janssen

NAME OF THE MEDICINAL PRODUCT
Ribomustin™ (Bendamustine hydrochloride)

QUALITATIVE AND QUANTITATIVE COMPOSITION
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 and Disposal.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
White, microcrystalline powder.

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, multi-centre, randomised 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 undesirable effects 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-centre, 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, multi-centre, 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).

Multiple Myeloma
In a prospective, multi-centre, randomised, 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%CI 12-21] versus 12 [95%CI 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 $t_{1/2ß}$ 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 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.

Preclinical Safety Data
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.

CLINICAL PARTICULARS
Therapeutic Indications
CLL **:** First-line treatment of chronic lymphocytic leukemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
NHL **:** Indolent non-Hodgkin's lymphomas in patients, who have progressed following treatment with rituximab containing regimen.
MM **:** Treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) after failure to first line treatment 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.

POSOLOGY AND METHOD OF ADMINISTRATION
Intravenous infusion over 30-60 minutes.

CLL **:** 100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2 of 4-week cycles.
NHL **:** 120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2 of 3-week cycles.
MM **:** 120-150 mg/m² body surface area bendamustine hydrochloride on days 1 and 2, combined with 60 mg/m² body surface area prednisone i.v. or per os on days 1 to 4; of 4-week cycles.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped 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 Special Warnings and Special Precautions for Use).

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

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

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

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 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
There is no experience in children and adolescents with Ribomustin™.

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

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Myelosuppression
Patients treated with bendamustine hydrochloride may experience myelosuppression (bone marrow failure).
In the event of treatment-related myelosuppression, leukocytes, platelets, hemoglobin, 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 > 4000/µL or > 100000/µL, respectively. Treatment-related myelosuppression may require dose termination 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 Posology and Method of 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 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.

Tumor lysis syndrome
Tumor lysis syndrome associated with RibomustinTM 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 Epidermal Necrolysis reported when bendamustine and allopurinol are administered concomitantly.

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 bendamustine hydrochloride because of possible irreversible infertility.

Extravasation
An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

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 Undesirable effects.

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

Undesirable effects
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, 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 media-stinal 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		Amenorrhea			Infertility	

and breast disorders						
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 leukemias is increased in patients treated with alkylating agents (including bendamustine). The secondary malignancy may develop several years after chemotherapy has been discontinued.

Interactions with Other Medicinal Products and Other Forms of Interaction
No *in-vivo* interaction studies have been performed.

No formal clinical assessments of PK drug-drug interactions between bendamustine and other drugs have been conducted.

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 and Lactation

Pregnancy

There are insufficient data from the use of Ribomustin™ in pregnant women. In non-clinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic (see Preclinical Safety Data). During pregnancy Ribomustin™ should not be used unless clearly necessary. 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 counselling should be considered.

Women of Childbearing Potential/Contraception

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™.

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™.

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 Undesirable Effects). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

Overdose

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

In a subsequent study with a 30-minute infusion of Ribomustin™ 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Mannitol

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

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

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.

Special Precautions for Storage
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
Type I brown glass vials 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 and Disposal
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.
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.
Any unused product or waste material should be disposed of in accordance with local requirements.

HOW SUPPLIED
Ribomustin™ 25 mg/vial powder for concentrate for solution for infusion
Box, 1 vial @ 25 mg
Reg. No.: DKI2155203480A1

Ribomustin™ 100 mg/vial powder for concentrate for solution for infusion
Box, 1 vial @ 100 mg
Reg. No.: DKI2155203480B1

HARUS DENGAN RESEP DOKTER

Manufactured by Oncotec Pharma Produktion GmbH, Germany
Secondary packaging and final batch released by Janssen Pharmaceutica NV, Belgium
Registered by PT Integrated Healthcare Indonesia, Jakarta – Indonesia
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935 3935

Based on IPI 02 June 2022 v.006

Informasi Produk untuk Pasien
RIBOMUSTIN 25 & 100 mg serbuk untuk larutan untuk injeksi
Bendamustin hidroklorida

Baca informasi ini secara seksama sebelum Anda mulai menggunakan obat ini:
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoketer Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Hal ini dapat membahayakan, bahkan jika gejala penyakit mereka sama seperti penyakit Anda.
- Jika Anda menemukan efek samping serius atau efek samping yang tidak tercantum dalam informasi produk ini, laporkan kepada dokter atau apoketer Anda

