RIBOMUSTIN®

bendamustine hydrochloride

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

RIBOMUSTIN 25 mg Powder for infusion

RIBOMUSTIN 100 mg Powder for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 mg vial contains 25 mg of bendamustine hydrochloride and 30 mg of mannitol.

Each 100 mg vial contains 100 mg of bendamustine hydrochloride and 120 mg of mannitol.

RIBOMUSTIN contains bendamustine hydrochloride, an alkylating drug, as the active ingredient. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent.

The pH of the reconstituted solution is 2.5 - 3.5.

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

3. PHARMACEUTICAL FORM

RIBOMUSTIN (bendamustine hydrochloride) powder for concentrate for solution for infusion is a lyophilised product.

It is administered by intravenous infusion after reconstitution with 10 mL (for the 25 mg vial) or 40 mL (for the 100 mg vial) water for injection and further dilution with physiological saline (0.9%).

White, microcrystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

First line treatment of Chronic Lymphocytic Leukaemia (Binet stage B or C).

Previously untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma. RIBOMUSTIN should be used in combination with rituximab in CD20 positive patients.

Relapsed/Refractory indolent Non-Hodgkin's lymphoma.

4.2 Dose and method of administration

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

Infusion must be administered under the supervision of a physician 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 $< 3x10^9$/L or $< 75x10^9$/L, respectively (see **section 4.4**).

Monotherapy for chronic lymphocytic leukaemia

100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks, for up to 6 cycles.

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

120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks, for at least 6 cycles.

Combination therapy with rituximab for first-line non-Hodgkin's lymphoma and mantle cell lymphoma

90 mg/m^2 on days 1 and 2 of a 4-week cycle for up to 6 cycles.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to < 3x10^9/L or < 75x10^9/L, respectively. Treatment can be continued after leukocyte values have increased to > 4x10^9/L and platelet values to > 100x10^9/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.

Special populations

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 Patients

There is no experience in children and adolescents with bendamustine.

Elderly Patients

There is no evidence that dose adjustments are necessary in elderly patients.

Method of administration

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.

3. Administration

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

4.3 Contraindications

RIBOMUSTIN is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment (serum bilirubin > 3.0 mg/dL)
- Jaundice
- Severe bone marrow suppression and severe blood count alteration (leukocyte and/or platelet values dropped to < $3x10^9$/L or <$75x10^9$/L, respectively)
- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopaenia
- Yellow fever vaccination
- RIBOMUSTIN is also contraindicated during breast-feeding.

4.4 Special warnings and precautions for use

Myelosuppression

Patients treated with RIBOMUSTIN may experience bone marrow failure. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Treatment-related myelosuppression may require dose adjustment and/or dose delays.

Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 0.6 x 10^9/L) and low CD4-positive T-cell (T-helper cell) counts (< 0.2 x 10^9/L) 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.

Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > $4x10^9$/L or > $100x10^9$/L, respectively.

RIBOMUSTIN should not be used during severe bone marrow suppression and severe blood count alterations (see **section 4.2**).

Infections

Serious and fatal infections, including fatal sepsis, have occurred with bendamustine treatment. These infections included bacterial (pneumonia) and opportunistic infections such as *Pneumocystis Jirovecii* Pneumonia (PJP), Varicella Zoster Virus (VZV), Cytomegalovirus (CMV), and progressive multifocal leukoencephalopathy (John Cunningham virus). 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 (< 0.2 x 10^9/L) *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis should be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections.

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. For patients with hepatitis B serology indicative of prior infection, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation. Monitoring should continue for several months following termination of therapy (see section 4.8).

Skin Reactions

A number of skin reactions have been reported. These events have included rash, severe cutaneous reactions and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have also been reported. Some events of SJS and TEN occurred when bendamustine hydrochloride was administered concomitantly with allopurinol or when bendamustine hydrochloride was given in combination with other anticancer agents. Cases of drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of bendamustine hydrochloride in combination with rituximab. 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. 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 bendamustine hydrochloride is suspected, treatment should be discontinued**.**

Patients with Cardiac Disorders

During treatment with RIBOMUSTIN the concentration of potassium in the blood 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 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 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 include adequate volume status, close monitoring of blood chemistry, particularly potassium and uric acid levels. The use of allopurinol during the first one to two weeks of RIBOMUSTIN therapy can be considered but not necessarily as standard. However, there have been a few cases of Stevens-Johnson Syndrome and Toxic Necrolysis reported when bendamustine and allopurinol are concomitantly administered.

Anaphylaxis

Infusion reactions to bendamustine hydrochloride have occurred in clinical trials. Symptoms are generally mild and 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.

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

Other Malignancies

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.

Paediatric Use

There is no experience in children and adolescents with RIBOMUSTIN.

4.5 Interactions with other medicines and other forms of interactions

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

When RIBOMUSTIN is combined with myelosuppresive 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 cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoroliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme (see **section 5.2**). Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir, cimetidine exists.

4.6 Fertility, pregnancy & lactation

Use in Pregnancy

Category C

There are insufficient data from the use of RIBOMUSTIN in pregnant women. In nonclinical studies bendamustine was embryo-/feto lethal, teratogenic and genotoxic.

During pregnancy RIBOMUSTIN should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with RIBOMUSTIN is absolutely necessary during pregnancy or if pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

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

Men being treated with RIBOMUSTIN 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 RIBOMUSTIN.

Use in Lactation

It is not known whether bendamustine passes into the breast milk, therefore, bendamustine is contraindicated during breast-feeding (see **section 4.3**). Breast-feeding must be discontinued during treatment with bendamustine.

4.7 Effects of ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, somnolence has been reported during treatment with RIBOMUSTIN (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

Clinical Trials Data

Chronic Lymphocytic Lymphoma:

The following tables describe the safety results reported in study 02CLLIII of 161 previously-untreated patients with Binet Stage B or C CLL requiring treatment.

