SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

RIBOMUSTIN 25 mg (powder for concentrate for solution for infusion).

RIBOMUSTIN 100 mg (powder for concentrate for solution for infusion).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RIBOMUSTIN 25 mg: One vial contains 25 mg bendamustine hydrochloride (sterile active ingredient). Contains sugar- Mannitol 30 mg /vial

RIBOMUSTIN 100 mg: One vial contains 100 mg bendamustine hydrochloride (sterile active ingredient). Contains sugar - Mannitol 120 mg /vial

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

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White, microcrystalline lyophilizate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ribomustin™ (bendamustine hydrochloride) powder for reconstitution 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

4.2.1 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 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 $10^9/\ell$ or < 75 x $10^9/\ell$, respectively (see section 4.3).

Monotherapy for chronic lymphocytic leukaemia

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

Multiple Myeloma

120-150 mg/m^2 body surface area RIBOMUSTIN 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 administration, see Section 4.2.4 *Method of Administration* and for preparation, see section 6.6.

4.2.2 Special Populations

Elderly patients

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

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment [serum bilirubin < 20,52 µmol/ℓ (< 1,2 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)].

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.

4.2.3 Paediatric Population

There is no experience in children and adolescents with RIBOMUSTIN.

4.2.4 Method of Administration

For single use only

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

See section 6.6 for instructions for reconstitution.

Any unused product or waste material should be disposed of in accordance with local requirements (see section 6.6).

4.3 Contraindications

- Hypersensitivity to bendamustine or to any of the excipients in RIBOMUSTIN (see section 6.1)
- Pregnancy and lactation (see section 4.6)

- Severe hepatic impairment [serum bilirubin > 51,3 µmol/ℓ (3 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 RIBOMUSTIN 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

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 RIBOMUSTIN is commenced.

Serious and fatal infections have occurred with RIBOMUSTIN, including tuberculosis, bacterial (sepsis, pneumonia) and opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP), *varicella zoster* virus (VZV) and cytomegalovirus (CMV).

Treatment with RIBOMUSTIN 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. Infection has been associated with hospitalisation, septic shock, and death.

Patients with lymphopenia and low CD4-positive T-cell count following treatment with RIBOMUSTIN are more susceptible to opportunistic infections including tuberculosis. Patients with myelosuppression following RIBOMUSTIN treatment should be advised to contact a medical practitioner if they have symptoms or signs of infection, including fever or respiratory symptoms.

Therefore, 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 RIBOMUSTIN should be considered if there are signs of (opportunistic) infections.

Cytomegalovirus and herpes virus reactivation have been reported and may occur.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received RIBOMUSTIN. Some cases resulted in acute hepatic failure or fatal outcome.

Patients should be tested for HBV infection before initiating treatment with RIBOMUSTIN. 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 RIBOMUSTIN should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see Side Effects).

Skin reactions

A number of skin reactions have been reported which include rash, severe cutaneous reactions, and bullous exanthema. Cases of Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported with the use of RIBOMUSTIN.

Some of these events occurred when RIBOMUSTIN was given in combination with other anticancer agents.

Cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with the use of RIBOMUSTIN in combination with rituximab.

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

Cardiac disorders

Fatal cases of myocardial infarction and cardiac failure have been reported with RIBOMUSTIN treatment. Patients with concurrent or history of cardiac disease should be observed closely. QTcf was prolonged by more than 30 msecs in 4 of 9 patients studied.

During treatment with RIBOMUSTIN 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 a potassium supplement must be given.

Nausea, vomiting

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

Tumour lysis syndrome

Tumour lysis syndrome (TLS) associated with RIBOMUSTIN treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of RIBOMUSTIN 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 hypouricaemic medicines (allopurinol and rasburicase) should be considered prior to and during therapy with RIBOMUSTIN.

There have been cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when RIBOMUSTIN and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to RIBOMUSTIN have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash.

Severe anaphylactic and anaphylactoid reactions have occurred. Patients must be questioned 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, RIBOMUSTIN should be discontinued.

Contraception

RIBOMUSTIN is teratogenic and mutagenic (see section 4.3 and 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 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.

