PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BEDURAS 25 mg powder for concentrate for solution for infusion.

BEDURAS 100 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BEDURAS 25 mg: One vial contains 25 mg bendamustine hydrochloride. Contains sugar (42,5 mg mannitol per vial).

BEDURAS 100 mg: One vial contains 100 mg bendamustine hydrochloride. Contains sugar (170 mg mannitol per 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 plug.

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

For intravenous infusion over 30 to 60 minutes.

Infusion must be administered under the supervision of a medical practitioner 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 dropped to < 3 x 10^9/L or < 75 x 10^9/L, respectively (see section 4.3).

Monotherapy for chronic lymphocytic leukaemia

100 mg/m^2 body surface area BEDURAS 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 BEDURAS on days 1 and 2 in combination with 375 mg/m^2 body surface area rituximab as a slow IV infusion on day 1; every 4 weeks.

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

120 mg/m^2 body surface area BEDURAS on days 1 and 2; every 3 weeks.

Multiple myeloma

120 – 150 mg/m^2 body surface area BEDURAS on days 1 and 2, 60 mg/m^2 body surface area prednisone IV 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 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 case of non-haematological toxicity dose reductions have to be based on the worst common toxicity criteria (CTC) grades in the preceding cycle. A 50 % dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity. If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

For preparation and administration instructions see section 6.6.

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.

Paediatric population

There is no experience in children and adolescents with BEDURAS.

Elderly patients

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

Method of administration

The solution is administered by intravenous (IV) infusion over 30 – 60 minutes. The vials are for single use only.

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

4.3 Contraindications

- Hypersensitivity to bendamustine hydrochloride or to any of the excipients in BEDURAS (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 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 hydrochloride, as in BEDURAS, 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). Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of bendamustine mainly in combination with rituximab or obinutuzumab. 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. 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 BEDURAS should be considered if there are signs of (opportunistic) infections.

Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected, appropriate diagnostic evaluations should be undertaken, and treatment suspended until PML is excluded.

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 hepatitis B virus (HBV) infection before initiating

treatment with BEDURAS.

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 BEDURAS 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), 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. When skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, BEDURAS should be withheld or discontinued. For severe skin reactions with suspected relationship to BEDURAS, 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 medicines (allopurinol and rasbuicase) 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 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 BEDURAS because of possible irreversible infertility (see section 4.6).

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.

There have been reports of 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.

Non-melanoma skin cancer

In clinical studies, an increased risk for non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) has been observed in patients treated with bendamustine containing therapies. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

4.5 Interaction with other medicines and other forms of interaction

No *in vivo* interaction studies have been performed.
When BEDURAS is combined with myelosuppressive medicines, the effect of bendamustine hydrochloride 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 hydrochloride.
Combination of bendamustine hydrochloride with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.
Cytostatic medicines 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 patients 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, aciclovir and cimetidine exists.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

Pregnancy

There is insufficient data from the use of bendamustine hydrochloride, as in BEDURAS, in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic. Therefore, BEDURAS is contraindicated during pregnancy (see section 4.3).

Breastfeeding

It is not known whether bendamustine passes into breast milk therefore, BEDURAS is contraindicated during breastfeeding (see section 4.3).

Breastfeeding must be discontinued during treatment with BEDURAS.

Fertility

Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with bendamustine hydrochloride.

4.7 Effects on ability to drive and use machines

Bendamustine has major influence on the ability to drive a vehicle 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 frequently occurring adverse reactions with bendamustine hydrochloride are haematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

Adverse reactions in patients treated with bendamustine hydrochloride:

MedDRA system organ class	Frequent	Less frequent	Unknown
Infections and infestations	Infection NOS* (including opportunistic infection (e.g. Herpes zoster, cytomegalovirus, hepatitis B))	*Pneumocystis jirovecii* pneumonia Sepsis Primary atypical pneumonia Tuberculosis	
Neoplasms	Tumour lysis	Myelodysplastic	

MedDRA system organ class	Frequent	Less frequent	Unknown
benign, malignant and unspecified (including cysts and polyps)	syndrome	syndrome Acute myeloid leukaemia	
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombo-cytopenia Lymphopenia Haemorrhage Anaemia Neutropenia	Pancytopenia Bone marrow failure Haemolysis	
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	

MedDRA system organ class	Frequent	Less frequent	Unknown
		Neurological disorders Ataxia Encephalitis	
Cardiac disorders	Cardiac dysfunction (such as palpitations, angina pectoris dysrhythmia, QT prolongation)	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
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Constipation Stomatitis	Haemorrhagic oesophagitis Gastrointestinal haemorrhage	
Hepatobiliary disorders			Hepatic failure
Skin and	Alopecia	Erythema	Stevens-

MedDRA system organ class	Frequent	Less frequent	Unknown
subcutaneous tissue disorders	Skin disorders NOS* Urticaria	Dermatitis Pruritus Macular papular rash Hyperhidrosis	Johnson syndrome Toxic epidermal necrolysis (TEN) Drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders			* Renal failure
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	Decreased:		

MedDRA system organ class	Frequent	Less frequent	Unknown
	haemoglobin levels Increased: creatinine, urea, AST, ALT, alkaline phosphatase, bilirubin Hypokalaemia		

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 (see section 4.4).

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

4.9 Overdose

After application of a 30 minute 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 minute 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

Category and class:

A. 26 Cytostatic agents

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumour medicine 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 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 medicines or rituximab. However, the number of assessed patients is small.

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{½ß}$ after 30 minutes IV infusion of 120 mg/m^2 area to participants was 28,2 minutes.

Following 30 minutes IV infusion the central volume of distribution was 19,3 L. Under steady-state conditions following IV 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 CYP1A4, CYP2C9/10, CYP2D6, CYP2E1 or CYP3A4.

Elimination

The mean total clearance after 30 minutes IV infusion of 120 mg/m^2 body surface area to participants 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, $t_{½ß}$, 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, $t_{½ß}$, volume of distribution and clearance.

Elderly

Participants 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

Mannitol.

6.2 Incompatibilities

BEDURAS must be diluted with 0,9 % sodium chloride and not with any other injectable solution.

6.3 Shelf life

Unopened vial:

24 months.

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 for injection.

Solution for infusion:

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3,5 hours at 25 °C 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.

6.4 Special precautions for storage

Unopened vial:

Store at or below 25 °C.

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

Reconstituted concentrate and solution for infusion:

For storage conditions after reconstitution or dilution, see section 6.3.

6.5 Nature and contents of container

BEDURAS 25 mg: Type I amber glass vial of 20 mL with 20 mm grey bromobutyl double slotted lyo stopper and 20 mm aluminium flip-off red seals. Pack sizes: 1, 5, 10 or 20 vials.

BEDURAS 100 mg: Type I amber glass vial of 50 mL with 20 mm grey bromobutyl double slotted lyo stopper and 20 mm aluminium flip-off red seals. Pack sizes: 1 or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When handling BEDURAS, 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 vial of BEDURAS 25 mg in 10 mL water for injection by shaking.
- Reconstitute each vial of BEDURAS 100 mg 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 BEDURAS immediately with 0,9 % NaCl solution to produce a final volume of about 500 mL.

BEDURAS must be diluted with 0,9 % sodium chloride and not with any other injectable solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

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Tel: 011 247 1600

8. REGISTRATION NUMBERS

BEDURAS 25 mg: 56/26/1123

BEDURAS 100 mg: 56/26/1124

9. DATE OF FIRST AUTHORISATION

12 August 2025

10. DATE OF REVISION OF THE TEXT

To follow