Table 1: Adverse events occurring in at least 5% of patients in either treatment group by system organ class and preferred term – safety population

System Organ Class Preferred Term	**BEN** (N = 161)	**CLB** (N=151)	**Total** (N=312)
Blood & lymphatic system disorders			
Neutropaenia	44 (27.3%)	21 (13.9%)	65 (20.8%)
Thrombocytopaenia	40 (24.8%)	31 (20.5%)	71 (22.8%)
Anaemia	35 (21.7%)	21 (13.9%)	56 (17.9%)
Leukopaenia	28 (17.4%)	5 (3.3%)	33 (10.6%)
lymphopaenia	10 (6.2%)	1 (0.7%)	11 (3.5%)
Gastrointestinal disorders			
Nausea	31 (19.3%)	21 (13.9%)	52 (16.7%)
Vomiting	25 (15.5%)	10 (6.6%)	35 (11.2%)

System Organ Class Preferred Term	BEN (N = 161)	CLB (N=151)	Total (N=312)
Diarrhoea	16 (9.9%)	6 (4.0%)	22 (7.1%)
General disorders & administration site conditions			
Pyrexia	40 (24.8%)	8 (5.3%)	48 (15.4%)
Asthenia	14 (8.7%)	7 (4.6%)	21 (6.7%)
Fatigue	14 (8.7%)	7 (4.6%)	21 (6.7%)
Chills	9 (5.6%)	2 (1.3%)	11 (3.5%)
Immune system disorders			
Hypersensitivity	8 (5.0%)	3 (2.0%)	11 (3.5%)
Infections & infestations			
Nasopharyngitis	11 (6.8%)	11 (7.3%)	22 (7.1%)
Infection	10 (6.2%)	2 (1.3%)	12 (3.8%)
Investigations			
Weight decreased	9 (5.6%)	5 (3.3%)	14 (4.5%)
Metabolism & nutrition disorders			
Hyperuricaemia	12 (7.5%)	2 (1.3%)	14 (4.5%)
Respiratory, thoracic & mediastinal disorders			
Cough	10 (6.2%)	7 (4.6%)	17 (5.4%)
Skin & subcutaneous tissue disorders			
Rash	15 (9.3%)	7 (4.6%)	22 (7.1%)
Pruritus	8 (5.0%)	4 (2.6%)	12 (3.8%)

Note: Patients are counted only once in each preferred term category and only once in each system organ class. Within each system organ class preferred terms were sorted descending according the frequency in the BEN group.

A total of 50 patients had 60 serious adverse events. Most frequently occurring serious adverse events in the bendamustine group were hypersensitivity and pneumonia (each with 3 patients) and anemia, vomiting, pyrexia and tumour lysis syndrome (each with 2 patients). Most frequent documented serious adverse event in the chlorambucil group was herpes zoster (with 2 patients). All other events were documented only once by patient.

Table 2: Serious adverse events by system organ class and preferred term – safety population

System Organ Class Preferred Term	BEN (N=161)	CLB (N=151)	Total (N=312)
Blood & lymphatic system disorders	**5 (3.1%)**	**1 (0.7%)**	**6 (1.9%)**
Anaemia	2 (1.2%)	0 (0.0%)	2 (0.6%)
Anaemia haemolytic autoimmune	1 (0.6%)	0 (0.0%)	1 (0.3%)
Autoimmune thrombocytopenia	1 (0.6%)	0 (0.0%)	1 (0.3%)
Haemolysis	1 (0.6%)	0 (0.0%)	1 (0.3%)
Pancytopaenia	1 (0.6%)	0 (0.0%)	1 (0.3%)
Haemolytic anaemia	0 (0.0%)	1 (0.7%)	1 (0.3%)
Cardiac disorders	**1 (0.6%)**	**1 (0.7%)**	**2 (0.6%)**
Myocardial infarction	1 (0.6%)	0 (0.0%)	1 (0.3%)
Cardiac failure	0 (0.0%)	1 (0.7%)	1 (0.3%)
Eye disorders	**1 (0.6%)**	**0 (0.0%)**	**1 (0.3%)**
Retinal detachment	1 (0.6%)	0 (0.0%)	1 (0.3%)
Gastrointestinal disorders	**2 (1.2%)**	**2 (1.3%)**	**4 (1.3%)**