Apa yang ada dalam informasi produk ini

1. Apakah RIBOMUSTIN itu dan digunakan untuk apa

Ribomustin adalah obat yang digunakan untuk pengobatan kanker jenis tertentu (disebut obat sitotoksik).
Ribomustin digunakan sendiri (terapi tunggal/monoterapi) atau kombinasi dengan obat lain untuk pengobatan jenis kanker sebagai berikut:
- Leukemia limfositik kronis dalam kasus di mana kombinasi kemoterapi dengan fludarabine tidak sesuai untuk Anda.
- Non-Hodgkin limfoma, yang tidak atau hanya sesaat memberikan respon terhadap rituximab,
- Multiple myeloma dalam kasus di mana terapi dengan thalidomide atau bortezomib tidak sesuai untuk Anda.

2. Sebelum menggunakan RIBOMUSTIN

Jangan gunakan RIBOMUSTIN :
- Jika Anda hipersensitif (alergi) terhadap zat aktif bendamustin hidroklorida atau zat lainnya yang terkandung dalam Ribomustin;
- Saat menyusui;
- Jika Anda mengalami gangguan hati berat (kerusakan pada sel-sel fungsional hati);
- Jika Anda mengalami perubahan warna menjadi kuning pada kulit atau bagian putih mata yang disebabkan oleh masalah hati atau darah (sakit kuning);
- Jika Anda mengalami gangguan fungsi sumsum tulang yang berat (penurunan aktivitas sumsum tulang) dan perubahan jumlah sel darah putih dan trombosit dalam darah Anda yang cukup serius (jumlah sel darah putih dan/atau trombosit turun menjadi <3000/µl atau <75.000/µl, secara berurutan) ;
- Jika Anda pernah melakukan operasi pembedahan besar kurang dari 30 hari sebelum memulai pengobatan;
- Jika Anda memiliki infeksi, terutama yang disertai dengan penurunan sel darah putih (*leukositopenia*);
- Bersamaan dengan pemberian vaksin penyakit demam kuning.

Hal khusus yang perlu diperhatikan saat menggunakan Ribomustin
- Bila terjadi penurunan kemampuan sumsum tulang untuk menggantikan sel-sel darah. Periksa jumlah sel darah putih dan trombosit dalam darah Anda sebelum memulai pengobatan dengan Ribomustin, sebelum setiap tahapan pengobatan berikutnya dan dalam interval antara tahap pengobatan.
- Bila terjadi infeksi. Hubungi dokter Anda jika Anda memiliki tanda-tanda infeksi, termasuk demam atau gejala paru-paru.
- Bila terjadi reaksi pada kulit Anda selama pengobatan dengan Ribomustin. Reaksi dapat meningkat derajat keparahannya.

– Bila Anda memiliki penyakit jantung (misalnya serangan jantung, nyeri dada, gangguan irama jantung yang berat).
– Bila Anda mengalami sakit di sendi, keluarnya darah dalam urin atau menurunnya jumlah urin. Jika penyakit Anda sangat berat, tubuh Anda mungkin tidak mampu membersihkan semua produk sisa dari sel-sel kanker yang mati. Ini disebut sindrom tumor lisis dan dapat menyebabkan gagal ginjal dan gangguan jantung dalam waktu 48 jam dari pemberian dosis pertama Ribomustin. Dokter Anda akan berhati-hati akan hal ini dan mungkin akan memberikan obat-obatan lain untuk membantu mencegahnya.
– Bila terjadi reaksi alergi atau hipersensitivitas yang berat. Anda harus memperhatikan adanya reaksi dari pemberian infus setelah siklus pertama terapi yang Anda terima.

Pria yang menerima pengobatan dengan Ribomustin disarankan untuk tidak melakukan hubungan intim selama pengobatan dan sampai dengan 6 bulan setelahnya. Sebelum memulai pengobatan, Anda harus meminta saran mengenai penyimpanan sperma karena adanya kemungkinan infertilitas *(*kemandulan*)* permanen.

Injeksi yang tidak disengaja ke dalam jaringan di luar pembuluh darah (injeksi extravasal) harus segera dihentikan. Cabut jarum setelah dilakukan aspirasi singkat. Setelah itu daerah jaringan yang terkena suntikan harus didinginkan. Lengan harus diangkat. Manfaat pemberian obat-obatan tambahan seperti kortikosteroid masih belum jelas manfaatnya (lihat bagian 4).