4.5 Interaction with other medicines and other forms of interaction

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

When RIBOMUSTIN is combined with myelosuppressive agents, the effect of RIBOMUSTIN 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 RIBOMUSTIN.

Combination of RIBOMUSTIN with ciclosporin or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

RIBOMUSTIN 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 (see section 4.3).

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

4.6 Fertility, pregnancy, and lactation

RIBOMUSTIN is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential/Contraception in males and females

RIBOMUSTIN therapy may cause teratogenicity and other reproductive adverse events due to its genotoxic nature. In males, RIBOMUSTIN may cause DNA damage in the sperm, potentially resulting in adverse events in the embryo or foetus of a female sexual partner. In females, RIBOMUSTIN may directly affect the embryo or foetus; or may cause DNA damage in the oocytes.

To minimise the risk of drug-induced heritable DNA damage and to ensure that genomic integrity of gametes at the time of conception is maintained, women of childbearing potential, that is female patients using RIBOMUSTIN and female sexual partners of male patients receiving this product are generally advised to use highly effective contraception during treatment and for an adequate period, following the end of treatment.

Male patients should be advised to use highly effective contraception while receiving treatment with RIBOMUSTIN, until the end of relevant systemic exposure to this product, including its potential genotoxic metabolites (i.e., five half-lives after the last dose) plus 90 days (i.e., 60–75 days for sperm production plus 10–14 days for the transport to the epididymis). Male patients should not father a child during and up to 3 months after treatment. They should seek advice about sperm conservation prior to treatment with RIBOMUSTIN because of possible irreversible infertility

Women of childbearing potential, that is female patients using RIBOMUSTIN and female sexual partners of male patients receiving this product, should be advised to use highly effective contraception until the end of relevant systemic exposure to RIBOMUSTIN, including its potential genotoxic metabolites (i.e., five half-lives after the last dose) plus 6 months (which covers the growth and maturation phase of folliculogenesis). It is therefore suggested that contraception continue for at least 6 months after treatment.

Pregnancy

Women should not become pregnant during treatment.

Breastfeeding

It is not known whether RIBOMUSTIN passes into breast milk.

Treatment with RIBOMUSTIN is contraindicated during breastfeeding (see section 4.3).

Mothers on RIBOMUSTIN must not breastfeed their babies.

Fertility

In nonclinical studies, RIBOMUSTIN was embryo-/foetolethal, teratogenic, mutagenic, and genotoxic.

4.7 Effects on ability to drive and use machines

RIBOMUSTIN influences the ability to drive and use machines. Ataxia, peripheral neuropathy, and somnolence have been reported during treatment with RIBOMUSTIN (see section 4.8). Patients should be instructed to avoid potentially hazardous tasks such as driving and using machines while on treatment with RIBOMUSTIN.

4.8 Undesirable effects

a. Summary of the safety profile

The most common side effects with RIBOMUSTIN are haematological adverse reactions (leukopenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

b. Tabulated summary of adverse reactions

The frequency of side effects is classified as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000) or very rare (< 1/10 000).

Infections and infestations

Very common:	Infection (not otherwise specified), including opportunistic infections (e.g. *Herpes zoster*, cytomegalovirus, hepatitis B)
Uncommon:	*Pneumocystis jirovecii* pneumonia
Rare:	Septicaemia
Very rare:	Primary atypical pneumonia, tuberculosis

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

Common:	Tumour lysis syndrome
Uncommon:	Myelodysplastic syndrome, acute myeloid leukaemia

Blood and lymphatic system disorders

Very common:	Leukopenia (not otherwise specified), thrombocytopenia, lymphopenia
Common:	Haemorrhage, anaemia, neutropenia
Uncommon:	Pancytopenia
Rare:	Bone marrow failure
Very rare:	Haemolysis

Immune system disorders

Common:	Hypersensitivity (not otherwise specified)
Rare:	Anaphylactic reaction, anaphylactoid reaction
Very rare:	Anaphylactic shock

Nervous system disorders

Very common:	Headache
Common:	Insomnia, dizziness
Rare:	Somnolence, aphonia

Very rare: Dysgeusia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, neurological disorders, ataxia, encephalitis