System Organ Class Preferred Term	BEN (N=161)	CLB (N=151)	Total (N=312)
Vomiting	2 (1.2%)	0 (0.0%)	2 (0.6%)
Abdominal pain	0 (0.0%)	1 (0.7%)	1 (0.3%)
Retroperitoneal haematoma	0 (0.0%)	1 (0.7%)	1 (0.3%)
General disorders & administration site conditions	**4 (2.5%)**	**1 (0.7%)**	**5 (1.6%)**
Pyrexia	2 (1.2%)	1 (0.7%)	3 (1.0%)
Chest pain	1 (0.6%)	0 (0.0%)	1 (0.3%)
General physical health deterioration	1 (0.6%)	0 (0.0%)	1 (0.3%)
Hepatobiliary disorders	**1 (0.6%)**	**1 (0.7%)**	**2 (0.6%)**
Gallbladder pain	1 (0.6%)	0 (0.0%)	1 (0.3%)
Hepatic lesion	0 (0.0%)	1 (0.7%)	1 (0.3%)
Immune system disorders	**3 (1.9%)**	**1 (0.7%)**	**4 (1.3%)**
Hypersensitivity	3 (1.9%)	1 (0.7%)	4 (1.3%)
Infections & infestations	**7 (4.3%)**	**7 (4.6%)**	**14 (4.5%)**
Pneumonia	3 (1.9%)	0 (0.0%)	3 (1.0%)
Herpes zoster	1 (0.6%)	2 (1.3%)	3 (1.0%)
Infection	1 (0.6%)	0 (0.0%)	1 (0.3%)
Respiratory tract infection	1 (0.6%)	0 (0.0%)	1 (0.3%)
Sepsis	1 (0.6%)	0 (0.0%)	1 (0.3%)
Acarodermatitis	0 (0.0%)	1 (0.7%)	1 (0.3%)
Hepatitis B	0 (0.0%)	1 (0.7%)	1 (0.3%)
Meningitis	0 (0.0%)	1 (0.7%)	1 (0.3%)
Pneumonia bacterial	0 (0.0%)	1 (0.7%)	1 (0.3%)
Upper respiratory tract infection	0 (0.0%)	1 (0.7%)	1 (0.3%)
Injury, poisoning & procedural complications	**0 (0.0%)**	**1 (0.7%)**	**1 (0.3%)**
Head injury	0 (0.0%)	1 (0.7%)	1 (0.3%)
Metabolism & nutrition disorders	**1 (0.6%)**	**0 (0.0%)**	**1 (0.3%)**
Dehydration	1 (0.6%)	0 (0.0%)	1 (0.3%)
Musculoskeletal & connective tissue disorders	**1 (0.6%)**	**0 (0.0%)**	**1 (0.3%)**
Sacral pain	1 (0.6%)	0 (0.0%)	1 (0.3%)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	**3 (1.9%)**	**0 (0.0%)**	**3 (1.0%)**
Tumour lysis syndrome	2 (1.2%)	0 (0.0%)	2 (0.6%)
Lung neoplasm	1 (0.6%)	0 (0.0%)	1 (0.3%)
Nervous system disorders	**1 (0.6%)**	**1 (0.7%)**	**2 (0.6%)**
Paraplegia	1 (0.6%)	0 (0.0%)	1 (0.3%)
Neuralgia	0 (0.0%)	1 (0.7%)	1 (0.3%)
Reproductive system & breast disorders	**1 (0.6%)**	**0 (0.0%)**	**1 (0.3%)**
Epididymitis	1 (0.6%)	0 (0.0%)	1 (0.3%)
Respiratory, thoracic & mediastinal disorders	**2 (1.2%)**	**3 (2.0%)**	**5 (1.6%)**
Lung infiltration	1 (0.6%)	0 (0.0%)	1 (0.3%)
Pleural effusion	1 (0.6%)	0 (0.0%)	1 (0.3%)
Epistaxis	0 (0.0%)	1 (0.7%)	1 (0.3%)
Laryngeal oedema	0 (0.0%)	1 (0.7%)	1 (0.3%)
Pulmonary embolism	0 (0.0%)	1 (0.7%)	1 (0.3%)

System Organ Class Preferred Term	BEN (N=161)	CLB (N=151)	Total (N=312)
Skin & subcutaneous tissue disorders	**1 (0.6%)**	**0 (0.0%)**	**1 (0.3%)**
Urticaria	1 (0.6%)	0 (0.0%)	1 (0.3%)
Surgical & medical procedures	**1 (0.6%)**	**0 (0.0%)**	**1 (0.3%)**
Cardiovascular event prophylaxis	1 (0.6%)	0 (0.0%)	1 (0.3%)
Vascular disorders	**2 (1.2%)**	**3 (2.0%)**	**5 (1.6%)**
Phlebitis	1 (0.6%)	1 (0.7%)	2 (0.6%)
Vasculitis	1 (0.6%)	0 (0.0%)	1 (0.3%)
Arterial occlusive disease	0 (0.0%)	1 (0.7%)	1 (0.3%)
Haemorrhage	0 (0.0%)	1 (0.7%)	1 (0.3%)

Note: Patients are counted only once in each preferred term category and only once in each system organ class. Within each system organ class preferred terms were sorted descending according the frequency in the BEN group.

Number of adverse events possible, probable or definite related to the study medication (including missing relationship) was higher in the bendamustine arm than in the chlorambucil arm. Especially blood and lymphatic system disorders, gastrointestinal disorders and pyrexia occurred more frequently under bendamustine than under chlorambucil.

Table 3: Drug related adverse events by CTC category in at least 5% of patients in either treatment group by system organ class and preferred term – safety population

System Organ Class Preferred Term	BEN (N=161)	CLB (N=151)	Total (N=312)
Blood & lymphatic system disorders			
Neutropaenia	43 (26.7%)	21 (13.9%)	64 (20.5%)
Thrombocytopaenia	37 (23.0%)	27 (17.9%)	64 (20.5%)
Anaemia	28 (17.4%)	15 (9.9%)	43 (13.8%)
Leukopaenia	28 (17.4%)	5 (3.3%)	33 (10.6%)
lymphopaenia	10 (6.2%)	1 (0.7%)	11 (3.5%)
Gastrointestinal disorders			
Nausea	31 (19.3%)	21 (13.9%)	52 (16.7%)
Vomiting	24 (14.9%)	9 (6.0%)	33 (10.6%)
Diarrhoea	13 (8.1%)	4 (2.6%)	17 (5.4%)
General disorders & administration site conditions			
Pyrexia	34 (21.1%)	3 (2.0%)	37 (11.9%)
Asthenia	12 (7.5%)	7 (4.6%)	19 (6.1%)
Fatigue	10 (6.2%)	4 (2.6%)	14 (4.5%)
Chills	8 (5.0%)	2 (1.3%)	10 (3.2%)
Infections & infestations			
Infection	8 (5.0%)	1 (0.7%)	9 (2.9%)
Metabolism & nutrition disorders			
Hyperuricaemia	9 (5.6%)	1 (0.7%)	9 (2.9%)
Skin & subcutaneous tissue disorders			
Rash	13 (8.1%)	5 (3.3%)	18 (5.8%)

Note: Patients are counted only once in each preferred term category and only once in each system organ class.

The most frequent adverse reactions leading to study withdrawal for patients receiving RIBOMUSTIN were hypersensitivity (2%) and pyrexia (1%).

Results from the NHL1-2003 Clinical Trial in Patients with Previously Untreated Advanced Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma:

Table 4 and **Table 5** describe safety data from the NHL1-2003 study with previously untreated advanced indolent NHL who received RIBOMUSTIN IV (90 mg/m^2) in combination with rituximab (375 mg/m^2).

