Approved Professional Information

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

BENDAMUSTINE 180 mg/4 ml DRL (Concentrate for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BENDAMUSTINE 180 mg/4 ml DRL: Each vial contains 180 mg/4 ml of bendamustine hydrochloride concentrate for solution for infusion.

1,0 ml of the concentrate contains 45 mg of bendamustine hydrochloride (as monohydrate).

Contains butylhydroxytoluene as antioxidant 0,001 % *m/v*

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, pale yellow to yellow viscous solution, free from visible extraneous matter

pH = 2,5 – 4,0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BENDAMUSTINE 180 mg/4 ml DRL is indicated for

- 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

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

For preparation and administration instructions see Method of Administration.

Posology

Monotherapy for chronic lymphocytic leukaemia

100 mg/m2 body surface area BENDAMUSTINE 180 mg/4 ml DRL 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 180 mg/4 ml DRL 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/m^2 body surface area BENDAMUSTINE 180 mg/4 ml DRL on days 1 and 2; every 3 weeks.

Multiple Myeloma

120 - 150 mg/m^2 body surface area BENDAMUSTINE 180 mg/4 ml DRL on days 1 and 2, 60 mg/m body surface area prednisone I.V. or orally on days 1 to 4; every 4 weeks.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to ≤ 3 x 109/ℓ or ≤ 75 x 109/ℓ, respectively. Treatment can be continued after leukocyte values have increased to > 4 x 109/ℓ and platelet values to > 100 x 109/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 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.

Special Populations

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.

Elderly

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

Children and Adolescents:

There is no experience in children and adolescents with BENDAMUSTINE 180 mg/ 4 ml DRL.

Method of administration

For intravenous infusion over 30 to 60 minutes.

Aseptic technique is to be used.

1. Dilution

Aseptically withdraw the volume needed for the required dose from the bendamustine hydrochloride 180 mg/4 ml concentrate for solution for infusion vial.

Dilute the total recommended dose of bendamustine hydrochloride 180 mg/4 ml concentrate for solution for infusion with 0,9 % NaCl solution to produce a final volume of about 500 ml.

While diluting the product it should be noted that the concentration (45 mg/ml) of bendamustine in BENDAMUSTINE 180 mg/4 ml DRL is higher than in usual bendamustine concentrates resulting from reconstitution of bendamustine powder containing medicinal products.

BENDAMUSTINE 180 mg/4 ml DRL must be diluted with 0,9 % NaCl solution and not with any other injectable solution.

2. Administration

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

The vials are for multiple dose use.

4.3 Contraindications

- Hypersensitivity to bendamustine or to any of the excipients in BENDAMUSTINE 180 mg/4 ml DRL (see 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 109/ℓ or < 75 x 109/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 180 mg/4 ml DRL 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 x 109/ℓ or > 100 x 109/ℓ, 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 neutropenia and/or lymphopenia and low CD4-positive T-cell count following treatment with BENDAMUSTINE 180 mg/4 ml DRL are more susceptible to (opportunistic) infections including tuberculosis.

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.

Cases of tuberculosis have been less frequently reported compared to other infections

Latent or dormant tuberculosis may become active.

The presence of tuberculosis should be excluded before treatment with BENDAMUSTINE 180 mg/4 ml DRL 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 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 of these events occurred when BENDAMUSTINE 180 mg/4 ml DRL 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 180 mg/4 ml DRL should be withheld or discontinued. For severe skin reactions where a relationship to BENDAMUSTINE 180 mg/4 ml DRL is suspected, treatment should be discontinued.

Patients with cardiac disorders

During treatment with BENDAMUSTINE 180 mg/4 ml DRL the concentration of potassium in the blood of patients with cardiac disorders must be closely monitored.

When serum potassium levels are < 3,5 mEq/L (3,5 mmol/L), an ECG recording must be performed, and potassium supplement must be given.

QTcf was prolonged by more than 30 msecs in 4 of 9 patients studied.