Penggunaan obat-obat lain
Beritahukan kepada dokter atau apoteker jika Anda sedang atau baru saja menggunakan obat lain, termasuk obat-obatan yang diperoleh tanpa resep dokter.

Jika Ribomustin digunakan bersamaan dengan obat-obatan yang menghambat pembentukan darah pada sumsum tulang, dapat meningkatkan efek pada sumsum tulang.

Jika Ribomustin digunakan bersamaan dengan obat-obatan yang mempengaruhi respon imun Anda, efek ini dapat meningkat.

Obat sitostatik dapat mengurangi efektivitas vaksinasi yang mengandung virus hidup. Selain itu obat-obatan sitostatik meningkatkan risiko infeksi pasca vaksinasi yang mengandung virus hidup (misalnya vaksinasi virus).

Kehamilan dan menyusui
Kehamilan
Ribomustin diketahui dapat menyebabkan kerusakan genetik dan telah menyebabkan gangguan pembentukan janin pada hewan percobaan. Anda tidak diperbolehkan menggunakan Ribomustin selama kehamilan kecuali diindikasikan secara khusus oleh dokter Anda. Bila Anda harus mendapatkan pengobatan, Anda harus berkonsultasi mengenai risiko potensi efek samping dari terapi terhadap janin yang belum lahir dan berkonsultasi mengenai kemungkinan efek terhadap genetik.
Jika Anda seorang wanita pada usia subur, Anda harus menggunakan metode kontrasepsi yang efektif baik sebelum dan selama pengobatan dengan Ribomustin. Jika kehamilan terjadi selama pengobatan dengan Ribomustin, Anda harus segera memberitahu dokter Anda dan berkonsultasi mengenai kemungkinan efek terhadap genetik.
Jika Anda seorang pria, Anda harus menghindari melakukan hubungan seksual selama pengobatan dengan Ribomustin dan hingga 6 bulan setelah pengobatan dihentikan. Sehubungan adanya risiko dimana pengobatan dengan Ribomustin akan menyebabkan infertilitas (kemandulan), Anda mungkin perlu mencari tahu mengenai konservasi (penyimpanan) sperma sebelum pengobatan dimulai.

Menyusui
Ribomustin tidak boleh diberikan selama menyusui. Jika pengobatan dengan Ribomustin diperlukan selama menyusui Anda harus menghentikan periode menyusui Anda.
Minta saran kepada dokter atau apoteker Anda sebelum meminum obat apapun.

Mengemudi dan menggunakan mesin
Tidak ada studi mengenai efek pada kemampuan mengemudi dan menggunakan mesin. Jangan mengemudi atau mengoperasikan mesin jika Anda mengalami efek samping, seperti kepala pusing atau kurangnya koordinasi.

3. Bagaimana cara menggunakan RIBOMUSTIN

Ribomustin diberikan melalui pembuluh darah selama 30-60 menit dalam beberapa dosis, baik obat tunggal (monoterapi) ataupun kombinasi dengan obat lain.
Pengobatan tidak boleh dimulai jika sel darah putih Anda (leukosit) turun di bawah jumlah 3.000 sel/µL dan/atau trombosit darah Anda turun di bawah jumlah 75.000 sel/µl.
Dokter Anda akan memeriksa jumlah ini secara berkala.

Leukemia *limfositik* kronis

Ribomustin diberikan 100 mg per meter persegi luas permukaan tubuh Anda (berdasarkan tinggi dan berat badan Anda)	Pada hari 1+2
Ulangi siklus setelah 4 minggu hingga 6 kali	

Non-Hodgkin *Limfoma*

Ribomustin diberikan 120 mg per meter persegi luas permukaan tubuh Anda (berdasarkan tinggi dan berat badan Anda)	Pada hari 1+2
Ulangi siklus setelah 3 minggu	

Multiple *myel*oma

Ribomustin diberikan 120-150 mg per meter persegi luas permukaan tubuh Anda (berdasarkan tinggi dan berat badan Anda)	Pada hari 1+2
Prednison 60 mg per meter persegi luas permukaan tubuh Anda (berdasarkan tinggi dan berat badan Anda) secara intravena	Pada hari 1 – 4
Ulangi siklus setelah 4 minggu	

Pengobatan harus dihentikan jika jumlah sel darah putih (leukosit) dan /atau trombosit turun menjadi <3000/µl atau <75.000/µl, secara berurutan. Pengobatan dapat dilanjutkan setelah jumlah sel darah putih telah meningkat menjadi > 4.000/µl dan trombosit menjadi > 100.000/µl.