Table 4: Haematological toxic events in patients receiving at least one dose of study treatment

	Grade 1		Grade 2		Grade 3		Grade 4		Grade 3–4	
	R-CHOP	**B-R**	**R-CHOP**	**B-R**	**R-CHOP**	**B-R**	**R-CHOP**	**B-R**	**R-CHOP**	**B-R**
Leucocytopaenia	13 (5%)	52 (19%)	39 (15%)	80 (30%)	110 (44%)	85 (32%)	71 (28%)	13 (5%)	181 (72%)*	98 (37%)*
Neutropaenia	6 (2%)	30 (11%)	19 (8%)	61 (23%)	70 (28%)	53 (20%)	103 (41%)	24 (9%)	173 (69%)*	77 (29%)*
Lymphocytopaenia	12 (5%)	14 (5%)	72 (29%)	38 (14%)	87 (35%)	122 (46%)	19 (8%)	74 (28%)	106 (43%)	196 (74%)
Anaemia	115 (46%)	102 (38%)	84 (33%)	44 (16%)	10 (4%)	6 (2%)	2 (<1%)	2 (<1%)	12 (5%)	8 (3%)
Thrombocytopaenia	89 (35%)	104 (39%)	20 (8%)	19 (7%)	11 (4%)	15 (6%)	5 (2%)	2 (<1%)	16 (6%)	13 (5%)

BR=bendamustine plus rituximab; R-CHOP=CHOP plus rituximab; *p<0.0001 between groups.

Table 5: All grades of non-haematological toxic events in patients receiving at least one dose of study treatment

	B-R (n=261)	**R-CHOP (n=253)**	***p* value**
Alopecia	0	245 (100%)*	<0.0001
Parethesia	18 (7%)	73 (29%)	<0.0001
Stomatitis	16 (6%)	47 (19%)	<0.0001
Skin (erythema)	42 (16%)	23 (9%)	0.024
Skin (allergic reaction)	40 (15%)	15 (6%)	0.0006
Infectious episodes	96 (37%)	127 (50%)	0.0025
Sepsis	1 (<1%)	8 (3%)	0.019

B-R=bendamustine plus rituximab; R-CHOP=CHOP plus rituximab.

* Includes only patients who received three or more cycles

Relapsed/Refractory Non-Hodgkin's Lymphoma

Table 6 lists adverse events occurring in at least 5% of patients in study SDX-105-03.

Table 6: Adverse events occurring in at least 5% of patients by preferred term

	Number (%) of patients*
System organ class Preferred term	**Bendamustine** (N=100)
Patients reporting at least 1 AE	**100 (100)**
Blood & lymphatic system disorder	
Neutropaenia	45 (45)
Anaemia	37 (37)
Thrombocytopaenia	36 (36)

	Number (%) of patients*
System organ class Preferred term	**Bendamustine** (N=100)
Leukopenia	16 (16)
Febrile neutropaenia	6 (6)
Cardiac disorders	
Tachycardia	5 (5)
Gastrointestinal disorders	
Nausea	77 (77)
Diarrhoea	42 (42)
Vomiting	40 (40)
Constipation	31 (31)
Stomatitis	21 (21)
Abdominal pain	14 (14)
Gastrooesophageal reflux disease	11 (11)
Dyspepsia	14 (14)
Dry mouth	9 (9)
Abdominal pain upper	5 (5)
General disorders & administration site conditions	
Fatigue	64 (64)
Pyrexia	36 (36)
Oedema peripheral	14 (14)
Chills	14 (14)
Asthenia	13 (13)
Pain	9 (9)
Infusion site pain	7 (7)
Thirst	6 (6)
Catheter site pain	5 (5)
Infections & infestations	
Herpes zoster	12 (12)
Urinary tract infection	11 (11)
Nasopharyngitis	9 (9)
Upper respiratory tract infection	9 (9)
Pneumonia	9 (9)
Sinusitis	8 (8)
Oral candidiasis	6 (6
Herpex simplex	6 (6)
Cytomegalovirus infection	5 (5)
Investigations	
Weight decreased	20 (20)
Blood creatinine increased	5 (5)
Metabolism & nutrition disorders	
Anorexia	24 (24)
Dehydration	15 (15)
Decreased appetite	12 (12)
Hypokalaemia	11 (11)
Hypomanesaemia	5 (5)
Musculoskeletal & connective tissue disorders	
Back pain	13 (13)
Pain in extremity	6 (6)

	Number (%) of patients*
System organ class Preferred term	**Bendamustine** (N=100)
Arthralgia	6 (6)
Bone pain	5 (5)
Mylagia	5 (5)
Nervous system disorders	
Headache	21 (21)
Dizziness	15 (15)
Dysgeusia	11 (11)
Psychiatric disorders	
Insomnia	15 (15)
Anxiety	8 (8)
Depression	5 (5)
Respiratory, thoracic & mediastinal disorders	
Dyspnoea	17 (17)
Cough	16 (16)
Pharyngolaryngeal pain	10 (10)
Nasal congestion	5 (5)
Skin & subcutaneous tissue disorders	
Rash	15 (15)
Dry skin	7 (7)
Pruritus	6 (6)
Hyperhidrosis	5 (5)
Vascular disorders	
Hypotension	8 (8)

* Patients are counted only once for each arm

The data described below reflect exposure to RIBOMUSTIN in 176 patients with indolent B-cell NHL treated in two single-arm studies (SDX-105-03 and SDX-105-01).

The adverse reactions occurring in at least 5% of the NHL patients, regardless of severity, are shown in **Table 7**.