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

Nausea, vomiting

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

Tumour lysis syndrome

Tumour lysis syndrome (TLS) associated with BENDAMUSTINE 180 mg/4 ml DRL treatment has been reported. The onset tends to be within 48 hours of the first dose of BENDAMUSTINE 180 mg/4 ml DRL and, without intervention, may lead to acute renal failure and death.

Preventive measures include adequate fluid volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels.

The use of hypouricemic medicines (allopurinol and rasburicase) should be considered prior to therapy.

There have been cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when BENDAMUSTINE 180 mg/4 ml DRL and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to BENDAMUSTINE 180 mg/4 ml DRL may occur. Symptoms include fever, chills, pruritus and rash.

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.

In patients who experienced Grade 3 or worse allergic-type reactions, BENDAMUSTINE 180 mg/4 ml DRL should be discontinued.

Contraception

BENDAMUSTINE 180 mg/4 ml DRL 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 180 mg/4 ml DRL because of possible irreversible infertility.

Extravasation

An extra-vascular 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.

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

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 180 mg/4 ml DRL is combined with myelosuppressive medicines, the effect of BENDAMUSTINE 180 mg/4 ml DRL 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 180 mg/4 ml DRL.

Combination of BENDAMUSTINE 180 mg/4 ml DRL 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 180 mg/4 ml DRL metabolism involves cytochrome P450 (CYP)1A2 isoenzyme. Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir, and cimetidine exists.

4.6 Fertility, pregnancy and lactation

Pregnancy

BENDAMUSTINE 180 mg/4 ml DRL is contraindicated in pregnancy (see section 4.3).

Fertility

Women of childbearing potential must use effective methods of contraception both before and during BENDAMUSTINE 180 mg/4 ml DRL therapy.

Men being treated with BENDAMUSTINE 180 mg/4 ml DRL 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 180 mg/4 ml DRL.

Breast-feeding

BENDAMUSTINE 180 mg/4 ml DRL is contraindicated during breastfeeding (see section 4.3).

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 180 mg/4 ml DRL (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

Summary of the safety profile

The most common side effects with BENDAMUSTINE 180 mg/4 ml DRL are haematological adverse reactions (leucopenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

Tabulated summary of adverse reactions

Infections and Infestations	
Frequent:	Infection (not otherwise specified)
Less frequent:	Septicaemia
	Primary atypical pneumonia, tuberculosis
Blood and lymphatic system disorders	
Frequent:	Leucopenia (not otherwise specified), thrombocytopenia
	Haemorrhage, anaemia, neutropenia, lymphopenia
Less frequent:	Haemolysis
Immune system disorders	
Frequent:	Hypersensitivity (not otherwise specified)
Less frequent:	Anaphylactic reaction, anaphylactoid reaction,
	anaphylactic shock
Metabolism and nutrition disorders	
Frequent:	Tumor lysis syndrome
Nervous system disorders	
Frequent:	Insomnia
Less frequent:	Somnolence, aphonia
	Dysgeusia, paraesthesia, peripheral sensory neuropathy,
	anticholinergic syndrome, neurological disorders, ataxia,
	encephalitis
Cardiac disorders	
Frequent:	Cardiac dysfunction, such as tachycardia, palpitations,
	angina pectoris; dysrhythmia, QT prolongation
Less frequent:	Pericardial effusion
	Tachycardia, myocardial infarction, cardiac failure
Vascular disorders	
Frequent:	Hypotension, hypertension
Less frequent:	Acute circulatory failure
	Phlebitis
Respiratory, thoracic and mediastinal disorders	

