SCHEDULING STATUS: S4

1. NAME OF MEDICINE:

RIBEND 25 mg (powder for concentrate for solution for infusion). For single use only.

RIBEND 100 mg (powder for concentrate for solution for infusion). For single use only.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

RIBEND 25 mg: One vial contains 25 mg bendamustine hydrochloride (sterile active ingredient).

RIBEND 100 mg: One vial contains 100 mg bendamustine hydrochloride (sterile active ingredient).

1 ml of the concentrate contains 2,5 mg bendamustine hydrochloride when reconstituted according to **section 4.2**.

Sugar free

For full list of excipients, **see section 6.1.**

3. PHARMACEUTICAL FORM:

RIBEND 25 mg: White, microcrystalline lyophilisate.

RIBEND 100 mg: White, microcrystalline lyophilisate.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

RIBEND 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

Posology

RIBEND is used for intravenous infusion over 30 to 60 minutes.

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

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity. Treatment should not be started if leukocyte and/or platelet values dropped to < 3 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 **RIBEND** 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 **RIBEND** on days 1 and 2 in combination with 375 mg/m2 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 RIBEND

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

Multiple Myeloma

120-150 mg/m^2 body surface area **RIBEND** on days 1 and 2, 60 mg/m^2 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 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 preparation and administration instructions see **Method of administration**.

Special populations

Elderly population:

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

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.

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)].

Paediatric population

There is no experience in children and adolescents with **RIBEND**.

Method of administration

When handling **RIBEND**, 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.

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

4.3 Contraindications

RIBEND is contraindicated:

- In hypersensitivity to bendamustine, 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 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 **RIBEND** 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 **RIBEND** are more susceptible to infections including tuberculosis. Patients with myelosuppression following **RIBEND** treatment should be advised to contact a healthcare provider if they have symptoms or signs of infection, including fever or respiratory symptoms. The presence of tuberculosis should be excluded before treatment with **RIBEND** 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 bendamustine hydrochloride was given in combination with other anticancer agents.

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

Patients with cardiac disorders

During treatment with **RIBEND** 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. It was reported that 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 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 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 **RIBEND** therapy can be considered. However, there have been cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine hydrochloride and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to **RIBEND** 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, **RIBEND** should be discontinued.

Contraception

RIBEND 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 **RIBEND** 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.

It was reported that necrosis after accidental extra-vascular administration and toxic epidermal necrosis, tumour lysis syndrome, and anaphylaxis.

It was reported that secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma.

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 **RIBEND**. 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 **RIBEND** should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

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

It was reported that no in-vivo interaction studies have been performed.

When **RIBEND** is combined with myelosuppressive agents, the effect of **RIBEND** 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 **RIBEND**.

Combination of **RIBEND** 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.

RIBEND metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir, and cimetidine exists.

<u>Incompatibilities</u>

RIBEND must not be mixed with other medicines except those mentioned in section 4.2, method of administration.

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 **RIBEND** therapy.

Men being treated with **RIBEND** are advised not to father a child during and up to 6 months following cessation of treatment.

Pregnancy:

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

It was reported that in nonclinical studies bendamustine was embryo-/foetolethal, teratogenic and genotoxic. Therefore, **RIBEND** is contraindicated during pregnancy.

Breastfeeding:

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

Fertility:

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

4.7 Effects on the ability to drive and use machines

It was reported no studies have been performed on the effects on the ability to drive and use machines. However, 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

Summary of the safety profile

The most frequent side effects with **RIBEND** are haematological adverse reactions (leucopenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

Listed summary of adverse reactions

Infections and infestations

Frequent: Infections (not otherwise specified), including opportunistic infection (e.g., Herpes zoster, cytomegalovirus hepatitis B).

Less frequent: Primary atypical pneumonia, septicaemia and tuberculosis, Pneumocystis jirovencii pneumonia.

Blood and lymphatic system disorders

Frequent: Anaemia, haemorrhage, leucopenia (not otherwise specified), lymphopenia, neutropenia, thrombocytopenia.

Less frequent: Haemolysis, pancytopenia, bone marrow failure.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Frequent: Tumour lysis syndrome

Less frequent: Myelodysplastic syndrome, acute myeloid, leukemia

Immune system disorders

Frequent: Hypersensitivity (not otherwise specified)

Less frequent: Anaphylactic reaction, anaphylactic shock and anaphylactoid reaction.

Nervous system disorders

Frequent: Insomnia, headache, dizziness.

Less frequent: Anticholinergic syndrome, aphonia, ataxia, dysgeusia, encephalitis, neurological disorders, paraesthesia, peripheral sensory neuropathy and somnolence.

Cardiac disorders

Frequent: Cardiac dysfunction, such as angina pectoris, dysrhythmia, palpitations, QT prolongation and tachycardia.

Less frequent: Cardiac failure, myocardial infarction, pericardial effusion and tachycardia.

Frequency not known: Atrial fibrillation

Vascular disorders

Frequent: Hypertension and hypotension.

Less frequent: Acute circulatory failure and phlebitis.

Respiratory, thoracic and mediastinal disorders

Frequent: Pulmonary dysfunction

Less frequent: Pulmonary fibrosis.

Gastrointestinal disorders

Frequent: Constipation, diarrhoea, nausea, stomatitis, and vomiting.

Less frequent: Gastrointestinal haemorrhage and haemorrhagic oesophagitis.

Hepato-biliary disorders

Frequency not known: hepatic failure

Skin and subcutaneous tissue disorders

Frequent: Alopecia, skin disorders (not otherwise specified), urticaria

Less frequent: dermatitis, erythema, hyperhidrosis, maculo-papular rash and pruritis.

Frequency not known: Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), 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: Anorexia, chills, dehydration, fatigue, mucosal inflammation and pyrexia, pain

Less frequent: multi-organ failure

Investigations

Frequent: Decreased haemoglobin, hypokalaemia, increased alkaline phosphate, increased ALT, increase AST, increased bilirubin, increased creatinine and increased urea and tumor lysis syndrome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications: hppts://www.sahpra.or.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.

It was reported in a subsequent study with a 30 min infusion of bendamustine hydrochloride at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m2. The dose limiting toxicity was grade 4, thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Counter measures

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

RIBEND 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 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/m2 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/m2 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 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.

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

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

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ˚C

Protect from moisture and sunlight.

6.5 Nature and contents of container

Immediate container

Clear brown glass vial (10R, 50H), type I

Bromobutyl rubber stopper, 20 mm

Flip-Off Seal, 20 mm

Secondary container

Colourful, carton folded box

Leaflet

6.6 Special precautions for disposal and other handling

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

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 **RIBEND** containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking.
- Reconstitute each vial of **RIBEND** 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 **RIBEND** immediately with 0,9 % NaCl solution to produce a final volume of about 500 ml.

RIBEND 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

Innovata Pharmaceuticals (Pty) LTD

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

TBI

9. Date of first authorization/Renewal of the authorization

TBI

10. Date of revision of the text

TBI

REFERENCES:

1. **Reference 1:** Ribomustin® PI, Astellas Pharma South Africa (Pty) Ltd: 29 July 2016.
2. **Reference 2:** Bendamustine hydrochloride 2.5 mg/ml powder for concentrate for solution for infusion. SmPC

   Date of first authorisation/Date of renewal of the authorisation: 07/12/2015

Date of revision of the text: 12/2020

Name of registration holder: Dr. Reddy's Laboratories (UK) Ltd, 6 Riverview Road,

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