Table 7: Non-haematological ADRs occurring in at least 5% of NHL patients treated with RIBOMUSTIN by system organ class and preferred term

	Number (%) of patients*	
System organ class Preferred term	**All Grades**	**Grade 3 / 4**
Total number of patients with at least 1 ADR	176 (100)	94 (53)
Cardiac disorders		
Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)
Diarrhoea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)

	Number (%) of patients*	
System organ class Preferred term	**All Grades**	**Grade 3 / 4**
Dyspepsia	20 (11)	0
Gastrooesophageal reflux disease	18 (10)	0
Dry moth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders & administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Oedema peripheral	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0
Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections & infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4 (2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile neutropaenia	11 (6)	11 (6)
Oral candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0
Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism & nutrition disorders		
Anorexia	40 (23)	3 (2)
Dehydration	24 (14)	8 (5)
Decreased appetite	22 (13)	1 (<1)
Hypokalaemia	15 (9)	9 (5)
Musculoskeletal & Connective tissue disorders		
Back pain	25 (14)	5 (3)
Arthralgia	11 (6)	0
Pain in extremity	8 (5)	2 (1)
Bone pain	8 (5)	0
Nervous system disorders		
Headache	36 (21)	0
Dizziness	25)(	0
Dysgeusia	13 (7)	0
Psychiatric disorders		
Insomnia	23 (13)	0
Anxiety	14 (8)	1 (<1)
Depression	10 (6)	0
Respiratory, thoracic & mediastinal disorders		
Cough	38 (22)	1 (<1)
Dyspnoea	28 (16)	3 (2)

	Number (%) of patients*	
System organ class Preferred term	**All Grades**	**Grade 3 / 4**
Pharyngolaryngeal pain	14 (8)	1 (<1)
Wheezing	8 (5)	0
Nasal congestion	8 (5)	0
Skin & subcutaneous tissue disorders		
Rash	28 (16)	1 (<1)
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8 (5)	0
Vascular disorders		
Hypotension	10 (6)	2 (1)

* Patients may have reported more than 1 adverse reaction.

NOTE: Patients counted only once in each preferred term category and once in each system organ class category.

Haematologic toxicities, based on laboratory values and CTC grade, in NHL patients treated in both single arm studies combined are described in Table 11. Clinically important chemistry laboratory values that were new or worsened from baseline and occurred in >1% of patients at Grade 3 or 4, in NHL patients treated in both single arm studies combined were hyperglycemia (3%), elevated creatinine (2%), hyponatremia (2%), and hypocalcemia (2%).

Table 8: Incidence of haematology laboratory abnormalities in patients who received RIBOMUSTIN in the NHL studies

	Percent of patients	
Haematology variable	**All Grades**	**Grade 3 / 4**
Lymphocytes decreased	99	94
Leukocytes decreased	94	56
Haemoglobin decreased	88	11
Neutrophils decreased	86	60
Platelets decreased	86	25

In both studies, serious adverse reactions, regardless of causality, were reported in 37% of patients receiving RIBOMUSTIN. The most common serious adverse reactions occurring in 5% of patients were febrile neutropaenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or postmarketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, pneumonitis, pulmonary alveolar haemorrhage and myelodysplastic syndrome.

Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumour lysis syndrome and infusion reactions (see **section 4.4**). Adverse reactions occurring less frequently but possibly related to RIBOMUSTIN treatment were haemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

Post Marketing Experience

The following adverse reactions have been identified during post-approval use of RIBOMUSTIN (Table 9).

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/ 1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports.

Table 9. Adverse Reactions Identified During Postmarketing Experience with Ribosmustin

Skin and subcutaneous tissue disorders	
Not known	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Common	Urticaria
Respiratory, thoracic and mediastinal disorders	
Not known	Pneumonitis, pulmonary alveolar haemorrhage

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: anaphylaxis; and injection or infusion site reactions including phlebitis, pruritus, irritation, pain, and swelling. Increases in alanine aminotransferase; aspartate aminotransferase; blood bilirubin and blood urea levels have been reported. Somnolence, atrial fibrillations and palpitations have also been reported.

Skin reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), some fatal, have been reported with the use of bendamustine hydrochloride (see PRECAUTIONS – Skin Reactions and Tumour Lysis Syndrome, .see **section 4.4**).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose

The maximum single dose of bendamustine received in clinical studies was 280 mg/m^2 body surface area.

Three out of the four patients treated with 280 mg/m^2 experienced ECG changes which were regarded as dose-limiting toxicities on days 7 and 21. These changes included prolonged QT (1 patient), displaced ST and T waves (2 patients) and left interior fascicle block (1 patient).

There is no specific antidote for bendamustine overdosage. Supportive therapy should be given when needed.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

Bendamustine hydrochloride is an alkylating antitumour agent 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. Bendamustine is active against both quiescent and dividing cells.

The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms.

The exact mechanism of action of bendamustine remains unknown.

Clinical trials

Chronic Lymphocytic Lymphoma

The safety and efficacy of RIBOMUSTIN were evaluated in an open-label, randomised, controlled multicenter trial (02CLLIII) comparing RIBOMUSTIN to chlorambucil. The trial was conducted in 319 previously-untreated patients with Binet Stage B or C CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopaenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

The patient populations in the RIBOMUSTIN and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (72% vs. 71% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (77% vs. 78%), enlarged liver (49% vs. 45%), hypercellular bone marrow (80% vs. 73%), lymphocyte count (mean 68.9×10^9/L vs. 62.4×10^9/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either RIBOMUSTIN at 100 mg/m2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle.

Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL.

The results of this open-label randomised study demonstrated a higher rate of overall response and a longer progression-free survival for RIBOMUSTIN compared to chlorambucil (see **Table 10**). Survival data are not mature.

Table 10: Efficacy data for CLL reported in study 02CLLIII

	RIBOMUSTIN (N=162)	**Chlorambucil (N=157)**	***p*-value**
Response Rate n(%)			
Overall response rate	110 (67.9%)	48 (30.6%)	<0.0001
(95% CI)	(51.0, 66.6)	(18.6, 32.7)	(64.3, 82.3)

Complete response (CR)*	50 (30.9)	3 (1.9)	
Nodular partial response (nPR)**	17 (10.5)	4 (2.5)	
Partial response (PR)†	**43 (26.5%)**	**41 (26.1%)**	
Progression-Free Survival††			
Median, month (95% CI)	21.6 (11.7, 23.5)	8.3 (5.6, 8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		

CI = confidence interval

* CLL response was valued as CR when all of the following criteria were met for at least 8 weeks after first response was observed:

- Enlarged lymph nodes are no longer detectable by palpation (X-ray or ultrasound are optional);
- Absence of hepatomegaly or splenomegaly, confirmed by palpation. CT and ultrasound were optional;
- No disease symptoms (B-symptoms);
- Blood counts:
  - Lymohocytes ≤ $4.0X10^9$/L
  - Neutrophils ≥ $1.5X10^9$/L
  - Platelets > $100X10^9$/L
  - Hemoglobin > 11 g/dL (without blood transfusion)
- Bone marrow biopsy (histology and cytology) was to be performed 8 weeks after meeting the above criteria. The bone marrow had to be at least normocellular for age, with less than 30% lymphocytes.

** nPR was defined as described for CR with lymphocyte being less than 30% in the bone marrow sample but still showing focal infiltration.

† PR was defined as ≥50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value, and either ≥50% reduction of enlarged lymph nodes (total of affected lymph nodes), or 50% reduction of hepatomegaly and/or spelomegaly, as well as one of the following haematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/L or 50% improvement over baseline, haemoglobin >11g/dL or 50% improvement over baseline without transfusions, for a period of at least 8 weeks.

†† PFS was defined as time from randomization to progression or relapse after inter-current remission or death from any cause.

Progression free survival based upon the Independent Committee Response Assessment (ICRA) criteria by treatment group in the follow-up report (ITT analysis) in Study 02CLLIII is shown in **Figure 1**.

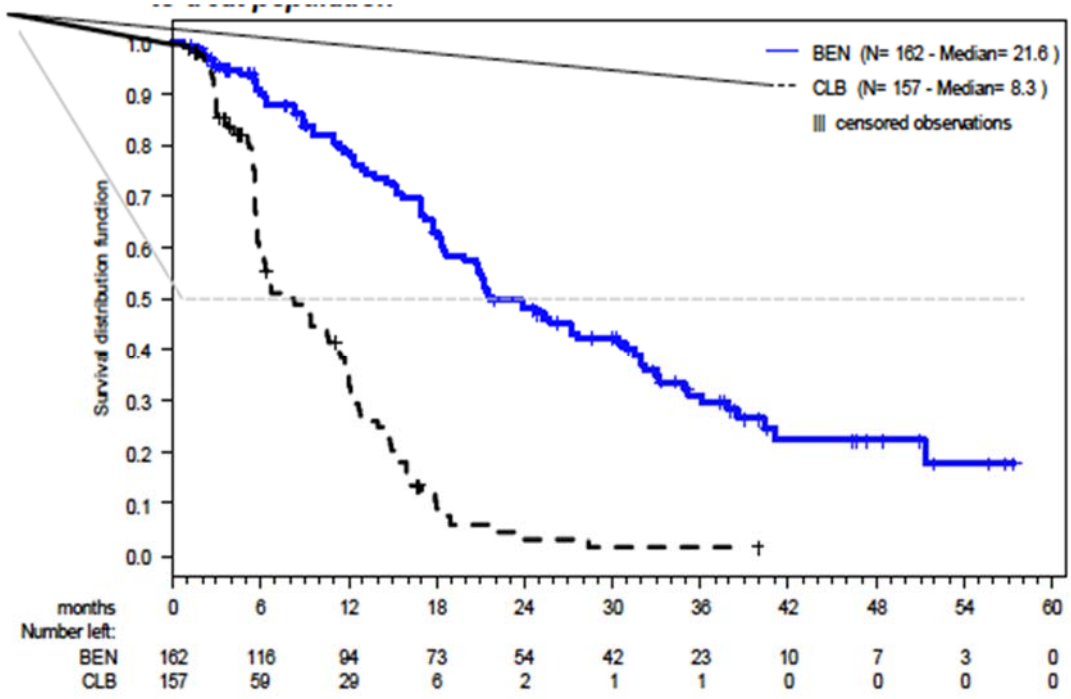

Figure 1. Progression-Free Survival

Previously Untreated Advanced Indolent Non-Hodgkin's Lymphoma (NHL) and Mantle Cell Lymphoma (MCL)

The safety and efficacy of RIBOMUSTIN in previously untreated advanced indolent NHL and MCL have been assessed in a Phase III trial.

The NHL1-2003 study is a prospective phase III, multicentre, randomised (1:1), non-inferiority, open-label clinical study of 549 patients, conducted to determine that RIBOMUSTIN (90 mg/m^2) in combination with rituximab 375 mg/m^2 is non-inferior to CHOP (cycles every 3 weeks of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 on day 1, and prednisone 100 mg/day for 5 days) plus rituximab 375 mg/m^2. Rituximab was administered in both treatment arms on day 1 of each cycle. Treatment was administered for a maximum of 6 cycles. Baseline demographics and patient characteristics are summarized in **Table 11**.

Table 11: Summary of Baseline Patient and Disease Characteristics in the NHL1-2003 Study

Patient Characteristics	B-R N=261	CHOP-R N=253
Age (years)	64 (34-83)	63 (31-82)
<60	94 (63%)	90 (36%)
61-70	107 (41%)	105 (42%)
>70	60 (23%)	58 (23%)
Stage		
II	9 (3%)	9 (4%)
III	50 (19%)	47 (19%)
IV	202 (77%)	197 (78%)
Histology		
Follicular	139 (53%)	140 (55%)
Mantle cell	46 (18%)	48 (19%)
Marginal zone	37 (14%)	30 (12%)
Lymphoplasmacytic*	22 (9%)	19 (8%)
Small lymphocytic	10 (4%)	11 (4%)
Low grade, unclassifiable	7 (3%)	5 (2%)
B symptoms	100 (38%)	74 (29%)
Bone marrow involved	177 (68%)	170 (67%)
Extranodal involved sites ≥ 1	212 (81%)	193 (76%)
LDH > 240 U/L	100 (38%)	84 (33%)
Median ß-2 microglobulin (mg/L)	2.6 (0.7-17.8)	2.4 (1.1-23.2)
Prognostic groups for all patients (IPI)		
> 2 risk factors	96 (37%)	89 (35%)
Prognostic groups according to FLIPI		
Low risk (0-1 risk factor)	16/139 (12%)	26/140 (19%)
Intermediate risk (2 risk factors)	5/139 (41%)	44/140 (31%)
Poor risk (3-5 risk factors)	63/136 (46%)	64/134 (48%)

Data are median (range), n (%), or n/N (%).

B-R=bendamustine plus rituximab; R-CHOP=CHOP plus rituximab; LDH=lactate dehyrogenase; IPI=International Prognostic Index; FLIPI-Folicular Lymphoma International Prognostic Index. *Waldenström macroglobulinaemia.

A significant benefit for progression-free survival was shown with B-R vs. R-CHOP for all histological subtypes except for marginal-zone lymphoma (see **Figure 2**).

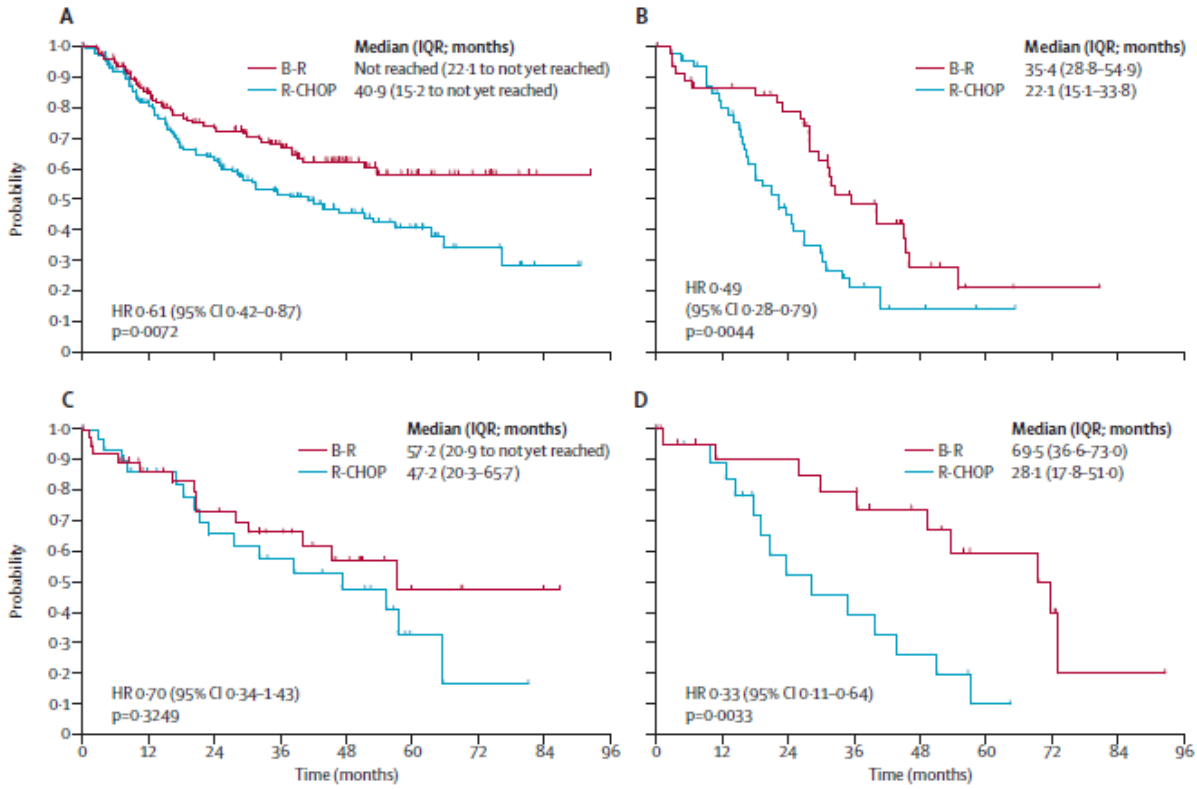

Figure 2: Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Walderstrom's macrglobulinaemia (D)

B-R=bendamustine plus rituximab; R-CHOP=Chop plus rituximab

The improvement in progression-free survival with B-R was independent of age, concentration of lactate dehydrohgenase (LDH), and FLIPI score (**Table 12**). Overall survival did not differ between the two treatment groups.

The rate of overall response did not differ between the treatment groups (93% for B-R vs. 91% for R-CHOP); however the rate of complete response was significantly increased in patients in the B-R group (104 [40%] vs. 76 [30%]; *p*=0.021).

Table 12: Exploratory subgroup analysis to assess the PFS benefit of B-R vs. R-CHOP

	HR (95% CI)	*p* value
Age (years)		
≤ 60 (n=199)	0.52 (0.33-0.79)	0.002
> 60 (n=315)	0.62 (0.45-0.84)	0.002
LDH concentration		
Normal (n=319)	0.48 (0.34-0.67)	< 0.0001
Elevated (n=184)	0.74 (0.50-1.08)	0.118
FLIPI subgroup		
Favourable (0-2 risk factors; n=143)	0.56 (0.31-0.98)	0.043
Unfavourable (3-5 risk factors; n=127)	0.63 (0.38-1.04)	0.068

PFS=progression-free survival; LDH=lactate dehydrogenase; FLIPI=Follicular Lymphoma International Prognostic Index; HR=hazard ratio.

Relapsed/Refractory NHL

The efficacy of RIBOMUSTIN was evaluated in a single arm study (SDX-105-03) of 100 patients with indolent B-cell NHL that had progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Patients were included if they relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab. All patients received RIBOMUSTIN intravenously at a dose of 120 mg/m^2, on Days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.

The median age was 60 years, 65% were male, and 95% had a baseline WHO performance status of 0 or 1. Major tumour subtypes were follicular lymphoma (62%), diffuse small lymphocytic lymphoma (21%), and marginal zone lymphoma (16%). Ninety-nine percent of patients had received previous chemotherapy, 91% of patients had received previous alkylator therapy, and 97% of patients had relapsed within 6 months of either the first dose (monotherapy) or last dose (maintenance regimen or combination therapy) of rituximab.

Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in **Table 13**.

Table 13: Efficacy data for progressing NHL* reported in study SDX-105-03

	RIBOMUSTIN (N=100)
Response Rate (%)	
Overall response rate (CR+CRu+PR)	74
(95% CI)	(64.3, 82.3)
Complete response (CRu)	13
Partial response unconfirmed (CRu)	4
Partial response (PR)	57
Duration of Response (DR)	
Median, month (95% CI)	9.2 months (7.1, 10.8)

CI = confidence interval

* IRC assessment was based on modified International Working Group response criteria (IWG-RC).

Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm.

Progression-free survival (PFS), a secondary endpoint in this study, was comparable across all patient groups defined by baseline characteristics (**Table 14**). The median PFS was 72 weeks in patients without previous alkylator therapy, and 51 weeks in patients who were sensitive to the previous alkylator therapy or chemotherapy. In the patients who had received previous radioimmunotherapy, the PFS was 53 weeks. Disease characteristics at baseline (FLIPI risk category, number of lymph nodal sites, or bulky disease) did not markedly affect duration of PFS.

Table 14: Progression-Free Survival by Baseline Characteristics

Response/Baseline Characteristics	**RIBOMUSTIN (N=100) Median, weeks (95% CI)**
Best response	
Complete response (n=14)	51.1 (46.3, 56.7)
Unconfirmed complete response (n=3)	64.9 (35.0, NA)
Partial response (n=58)	42.3 (35.9, 53.3)

Response/Baseline Characteristics	RIBOMUSTIN (N=100) Median, weeks (95% CI)
Previous alkylator therapy	
With previous alkylator therapy (n=91)	36.3 (33.4, 51.1)
Without previous alkylator therapy (n=9)	71.6 (36.6, 71.6)
Sensitivity to last alkylator therapy	
Sensitive (n=51)	51.1 (36.3, 56.7)
Refractory (n=36)	32.7 (19.1, 52.3)
Unknown (n=10)	30.0 (20.6, 35.0)
Sensitivity to last chemotherapy therapy	
Sensitive (n=51)	51.1 (39.0, 56.7)
Refractory (n=36)	32.7 (19.1, 52.3)
Unknown (n=12)	30.1 (20.6, 42.4)
Number of previous chemotherapy courses	
≤3 courses (n=92)	42.4 (35.0, 52.3)
>3 courses (n=8)	30.1 (24.3, 35.9)
Previous radioimmunotherapy	
With previous radioimmunotherapy (n=24)	53.3 (34.7, 71.6)
Without previous radioimmunotherapy (n=76)	39.0 (34.0, 51.1)
Follicular Lymphoma International Prognostic Index (risk category)	
Low rsik (n=18)	40.3 (32..7, 51.9)
Intermediate risk (n=26)	39.0 (30.1, NA)
High risk (n=18)	35.6 (27.4, 54.1)
Number of lymph nodal sites	
≤4 involved lymph nodes (n=52)	40.3 (32.0, 51.9)
>4 involved lymph nodes (n=48)	46.3 (34.0, 54.1)
Bulky disease at baseline	
Lymph nodes <10 cm (n=89)	42.3 (35.0, 51.9)
Lymph nodes ≥10 cm (n=8)	40.3 (6.1, NA)

CI = confidence interval; NA = not applicable.

5.2 Pharmacokinetic properties

Distribution:

Following 30 min I.V. infusion the central volume of distribution was 19.3 L. 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 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 CYP 1A2, CYP 2C9/10, CYP 2D6, CYP 2E1 and CYP 3A4.

Elimination:

the elimination half-life $t_{1/2ß}$ after 30 min I.V. infusion of 120 mg/m^2 to 12 subjects was 28.2 minutes. The mean total clearance after 30 min I.V. infusion of 120 mg/m^2 body surface area to 12 subjects was 639.4 mL/minute. About 20% of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Special populations

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.

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, $t_{1/2ß}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Elderly subjects:

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

5.3 Preclinical safety data

Genotoxicity

Animal studies showed that bendamustine is embryotoxic and teratogenic. Bendamustine induces aberrations of the chromosomes and is mutagenic *in-vivo* as well as *in-vitro*.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: histological investigations in dogs showed macroscopic visible hyperaemia of the mucosa and haemorrhagia in the gastrointestinal tract. Microscopic investigations showed extensive changes of the lymphatic issue indicating an immunosuppression and tubular changes of kidneys and testis, as well as atrophic, necrotic changes of the prostate epithelium.

Carcinogenicity

In long-term studies in female mice bendamustine is carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol.

6.2 Incompatibilities

In the absence of data bendamustine should not be mixed with other medicinal products, except those mentioned in **section 6.6**.

6.3 Shelf life

Unopened vials

36 months

The powder should be reconstituted immediately after opening of the vial. The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution.

Reconstituted solution

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 ºC/ 60%RH and 2 days at 2 ºC to 8 ºC in polyethylene bags.

6.4 Special precautions for storage

Unopened vials

Store below 25°C. Keep the container in the outer carton in order to protect from light.

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. See **section 6.3**

6.5 Nature and contents of container

RIBOMUSTIN is supplied in Type I brown glass vials of 26 ml or 60 ml with rubber stopper and an aluminum flip-off cap.

26 mL-vials contain 25 mg bendamustine hydrochloride; supplied in cartons containing 1 vial.

60 mL-vials contain 100 mg bendamustine hydrochloride; supplied in cartons containing 1 vial.

The vials are for single use only.

Not all presentations may be marketed.

6.6 Special precautions for disposal and 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. See **section 4.2**.

The vials are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398
Email: medinfo@janau.jnj.com

9. DATE OF FIRST APPROVAL

14 May 2015

10. DATE OF REVISION OF THE TEXT

24 January 2018

Summary table of changes

Section changes	Summary of new information
All 4.4 4.8	1. Datasheet reformat 2. Addition of information on 'Infections' and 'Skin reactions' 3. Addition of paragraph relating to adverse event reporting 4. Addition of adverse events to post-marketing section to align with EU SmPC