Cardiac disorders

Common: Cardiac dysfunction, such as palpitations, angina pectoris; dysrhythmia, QT prolongation

Uncommon: Pericardial effusion, myocardial infarction, cardiac failure

Very rare: Tachycardia

Not known (cannot be estimated from the available data): Atrial fibrillation

Vascular disorders

Common: Hypotension, hypertension

Rare: Acute circulatory failure

Very rare: Phlebitis

Respiratory, thoracic and mediastinal disorders

Common: Pulmonary dysfunction

Very rare: Pulmonary fibrosis

Not known (cannot be estimated from the available data): Pneumonitis, pulmonary alveolar haemorrhage

Gastrointestinal disorders

Very common: Nausea, vomiting

Common: Diarrhoea, constipation, stomatitis

Very rare: Haemorrhagic oesophagitis, gastrointestinal haemorrhage

Hepatobiliary disorders

Not known (cannot be estimated from the available data): Hepatic failure

Skin and subcutaneous tissue disorders

Common: Alopecia, skin disorders (not otherwise specified)

Rare: Erythema, dermatitis, pruritus, maculo-papular rash, hyperhidrosis

Not known (cannot be estimated from the available data):

Stevens-Johnson syndrome, Toxic Epidermal Necrolysis

Drug reaction with eosinophilia and systemic symptoms (DRESS)*

* combination therapy with rituximab

Renal and urinary disorders

Not known (cannot be estimated from the available data): Renal failure.

Risk of nephrogenic diabetes insipidus

Reproductive system and breast disorders

Common: Amenorrhoea

Very rare: Infertility

General disorders and administration site conditions

Very common: Mucosal inflammation, fatigue, pyrexia

Common: Pain, chills, dehydration, anorexia

Very rare: Multi-organ failure

Investigations

Very common: Decreased haemoglobin, increased creatinine, increased urea

Common: Increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, hypokalaemia.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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.

RIBOMUSTIN and its metabolites are dialysable to a small extent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 $t_{1/2ß}$ 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 litres. Under steady-state conditions following i.v. bolus injection the volume of distribution was 15,8 – 20,5 ℓ.

More than 95 % of the substance is bound to plasma proteins (primarily albumin).

Biotransformation

A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and 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.

Hepatic impairment

In patients with 30 to 70 % tumour infiltration of the liver and mild or moderate hepatic impairment [serum bilirubin < 20,52 µmol/ℓ (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 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

Nitrogen

6.2 Incompatibilities

RIBOMUSTIN must not be mixed with other medicinal liquids, solutions, etc., except those mentioned in section 6.6.

6.3 Shelf-life

36 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 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.

6.4 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.

For storage conditions after reconstitution or dilution of the medicinal product, see Section 6.3.

6.5 Nature and contents of container

RIBOMUSTIN 25 mg is available in Type I brown glass vials of 26 ml with 20 mm grey bromobutyl/silicate rubber stopper and an aluminium flip-off cap with a blue polypropylene disc. 26 ml vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 and 20 vials.

RIBOMUSTIN 100 mg is available in Type I brown glass vials of 60 ml with 20 mm grey bromobutyl/silicate rubber stopper and an aluminium flip-off cap with a blue polypropylene disc. 60 ml vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

6.6 Special precautions for disposal and other handling

When handling RIBOMUSTIN, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution. If possible, it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbing disposable foil. Pregnant personnel should be excluded from handling cytostatics.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/ml (0,9 %) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution

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

RIBOMUSTIN must be diluted with 0,9 % NaCl solution and not with any other injectable solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Kiara Health (Pty) Ltd, 72 Steel Road, Spartan, Kempton Park, 1619, South Africa

customercare@kiarahealth.com

8. REGISTRATION NUMBERS

RIBOMUSTIN 25 mg: 45/26/1127

RIBOMUSTIN 100 mg: 45/26/1128

9. DATE OF FIRST AUTHORISATION

10 October 2013

10. DATE OF REVISION OF TEXT

27 August 2025