 4.8). 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 FRESENIUS should be considered if there are signs of (opportunistic) infections. The presence of tuberculosis should be excluded before treatment with BENDAMUSTINE FRESENIUS is commenced.

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 FRESENIUS 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 medicines, 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 FRESENIUS should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued.

Cardiac disorders

During treatment with BENDAMUSTINE FRESENIUS 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 and close monitoring of blood chemistry, particularly potassium and uric acid levels, and the use of hypouricemic medicines (allopurinol) 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. Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of BENDAMUSTINE FRESENIUS.

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of BENDAMUSTINE FRESENIUS.
They should seek advice about sperm conservation prior to treatment with BENDAMUSTINE FRESENIUS 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.

Other malignancies

There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma.

4.5 Interaction with other medicines and other forms of interaction

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

When BENDAMUSTINE FRESENIUS is combined with myelosuppressive medicines, the effect of bendamustine and/or the co-administered medicines 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 FRESENIUS with ciclosporin 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 hydrochloride metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme (see section 5.2). Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir, and cimetidine exist.

Incompatibilities:

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception/ fertility

Women of childbearing potential must use highly effective contraception during treatment and for 6 months after the last dose of BENDAMUSTINE FRESENIUS.

Men being treated with BENDAMUSTINE FRESENIUS are advised not to father a child during and for up to 3 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 FRESENIUS**.**

Pregnancy

There are no adequate data from the use of bendamustine hydrochloride in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/foetolethal, teratogenic and genotoxic. (see section 5.3). Therefore, BENDAMUSTINE FRESENIUS is contraindicated during pregnancy (see section 4.3).

Breastfeeding

It is not known whether bendamustine hydrochloride passes into the breast milk, therefore, BENDAMUSTINE FRESENIUS is contraindicated during breastfeeding (see section 4.3). Breastfeeding must be discontinued during treatment with BENDAMUSTINE FRESENIUS.

4.7 Effects on ability to drive and use machines

BENDAMUSTINE FRESENIUS 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 side effects with BENDAMUSTINE FRESENIUS are haematological adverse reactions (leukopenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting). The table below reflects the data obtained with bendamustine hydrochloride.

Table 1: Adverse reactions in patients treated with bendamustine hydrochloride.

MedDRA system organ class	**Frequent**			**Less Frequent**		**Frequency unknown**
Infections and infestations	Infection NOS* Including Opportunistic infection (including Herpes zoster, cytomegalovirus, hepatitis B)		Pneumocystis jirovecii pneumonia	Sepsis tuberculosis	Pneumonia primary atypical	
Neoplasms benign, malignant and unspecified (including cyst and polyp)		Tumour lysis syndrome	Myelodysplastic syndrome, acute myeloid leukaemia			
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombocytopenia, Lymphopenia	Haemorrhage, Anaemia, Neutropenia		Bone marrow failure Pancytopenia	Haemolysis	
Immune system disorders		Hypersensitivity NOS*		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Metabolism and nutrition disorders		Tumour lysis syndrome				

MedDRA system organ class	**Frequent**			**Less Frequent**		**Frequency unknown**
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, Dysrhythmia	Pericardial effusion, Myocardial infarction, Cardiac failure		Tachycardia	Atrial fibrillation
Vascular disorders		Hypotension, Hypertension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	Pneumonitis, pulmonary alveolar haemorrhage

MedDRA system organ class	**Frequent**			**Less Frequent**		**Frequency unknown**
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea, Constipation, Stomatitis			Haemorrhagic oesophagitis, Gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS*, Urticaria		Erythema, Dermatitis, Pruritus, Maculopapular, Rash, Hyperhidrosis		Bullous Exanthema Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders						Renal failure, Nephrogenic diabetes insipidus
Reproductive system and		Amenorrhea			Infertility	

MedDRA system organ class	Frequent			Less Frequent		Frequency unknown
breast disorders						
Hepatobiliary disorders						Hepatic failure
General disorders and administration site conditions	Mucosal inflammation, Fatigue, Pyrexia	Pain, Chills, Dehydration, Anorexia			Multi organ failure	
Investigations	Decrease haemoglobin, Increase creatinine, Increase urea	Increase AST, Increase ALT, Increase alkaline phosphatase, Increase bilirubin, Hypokalemia				

*NOS = Not otherwise specified

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 medicines (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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

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/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 dialysable 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).

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.

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 and CYP3A4.

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 to 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 medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 3 years.

Reconstituted concentrate:

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

The reconstituted concentrate should be diluted immediately with 9 mg/mL (0,9 %) sodium chloride solution.

Solution for infusion:

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3,5 hours at 25 °C/ 60 % RH and 2 days at 2 °C to 8 °C 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

BENDAMUSTINE FRESENIUS may be stored at or below 25 °C.

Keep out of reach of children.

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

6.5 Nature and contents of container

BENDAMUSTINE 25 mg FRESENIUS: Type I, amber, tubular glass vials of 20 mL with a grey chlorobutyl rubber stopper and sealed with an aluminium flip-off overseal.

BENDAMUSTINE 100 mg FRESENIUS: Type I, amber, tubular glass vials of 50 mL with a grey chlorobutyl rubber stopper and sealed with an aluminium flip-off overseal.

Each vial may be shrink wrapped along with a plastic bottom.

Pack sizes:

BENDAMUSTINE 25 mg FRESENIUS: 20 mL vials; 1, 5, 10 and 20 vials.

BENDAMUSTINE 100 mg FRESENIUS: 50 mL vials; 1 and 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When handling BENDAMUSTINE FRESENIUS, 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 FRESENIUS containing 25 mg bendamustine hydrochloride in 10 mL water for injection by shaking.

Reconstitute each vial of BENDAMUSTINE FRESENIUS 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 to slightly yellow solution.

2. Dilution

As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of BENDAMUSTINE FRESENIUS immediately with a 500 mL infusion bag of 0,9 % NaCl solution.

BENDAMUSTINE FRESENIUS 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.

The vials are for single use only.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

BENDAMUSTINE 25 mg FRESENIUS: 50/26/0675

BENDAMUSTINE 100 mg FRESENIUS: 50/26/0676

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 August 2020

10 DATE OF REVISION OF THE TEXT

10 March 2025