Frequent:	Pulmonary dysfunction
Less frequent:	Pulmonary fibrosis
Frequency not known:	Pneumonitis, pulmonary alveolar haemorrhage
Gastrointestinal disorders	
Frequent:	Nausea, vomiting, diarrhoea, constipation, stomatitis
Less frequent:	Haemorrhagic oesophagitis, gastrointestinal haemorrhage
Skin and subcutaneous tissue disorders	
Frequent:	Alopecia, skin disorders (not otherwise specified) Urticaria
Less frequent:	Erythema, dermatitis, pruritus, maculo-papular rash, hyperhidrosis
Frequency unknown:	Drug reaction with eosinophilia and Systemic Symptoms (DRESS)
Reproductive system and breast disorders	
Frequent:	Amenorrhoea
Less frequent:	Infertility
General disorders and administration site conditions	
Frequent:	Mucosal inflammation, fatigue, pyrexia Pain, chills, dehydration, anorexia
Less frequent:	Multi-organ failure
Investigations	
Frequent:	Decreased haemoglobin, increased creatinine, increased urea Increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, hypokalaemia

Description of selected adverse reactions

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

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found on-line under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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.

Treatment

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 180 mg/4 ml DRL and its metabolites are dialysable to a small extent.

5 PHARMACOLOGICAL PROPERTIES

Category A. 26 Cytostatics

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents

ATC code: LO1AA09

5.1 Pharmacodynamic properties

Mechanism of action

Bendamustine hydrochloride is an alkylating antitumour agent. 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 various leukaemias) 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 t1/2ß after 30 min I.V. infusion of 120 mg/m^2 area to 12 subjects was 28,2 minutes.

Following 30 min I.V. infusion the central volume of distribution was 19,3 litre. 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 dihydroxybendamustine. 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.

Special Patient Populations:

Patients with hepatic impairment:

In patients with 30 to 70 % tumour infiltration of the liver and mild or moderate hepatic impairment [serum bilirubin < 34,2 µmol/ℓ (2,0 mg/dl)] the pharmacokinetic behaviour was not changed.

There was no significant difference to patients with normal liver and kidney function with respect to Cmax, tmax, AUC, t1/2ß , volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Patients with 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 Cmax, tmax, AUC, t1/2ß, volume of distribution and clearance.

Elderly:

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylhydroxytoluene, Macrogol 300

6.2 Incompatibilities

BENDAMUSTINE 180 mg/4 ml DRL must not be mixed with other medicinal products except 0,9 % NaCl solution (see section 4.2).

6.3 Shelf life

36 months

6.4 Special precautions for storage

Unopened vial:

Store and transport refrigerated at 2 ºC to 8 ºC. Do not freeze.

Keep the vial in the outer carton in order to protect the content from light.

KEEP OUT OF REACH OF CHILDREN

After opening vial:

From a microbiological point of view, once opened, the product may be stored for a maximum of 28 days at 2 to 8 ºC.

Diluted Solution:

Solution for infusion:

After dilution, chemical and physical stability has been demonstrated for 3,5 hours at 25 ºC/60 % RH and 2 days at 2 ºC to 8 ºC in polyethylene bags.

Minimisation of the risk of contamination of the multidose vial during withdrawal of each dose is the responsibility of the user. Record date and time of the first dose withdrawal on the vial label. Between uses, return the multidose vial to the recommended storage condition of 2 °C to 8 °C.

6.5 Nature and contents of container

BENDAMUSTINE 180 mg/4 ml DRL is available in a 5 ml Type I amber glass vials with 20 mm grey chlorobutyl coated rubber stopper and an aluminium flip-off seal with a red plastic disc.

Each vial contains bendamustine hydrochloride 180 mg/4 ml concentrate for solution for infusion and are supplied in packs of 1 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When handling BENDAMUSTINE 180 mg/4 ml DRL, 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 concentrate for solution for infusion has to be diluted with sodium chloride 9 mg/ml (0,9 %) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

No special requirements for disposal.

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Dr Reddy's Laboratories (Pty) Ltd

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2057

8 REGISTRATION NUMBER(S)

BENDAMUSTINE 180 mg / 4 ml DRL: 56/26/0216

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 21 February 2023

10 DATE OF REVISION OF THE TEXT

N/A