SCHEDULING STATUS: S4

1. NAME OF MEDICINE

SPALBEND 25 or 100 (powder for concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SPALBEND 25: Each vial contains 25 mg bendamustine hydrochloride (as bendamustine hydrochloride monohydrate)

SPALBEND 100: Each vial contains 100 mg bendamustine hydrochloride (as bendamustine hydrochloride monohydrate)

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

SPALBEND 25: Contains sugar (mannitol 30 mg /vial)

SPALBEND 100: Contains sugar (mannitol 120 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 lyophilized powder or cake

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SPALBEND is indicated in patients with the following conditions:

- 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

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 SPALBEND 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 SPALBEND 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 SPALBEND on days 1 and 2; every 3 weeks.

Multiple myeloma

120 - 150 mg/m^2 body surface area SPALBEND on days 1 and 2, 60 mg/m^2 body surface area prednisone IV or per 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 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.

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 section 5.2).

Method of administration

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

Infusion must be administered under the supervision of a healthcare professional qualified and experienced in the use of chemotherapeutic medicines.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy and lactation
- 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 **SPALBEND** 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 10^9/L or > 100 x 10^9/L, respectively.

Infections

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) may be increased. Cases of tuberculosis have been less frequently reported compared to other infections. Latent or dormant tuberculosis may become active.

Infection, including pneumonia and sepsis, has been reported. Infection has been associated with hospitalisation, septic shock and death. Patients with neutropenia and/or lymphopenia following treatment with **SPALBEND** are more susceptible to infections including tuberculosis. Patients with myelosuppression following **SPALBEND** treatment should be advised to contact a medical practitioner if they have symptoms or signs of infection, including fever or respiratory symptoms. The presence of tuberculosis should be excluded before treatment with **SPALBEND** is commenced.

Skin reactions

A number of skin reactions have been reported. These events have included rash, toxic skin reactions and bullous exanthema. Some of these events occurred when **SPALBEND** was given in combination with other anticancer medicines.

Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, **SPALBEND** should be withheld or discontinued. For severe skin reactions where a relationship to **SPALBEND** is suspected, treatment should be discontinued.

Patients with cardiac disorders

During treatment with **SPALBEND** the concentration of potassium in the blood 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.

Nausea, vomiting

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

Tumour lysis syndrome

Tumour lysis syndrome associated with bendamustine, as contained in **SPALBEND,** treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of **SPALBEND** 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 allopurinol during the first one to two weeks of **SPALBEND** therapy can be considered. However, there have been cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when **SPALBEND** and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to bendamustine, as contained in **SPALBEND,** have occurred commonly in clinical trials. 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, **SPALBEND** should be discontinued.

Contraception

SPALBEND 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 **SPALBEND** 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.

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

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).

Secondary tumours

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 **SPALBEND** is combined with myelosuppressive medicines, the effect of **SPALBEND** 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 **SPALBEND**.

Combination of **SPALBEND** with ciclosporin or tacrolimus may result in excessive immunosuppression with risk of lymph proliferation.

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 patients who are already immunosuppressed by their underlying disease.

Bendamustine 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of **SPALBEND** in pregnant women.

In nonclinical studies **SPALBEND** was embryo-/foetolethal, teratogenic and genotoxic. Therefore, **SPALBEND** is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential/contraception

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

Men being treated with **SPALBEND** 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 **SPALBEND**.

Breastfeeding

It is not known whether **SPALBEND** passes into the breast milk. Treatment with **SPALBEND** is therefore contraindicated during breastfeeding (see section 4.3). Mothers on **SPALBEND** must not breastfeed their babies.

4.7 Effects on ability to drive and use machines

SPALBEND has major influence on the ability to drive and use machines.

Ataxia, peripheral neuropathy and somnolence have been reported during treatment with bendamustine hydrochloride as contained in **SPALBEND** (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 frequent side effects with **SPALBEND** are haematological adverse reactions (leucopenia, thrombocytopenia), 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**	**Frequency unknown**
Infections and infestations	Infection NOS*, Including Opportunistic infection (e.g. Herpes zoster, cytomegalovirus, hepatitis B)	Pneumocystis jirovecii pneumonia, Sepsis, Pneumonia primary atypical	
Neoplasma benign, malignant and unspecified (including cyst and polyp)	Tumour lysis syndrome	Myelodysplastic syndrome, acute myeloid leukemia	
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombocytopenia, 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, Neurological disorders, Ataxia, Encephalitis	
Cardiac disorders	Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia	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	
Skin and subcutaneous tissue disorders	Alopecia, Skin disorders NOS* Urticaria	Erythema, Dermatitis, Pruritus, Maculopapular rash, Hyperhidrosis	Stevens – Johnson syndrom Epidermal Necrolysis (TEN) Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Reproductive system and breast disorders	Amenorrhea	Infertility	
Renal and urinary disorders			Renal failure
Hepatobiliary disorder			Hepatic failure
General disorders and administration site conditions	Mucosal inflammation, Fatigue, Pyrexia Pain, Chills, Dehydration, Anorexia	Multi organ failure	
Investigations	Haemoglobin decrease,		

	Creatinine increase, Urea increase AST increase, ALT increase, Alkaline phosphatase increase, Bilirubin increase, Hypokalemia		

NOS = Not otherwise specified

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 to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

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

Counter measures

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

Bendamustine and its metabolites are dialysable to a small extent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents

ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumour compound. 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 medicines 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 IV infusion of 120 mg/ m^2 area to 12 subjects was 28,2 minutes. Following 30 min 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 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 IV 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:

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

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

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

From a microbiological point of view, the product should be used immediately.

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.

KEEP OUT OF REACH OF CHILDREN

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 ºC and 2 days at 2 ºC to 8 ºC in polyethylene bags.

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

6.5 Nature and contents of container

SPALBEND 25: Type I amber glass vials of 20 ml with 20 mm bromobutyl (single slotted) lyo stopper along with 20 mm easy to open C/L ALU, seals with matte finish plastic german blue in packs of 1, 5 or 10

SPALBEND 100: Type I amber glass vials of 50 ml with 20 mm bromobutyl (single slotted) lyo stopper along with 20 mm easy to open C/L ALU, seals with matte finish plastic german blue packs of 1, 5 or 10

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

When handling bendamustine, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes!). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution. If possible, it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, 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 bendamustine hydrochloride 2.5 mg/mL powder for concentrate for solution for infusion containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking.

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

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

2. Dilution

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

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

3. Administration

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

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

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban, 4091

8 REGISTRATION NUMBER(S)

Spalbend 25: 55/26/0639

Spalbend 100: 55/26/0640

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT