เอกสารกำกับยาภาษาอังกฤษ

RIBOMUSTIN™

PRODUCT NAME

RIBOMUSTIN™ (Bendamustine hydrochloride) Powder for concentrate for solution for infusion.

DOSAGE FORMS AND STRENGTHS

Bendamustine hydrochloride is a white, microcrystalline powder for reconstitution and dilution for solution for intravenous infusion.

One vial contains 25 mg bendamustine hydrochloride.

One vial contains 100 mg bendamustine hydrochloride.

1 mL of the concentrate contains 2.5 mg bendamustine hydrochloride when reconstituted according to *Instructions for Use and Handling.*

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

***CLL*:** Indicated for the treatment of patients with chronic lymphocytic leukaemia.

***NHL*:** Relapsed/Refractory indolent Non-Hodgkin's lymphoma.

Previously untreated NHL:

Previously untreated indolent CD20-positive, stage III-IV Non-Hodgkin's lymphoma, in combination with rituximab.

Previously untreated MCL:

Previously untreated CD20-positive, stage III-IV Mantle Cell Lymphoma in combination with rituximab, in patients ineligible for autologous stem cell transplantation.

Dosage and Administration

For intravenous infusion over 30-60 minutes.

***CLL*:**

100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2 of 4- week cycles, 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 to 8 cycles (maximum 8 cycles).

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

90 mg/m^2 on day 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 drop to 3000/µL or < 75000/µL, respectively. Treatment can be continued after leukocyte values have increased to > 4000/µL and platelet values to > 100000/µL.

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 *Warnings and Precautions*).

In case of non-hematological toxicity dose reductions have to be based on the worst common toxicity criteria (CTC) grades in the preceding cycle. A 50% dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity.

If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

For preparation and administration instructions, see Instructions for Use and Handling.

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 are available in patients with severe hepatic impairment (serum bilirubin values of > 3.0 mg/dL) (see *Contraindications*).

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.

Pediatric patients

As there are limited data, the safety and efficacy of bendamustine in pediatric patients has not been established.

Elderly patients

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see *List of Excipients*).

During breast-feeding

Severe hepatic impairment (serum bilirubin > 3.0 mg/dL)

Jaundice

Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3000/µL or < 75000/µL, respectively)

Major surgery less than 30 days before start of treatment

Infections, especially involving leukocytopenia

Yellow fever vaccination

Warnings and Precautions

Myelosuppression

Patients treated with bendamustine hydrochloride may experience myelosuppression (bone marrow failure). In the event of treatment-related myelosuppression, leukocytes, platelets, hemoglobin, and neutrophils should be monitored and re-evaluated prior to initiation of the next cycle of therapy. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4000/µL or > 100000/µL, respectively. Treatment-related myelosuppression may require dose adjustment and/or dose delays.

Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/µL) and low CD4-positive T-cell (T-helper cell) counts (< 200/µL) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections.

Ribomustin™ should not be used during severe bone marrow suppression and severe blood count alterations. See *Dosage and Administration*.

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) and Cytomegalovirus (CMV). Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following the use of bendamustine mainly in combination with rituximab or obinutuzumab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. In case of low CD4-positive T-cell counts (<200/µL) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections. Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate evaluations should be undertaken and treatment suspended until PML is excluded.

Skin reactions

A number of skin reactions have been reported. These events have included rash, toxic skin 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. Where skin reactions occur, they may be progressive and increase in severity with further treatment; therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or 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 bendamustine hydrochloride the concentration of potassium in the

blood should be closely monitored. Potassium supplementation should 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.

Tumor lysis syndrome

Tumor 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.

Anaphylaxis

Infusion reactions to bendamustine hydrochloride have occurred commonly 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 administration of antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.

Patients who experienced Grade 3 or worse allergic-type reactions were typically not re-challenged.

Contraception

Bendamustine hydrochloride is teratogenic and mutagenic.

Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with Ribomustin™ 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, such as the use of corticosteroids, are not of clear benefit.

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.

Other malignancies

There are reports of secondary tumors, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with bendamustine therapy has not been determined.

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. Carriers of HBV who require treatment with bendamustine hydrochloride should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. See *Adverse Reactions*.

Interactions

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 cyclosporine 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.

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

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are insufficient data from the use of Ribomustin™ in pregnant women. In non-clinical studies bendamustine was embryo-/fetolethal, teratogenic and genotoxic (see *Non-Clinical Information*). Women of childbearing potential must use effective methods of contraception both before, during, and one month following Ribomustin™ therapy.

During pregnancy Ribomustin™ should not be used unless the benefit outweighs the risk. The mother should be informed about the risk to the fetus. 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 counseling should be considered.

Breast-feeding

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

Fertility

Men being treated with bendamustine 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™.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, ataxia, peripheral neuropathy and somnolence have been reported during treatment with Ribomustin™ (see *Adverse Reactions*). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

Adverse Reactions

The most common adverse reactions with bendamustine hydrochloride are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

The table below reflects the data obtained with bendamustine hydrochloride in clinical trials.

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10000 to <1/1000**	**Very rare <1/10000**	**Not known (cannot be estimated from the available data)**
Infections and Infestations	Infection NOS*			Sepsis	Pneumonia primary atypical	
Neoplasm benign, malignant		Tumor lysis syndrome				
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombocytopenia	Hemorrhage, Anemia, Neutropenia			Hemolysis	
Immune system disorders		Hypersensitivity NOS*		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Nervous system disorders		Insomnia		Somnolence, Aphonia	Dysgeusia, Paresthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders,	

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10000 to <1/1000**	**Very rare <1/10000**	**Not known (cannot be estimated from the available data)**
					Ataxia, Encephalitis	
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris, Atrial fibrillation	Pericardial effusion		Tachycardia, Myocardial infarction, Cardiac failure	
Vascular disorders		Hypotension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	
Gastrointestinal disorders	Nausea, vomiting	Diarrhea, Constipation, Stomatitis				Hemorrhagic esophagitis, Gastrointestinal hemorrhage
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS*		Erythema, Dermatitis, Pruritus, Maculopapular rash, Hyperhidrosis		
Reproductive system and breast disorders		Amenorrhea			Infertility	

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10000 to <1/1000**	**Very rare <1/10000**	**Not known (cannot be estimated from the available data)**
General disorders and administration site conditions	Mucosal inflammation, Fatigue, Pyrexia	Pain, Chills, Dehydration, Anorexia			Multi-organ failure	
Investigations	Hemoglobin decrease, Creatinine increase, Urea increase	AST increase, ALT increase, Alkaline phosphatase increase, Bilirubin increase, Hypokalemia				

NOS* = Not otherwise specified

A small number of cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients some using bendamustine in combination with allopurinol or in combination with allopurinol and rituximab. In addition, a few cases of hepatitis B reactivation resulting in hepatic failure have been reported in patients treated with bendamustine. Pancytopenia, headache, dizziness, opportunistic infection (e.g. herpes zoster, cytomegalovirus, pneumocystis jirovecii pneumonia), bone marrow failure, hepatic failure, renal failure, nephrogenic diabetes insipidus, drug reaction with eosinophilia and systemic symptoms (combination therapy with rituximab) have also been reported in patients treated with bendamustine.

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.

There have been isolated reports of necrosis after accidental extra-vascular administration, tumor 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.

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

Tables below 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). Adverse event data provided below is based on published data and is therefore limited in nature.

Table 1: 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 2: 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
Paraesthesia	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

Overdose

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

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

Counter measures

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

Bendamustine hydrochloride and its metabolites are dialyzable to a small extent.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

Bendamustine is an alkylating antitumor agent with unique activity containing a purine-like benzimidazole ring. The antineoplastic and cytocidal effect of bendamustine 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 exact mechanism of action of bendamustine remains unknown.

The antitumor effect of bendamustine hydrochloride has been demonstrated by several *in-vitro* studies in different human tumor cell lines (breast cancer, non-small cell and small cell lung cancer, ovary carcinoma and different leukemia) and *in-vivo* in different experimental tumor models with tumors of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukemia and small cell lung cancer).

Bendamustine hydrochloride showed an activity profile in human tumor cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumor 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.

Chronic lymphocytic leukemia

The indication for use in chronic lymphocytic leukemia is supported by a single open-label study comparing bendamustine with chlorambucil. In the prospective, multicenter, randomized study, 319 previously untreated patients with chronic lymphocytic leukemia stage Binet B or C requiring therapy were included. The first line therapy with bendamustine hydrochloride 100 mg/m² i.v. on days 1 and 2 (BEN) was compared to treatment with chlorambucil 0.8 mg/kg days 1 and 15 (CLB) for 6 cycles in both arms. Patients received allopurinol in order to prevent tumor lysis syndrome.

Patients with BEN have a significantly longer median progression-free survival than patients with CLB treatment (21.5 versus 8.3 months, $p < 0.0001$ in the latest follow-up). Overall survival was not statistically significantly different (median not reached). The median duration of remission is 19 months with BEN and 6 months with CLB treatment ($p < 0.0001$). The safety evaluation in both treatment arms did not reveal any unexpected adverse reactions in nature and frequency. The dose of BEN was reduced in 34% of the patients. Treatment with BEN was discontinued in 3.9% of patients due to allergic reactions.

Indolent non-Hodgkin's lymphomas

The indication for indolent non-Hodgkin's lymphomas relied on two uncontrolled phase II trials.

In the pivotal, prospective, multi-center, open study 100 patients with indolent B-cell non-Hodgkin´s lymphomas refractory to rituximab mono- or combination therapy were treated with BEN single agent. Patients received a median of 3 previous chemotherapy or biologic therapy courses. The median number of previous rituximab-containing courses was 2. The patients had no response or progress within 6 months after rituximab treatment. The dose of BEN was 120 mg/m² i.v. on days 1 and 2 planned for at least 6 cycles. Duration of treatment depended on response (6 cycles planned). The overall response rate was 75% including 17% complete (CR and CRu) and 58% partial response as assessed by independent review committee. The median duration of remission was 40 weeks. BEN was generally well tolerated when given in this dose and schedule.

The indication is further supported by another prospective, multicenter, open study including 77 patients. The patient population was more heterogeneous including: indolent or transformed B-cell non-Hodgkin's lymphomas refractory to rituximab mono- or combination therapy. The patients had no response or progress within 6 months or had an untoward reaction to prior rituximab treatment. Patients received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses was 2. The overall response rate was 76% with a median duration of response of 5 months (29 [95% CI 22.1, 43.1] weeks).

Bendamustine in combination with rituximab (BR) was investigated in a trial with the title "A Multicenter Phase II Study to Investigate the Safety and Activity of SDX-105 (Bendamustine) in Combination with Rituximab in Patients with Relapsed Indolent or Mantle Cell Non-Hodgkin's Lymphoma (NHL)". Patients received a dose of 375 mg/m^2 of rituximab 7 days before the first 28-day cycle of bendamustine and rituximab. Subsequently rituximab was given on the first day of a cycle at a single dose of 375 mg/m^2, followed on the second and third day of a cycle by bendamustine at a dose of 90 mg/m^2 per day of treatment. Four 28-day cycles were planned. Sixty-seven patients were enrolled in the trial and 66 received at least one dose of bendamustine and rituximab. The results of this study show the combination therapy of bendamustine and rituximab to be an efficacious treatment for patients with relapsed indolent or mantle cell NHL leading to an overall response rate of 92% and a CR rate of 41%. The responses obtained were durable with a median duration of response of 91 weeks and a median progression-free survival of 100 weeks. A high rate of durable response was also

observed in both patients with prior rituximab treatment and those refractory to their last alkylator treatment.

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 3.

Patients were stratified by histological lymphoma subtype, then randomly assigned according to a pre-specified randomisation list to receive either intravenous bendamustine (90 mg/m² on days 1 and 2 of a 4-week cycle) or CHOP (cycles every 3 weeks of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1·4 mg/m² on day 1, and prednisone 100 mg/day for 5 days) for a maximum of six cycles. Patients in both groups received rituximab 375 mg/m² on day 1 of each cycle. Patients aged 18 years or older with a WHO performance status of 2 or less were eligible if they had newly diagnosed stage III or IV indolent or mantle-cell lymphoma. Patients and treating physicians were not masked to treatment allocation. The primary endpoint was progression-free survival, with a non-inferiority margin of 10%.

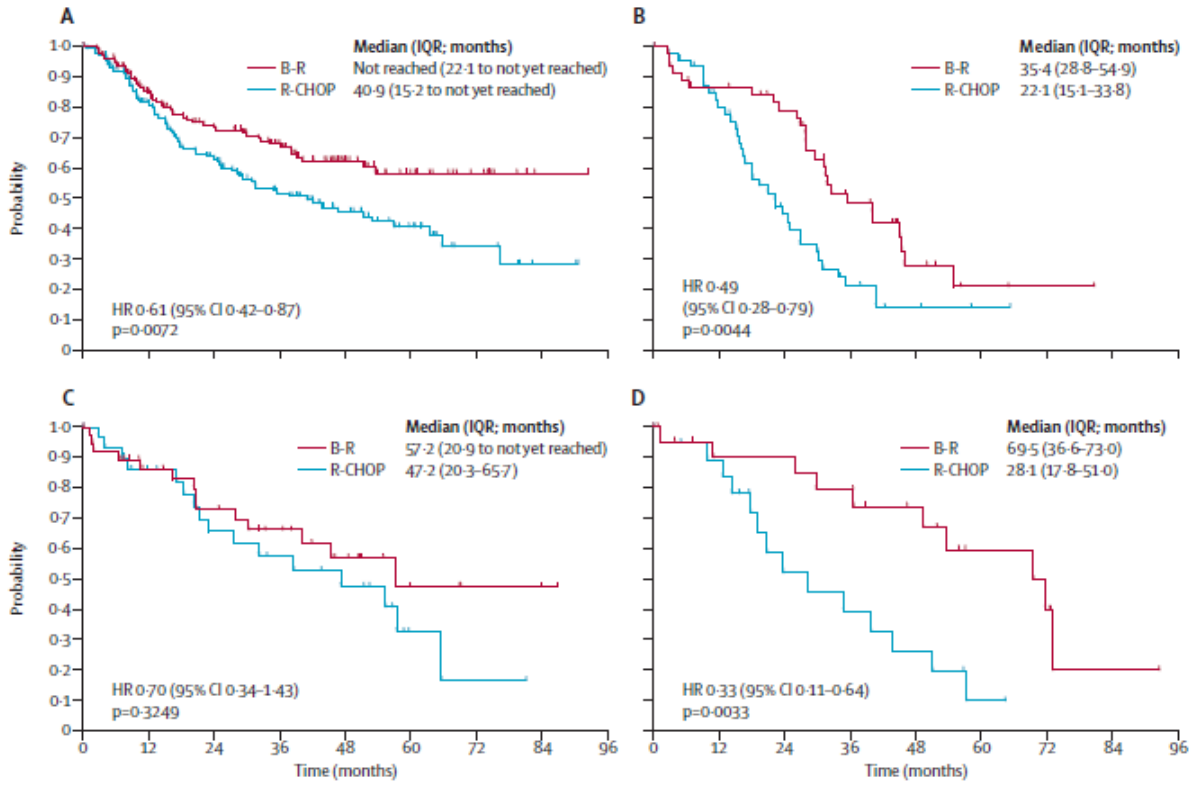
Table 3: Summary of Baseline Patient and Disease Characteristics in the NHL1-2003 Study

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%)
Extra nodal 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)	57/139 (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 dehydrogenase; IPI=International Prognostic Index; FLIPI-Follicular Lymphoma International Prognostic Index. *Waldenström macroglobulinaemia.

At median follow-up of 45 months (IQR 25–57), median progression-free survival was significantly longer in the bendamustine plus rituximab group than in the R-CHOP group (69·5 months [26·1 to not yet reached] vs. 31·2 months [15·2–65·7]; hazard ratio 0·58, 95% CI 0·44–0·74; p<0·0001).

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 1).



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

<u>Figure 1:</u> Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D)

The improvement in progression-free survival with B-R was independent of age, concentration of lactate dehydrogenase (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 4: 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.

Multiple myeloma

In a prospective, multicenter, randomized, open study 131 patients with advanced multiple myeloma (Durie-Salmon stage II with progress or stage III) were included. The first line therapy with bendamustine hydrochloride in combination with prednisone (BP) was compared to treatment with melphalan and prednisone (MP). Neither transplant-eligibility nor the presence of specific co-morbidities played a role for inclusion into the trial. The dose was bendamustine hydrochloride 150 mg/m² i.v. on days 1 and 2 or melphalan 15 mg/m² i.v. on day 1 each in combination with prednisone. Duration of treatment depended on response and averaged 6.8 in the BP and 8.7 cycles in the MP group.

Patients with BP treatment have a longer median progression free survival than patients with MP (15 [95%Cl 12-21] versus 12 [95%Cl 10-14] months) (p=0.0566). The median time to treatment failure is 14 months with BP and 9 months with MP treatment. The duration of remission is 18 months with BP and 12 months with MP treatment. The difference in overall survival is not significantly different (35 months BP versus 33 months MP). Tolerability in both treatment arms was in line with the known safety profile of the respective medicinal products with significantly more dose reductions in the BP arm.

Pharmacokinetic Properties

Distribution

The elimination half-life $t_{1/2\beta}$ 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 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 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 > oxidized metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment

In patients with 30 - 70% tumor infestation of the liver and mild hepatic impairment (serum bilirubin < 1.2 mg/dL) the pharmacokinetic behavior was not changed. There was no significant difference to patients with normal liver and kidney function with respect to C_{max}, t_{max}, AUC, $t_{1/2ß,}$ volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment

In patients with creatinine clearance >10 mL/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to C_{max}, t_{max}, AUC, $t_{1/2ß}$, volume of distribution and clearance.

Elderly subjects

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

NON-CLINICAL INFORMATION

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 hyperemia of the mucosa and hemorrhagia in the gastrointestinal tract. Microscopic investigations showed extensive changes of the lymphatic tissue indicating an immunosuppression and tubular changes of kidneys and testis, as well as atrophic, necrotic changes of the prostate epithelium.

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

PHARMACEUTICAL PARTICULARS

List of Excipients

Mannitol

Incompatibilities

This medicinal product should not be mixed with other medicinal products except those mentioned in *Instructions for Use and Handling and Disposal*.

Shelf Life

Observe expiry date on the outer pack.

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

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

Solution for infusion

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.

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.

Storage Conditions

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

Store below 30°C in original packaging.

For storage conditions of the reconstituted or diluted medicinal product, see *Shelf Life*.

Keep out of the sight and reach of children.

Nature and Contents of Container

Bendamustine is provided 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 and 60 mL-vials contain 100 mg bendamustine hydrochloride.

Instructions for Use 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.

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 colorless 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.

The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.3 - 0.5 mg/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.

The vials are for single use only.

Instructions for Disposal

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

Warning according to the announcement from ministry of public health

This medicinal product may cause serious harm. It must be used only under physician's supervision.

Product name	**Manufactured by**	**Market authorization number**	**Date of Authorization**
RIBOMUSTIN 25 MG	Cenexi-Laboratoires Thissen S.A., Braine – L' Alleud, Belgium	1C 15212/63(N)	3 July 2015
RIBOMUSTIN 100 MG	Cenexi-Laboratoires Thissen S.A., Braine – L' Alleud, Belgium	1C 15213/63(N)	3 July 2015
RIBOMUSTIN 25 MG	Oncotec Pharma Produktion GMBH, Dessao-Roblau, Germany	1C 15142/63(N)	3 July 2015 SMP release date: 27 August 2020
RIBOMUSTIN 100 MG	Oncotec Pharma Produktion GMBH, Dessao-Roblau, Germany	1C 15143/63(N)	3 July 2015 SMP release date: 27 August 2020

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IMPORTED BY

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com