Gangguan fungsi hati atau ginjal
Tergantung pada derajat gangguan fungsi hati Anda, kemungkinan perlu untuk menyesuaikan dosis Anda (sebesar 30% pada kasus disfungsi hati yang sedang). Penyesuaian dosis tidak diperlukan pada kasus gangguan fungsi ginjal. Dokter Anda akan memutuskan apakah penyesuaian dosis diperlukan.

Bagaimana Ribomustin diberikan
Pengobatan dengan Ribomustin hanya dapat dilakukan oleh dokter yang berpengalaman dalam mengobati tumor. Dokter Anda akan memberikan dosis Ribomustin yang tepat untuk Anda dan melakukan tindakan-tindakan yang perlu diperhatikan.
Dokter Anda akan memberikan larutan infus yang telah disiapkan sesuai dengan yang telah diresepkan untuk Anda. Larutan disuntikkan melalui pembuluh darah vena selama 30 - 60 menit.

Durasi penggunaan
Tidak ada batas waktu yang ditetapkan sebagai aturan umum untuk pengobatan dengan Ribomustin. Lamanya pengobatan tergantung pada derajat penyakit dan respon terhadap pengobatan.
Jika Anda khawatir atau memiliki pertanyaan mengenai pengobatan dengan Ribomustin, silakan berbicara dengan dokter atau perawat Anda.

Jika Anda lupa menggunakan RIBOMUSTIN
Jika Anda lupa untuk menggunakan satu dosis Ribomustin, dokter biasanya akan tetap mempertahankan jadwal dosis normal Anda.

Jika Anda berhenti menggunakan RIBOMUSTIN
Dokter yang merawat Anda akan memutuskan apakah perlu menghentikan pengobatan atau mengganti dengan pengobatan yang lain.
Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat lainnya, Ribomustin juga dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Berikut ini merupakan definisi berdasarkan frekuensi yang biasa digunakan ketika menilai efek samping:

Sangat umum	Dialami oleh lebih dari 1 dari 10 pasien
Umum	Dialami oleh 1 sampai 10 dari 100 pasien
Jarang	Dialami oleh 1 sampai 10 dari 1000 pasien
Langka	Dialami oleh 1 sampai 10 dari 10.000 pasien
Sangat langka	Dialami oleh kurang dari 1 dari 10.000 pasien
Belum diketahui	Frekuensi belum dapat diperkirakan dari data yang tersedia

Perubahan pada jaringan (disebut nekrosis) sangat jarang terjadi pada kasus injeksi yang tidak disengaja masuk ke dalam jaringan di luar pembuluh darah (ekstravaskular). Sensasi terbakar ketika jarum infus dimasukkan merupakan tanda bahwa pemberian obat terjadi di luar pembuluh darah. Hal ini dapat menyebabkan nyeri dan kerusakan kulit yang sukar disembuhkan.
Efek samping berupa gangguan pada fungsi sumsum tulang biasanya akan kembali normal setelah pengobatan. Gangguan terhadap fungsi sumsum tulang ini dapat meningkatkan risiko infeksi.

Sangat umum:
- Jumlah sel darah putih yang rendah (leukositopenia)
- Penurunan pigmen merah dalam darah (hemoglobin)
- Jumlah trombosit yang rendah (trombositopenia)
- Infeksi
- Merasa sakit (mual)
- Muntah
- Radang pada mukosa
- Peningkatan kreatinin dalam darah
- Peningkatan urea dalam darah
- Demam
- Kelelahan

Umum:
- Perdarahan (haemorrhage)
- Gangguan metabolisme akibat pelepasan sel-sel kanker yang mati ke dalam aliran darah
- Pengurangan jumlah sel darah merah yang dapat membuat kulit pucat dan menyebabkan kelelahan atau sesak napas (anemia)
- Jumlah neutrofil yang rendah (neutropenia)
- Reaksi hipersensitivitas seperti peradangan alergi pada kulit (dermatitis), ruam yang mengganggu (urtikaria)
- Peningkatan enzim hati (AST/ALT)
- Peningkatan enzim alkaline fosfatase
- Peningkatan pigmen empedu
- Level kalium dalam darah yang rendah
- Gangguan fungsi (disfungsi) jantung
- Gangguan irama jantung (aritmia)
- Tekanan darah rendah atau tinggi (hipotensi atau hipertensi)
- Gangguan fungsi paru
- Diare
- Sembelit
- Sakit pada mulut (stomatitis)
- Hilang nafsu makan
- Rambut rontok

- Ganti kulit
- Tidak haid/datang bulan (amenorea)
- Nyeri
- Insomnia
- Kedinginan
- Dehidrasi

Jarang :
- Akumulasi cairan dalam kantung jantung (cairan masuk ke dalam ruang perikardial)

Langka :
- Infeksi pada darah (sepsis)
- Reaksi alergi/hipersensitivitas yang berat (reaksi anafilatik)
- Gejala yang mirip dengan reaksi anafilatik (reaksi anafilaktoid)
- Mengantuk
- Hilang suara (afonia)
- Kolaps /syok peredaran darah akut
- Kemerahan pada kulit (eritema)
- Radang kulit (dermatitis)
- Gatal (pruritis)
- Ruam kulit (eksantema makula)
- Keringat berlebihan (hyperhidrosis)

Sangat langka :
- Radang atipikal primer pada paru (pneumonia)
- Penghancuran sel darah merah
- Penurunan cepat tekanan darah kadang-kadang diikuti dengan reaksi kulit atau ruam (syok anafilaktik)
- Gangguan pada indera perasa/sensoris
- Perubahan sensasi (parestesia)
- Rasa tidak enak dan nyeri pada tungkai atau lengan (neuropati perifer)
- Penyakit sistem saraf (sindrom antikolinergik)
- Gangguan neurologis
- Kurangnya koordinasi (ataksia)
- Radang otak (ensefalitis)
- Peningkatan denyut jantung (takikardia)
- Serangan jantung, nyeri dada (infark miokard)
- Gagal jantung
- Radang pembuluh darah (flebitis)
- Pembentukan jaringan di paru (fibrosis paru)
- Pendarahan radang tenggorokan (esofagitis hemoragik)
- Perdarahan lambung atau usus
- Infertilitas
- Kegagalan fungsi pada beberapa organ tubuh

Terdapat laporan adanya tumor sekunder (sindrom myelodysplastic, AML, karsinoma bronkus) setelah pengobatan dengan Ribomustin. Apakah ada hubungan yang jelas antara tumor tersebut dengan Ribomustin masih belum dapat ditentukan.
Sejumlah kecil kasus reaksi kulit yang berat (*Stevens-Johnson Syndrome* dan Toksik Epidermal Nekrolisis) juga dilaporkan. Hubungan kasus ini dengan Ribomustin masih belum jelas.
Jika salah satu dari efek samping tersebut menjadi serius, atau jika Anda memperhatikan ada efek samping yang tidak tercantum dalam informasi ini, mohon beritahukan kepada dokter Anda.

5. Bagaimana cara menyimpan RIBOMUSTIN

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan menggunakan Ribomustin setelah tanggal kadaluarsa yang tertera pada karton dan label. Tanggal kadaluarsa mengacu pada hari terakhir dari bulan tersebut.

Simpan dalam kemasan asli agar terlindung dari cahaya.

Batas kadaluarsa obat setelah dibuka atau dilarutkan
Larutan infus stabil dalam kantong polietilen yang disimpan pada suhu kamar dengan 60% kelembaban relatif selama 3,5 jam, dan jika disimpan dalam lemari es larutan stabil selama 2 hari. Ribomustin tidak mengandung bahan pengawet. Jangan gunakan larutan setelah melewati batas waktu tersebut.

Merupakan tanggung jawab dari pengguna untuk dapat mempertahankan kondisi steril (asepsis).

Obat tidak boleh dibuang bersama air limbah atau sampah rumah tangga. Tanyakan kepada apoteker Anda bagaimana membuang obat-obatan yang tidak Anda gunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Informasi lainnya

Apa isi RIBOMUSTIN
Zat aktif adalah bendamustin hidroklorida.
1 vial mengandung 25 mg bendamustin hidroklorida
1 vial mengandung 100 mg bendamustin hidroklorida

Setelah rekonstitusi, 1 ml konsentrat mengandung 2.5 mg bendamustin hidroklorida.

Bahan lainnya adalah mannitol.

Seperti apa penampakan RIBOMUSTIN dan isi kemasan
Botol kaca berwarna coklat dengan tutup karet dan flip-off aluminium.
Serbuk berbentuk putih dan kristal.
Ribomustin tersedia dalam kemasan yang mengandung :
1 vial injeksi dengan 25 mg bendamustine hidroklorida
dan
1 vial injeksi dengan 100 mg bendamustine hidroklorida.

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