CAUTION : CYTOTOXIC AGENT

PROPOSED PACKAGE INSERT

Name of the Product

Bendamustine Hydrochloride Kabi 25mg Powder for Concentrate for Solution for Infusion

Bendamustine Hydrochloride Kabi 100mg Powder for Concentrate for Solution for Infusion

Name and strength of Active ingredient

Bendamustine Hydrochloride Kabi 25mg Powder for Concentrate for Solution for Infusion contain Bendamustine hydrochloride 25mg

Bendamustine Hydrochloride Kabi 100mg Powder for Concentrate for Solution for Infusion contain Bendamustine hydrochloride 100mg

Bendamustine Hydrochloride for Injection

DESCRIPTION:
Bendamustine Hydrochloride Kabi 25 mg or 100 mg Powder:
White to off white lyophilized powder or cake contained in an amber glass vial.

After reconstitution with water for injection and further dilution with 0.9% w/v NaCl solution: Clear colorless to a pale yellow solution.

COMPOSITION:

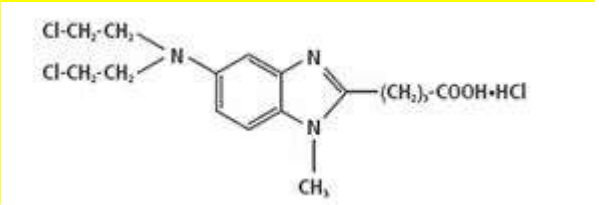
25 mg/vial
Each vial contains:

Bendamustine Hydrochloride	25 mg
Mannitol Ph.Eur	30 mg

100 mg/vial
Each vial contains:

Bendamustine Hydrochloride	100 mg
Mannitol Ph.Eur	120 mg

CHEMICAL STRUCTURE:
The chemical name of bendamustine hydrochloride is 5- [Bis (2-chloroethyl)amino]-1-methyl-2-benzimidazolebutyric acid hydrochloride or 4-[5-[Bis (2-chloroethyl)amino]-1-methyl benzimidazol-2-yl] butanoic acid hydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$, and the molecular weight is 394.72.



PHARMACOLOGY:

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.

Pharmacokinetics:

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 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 or CYP 3A4.

Elimination
About 20 % of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine >oxidised metabolite >N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment
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.

Elder subjects
Higher age does not influence the pharmacokinetics of bendamustine.

INDICATIONS:
Bendamustine Hydrochloride Kabi (100 mg and 25 mg) is indicated for monotherapy in patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

Bendamustine Hydrochloride Kabi (100 mg and 25 mg) is indicated for monotherapy in patients with indolent Bcell nonHodgkin's lymphomas that has progressed during or withi n sixmonths of treatment with rituximab or a rituximab-containing regimen.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the 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 < 3,000/µl or < 75,000/µl, respectively)
- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopenia
- Yellow fever vaccination

ADVERSE EFFECTS:

The most common adverse reactions with bendamustine 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.

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Infections and Infestations	Infection NOS*			Sepsis	Pneumonia primary atypical	
Neoplasm benign, malignant		Tumor lysis syndrome				
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombo-cytopenia	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,	
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	
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 hydrochloride 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 hydrochloride. Pancytopenia, headache, dizziness, opportunistic infection (e.g. herpes zoster, cytomegalovirus, pneumocystis jirovecii pneumonia), bone marrow failure, hepatic failure, renal failure, drug reaction with eosinophilia and systemic symptoms (combination therapy with rituximab) have also been reported in patients treated with bendamustine hydrochloride.

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.

Description of selected adverse reactions

There have been isolated reports of necrosis after accidental extra-vascular administration and tumour lysis syndrome, and anaphylaxis.

The risk of myelodysplastic syndrome and acute myeloid leukaemias is increased in patients treated with alkylating agents (including bendamustine). The secondary malignancy may develop several years after chemotherapy has been discontinued.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

DRUG INTERACTIONS:
No *in-vivo* interaction studies have been performed.

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

Combination of bendamustine 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. Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.

PRECAUTIONS AND WARNINGS:

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. Bendamustine hydrochloride should not be used during severe bone marrow suppression and severe blood count alterations.

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). 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.

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, Bendamustine hydrochloride 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 bendamustine hydrochloride treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of bendamustine hydrochloride and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate 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 bendamustine hydrochloride 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 rechallenged.

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, such as the use of corticosteroids are not of clear benefit.

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.

Pregnancy and Lactation

Pregnancy
There are insufficient data from the use of bendamustine hydrochloride in pregnant women. In non-clinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic. Women of childbearing potential must use effective methods of contraception both before, during, and one month following bendmustine hydrochloride therapy.

During pregnancy bendamustine hydrochloride should not be used unless the benefit outweighs the risk. The mother should be informed about the risk to the fetus. If treatment with bendamustine hydrochloride 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 hydrochloride passes into the breast milk, therefore, bendamustine hydrochloride is contraindicated during breast-feeding. Breast-feeding must be discontinued during treatment with bendamustine hydrochloride.

Fertility
Men being treated with bendamustine hydrochloride 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 bendamustine hydrochloride.

DOSAGE AND ADMINISTRATION:
For intravenous infusion over 30 - 60 minutes.
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 have dropped to < 3,000/µl or < 75,000/µl, respectively.

Monotherapy for chronic lymphocytic leukaemia
100 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab
120 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks.

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. 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.

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).

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.

Instructions for Use and Handling
When handling bendamustine hydrochloride, 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% w/v NaCI Solution) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution

Reconstitute each vial of bendamustine containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking.

Reconstitute each vial of bendamustine 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 to a pale yellow solution.

2. Dilution
As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of bendamustine immediately with 0.9% w/ v NaCl solution to produce a final volume of about 500 ml.

Bendamustine must be diluted with 0.9% w/v 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.

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

OVERDOSE:
After application of a 30 min infusion of bendamustine once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m^2. Cardiac events of CTC grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min 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 haematological growth factors may be given as effective countermeasures to control haematological side effects.

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

Effects on Ability to Drive and Use Machine

Bendamustine has major influence on the ability to drive and use machines.

Ataxia, peripheral neuropathy and somnolence have been reported during treatment with bendamustine. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

STORAGE:

Store below 30°C in original packaging.
Keep the vial in the outer carton in order to protect from light.
For storage conditions of the reconstituted or diluted medicinal product, see section shelf life.
Keep out of sight and reach of children.

INCOMPATIBILITIES:

This medicinal product must not be mixed with other medicinal products except those mentioned under the section Instruction of Use and Handling.

SHELF LIFE:

Unopened: 36 months.

The powder should be reconstituted immediately after opening of the vial.
The reconstituted concentrate should be diluted immediately with 0.9% w/v NaCl solution

Solution for infusion

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 °C/ 60 % RH and 48 hours at 2 °C to 8 °C 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 and would normally not be longer than 48 hours at 2 to 8°C and 3.5 hours at 25 °C/ 60% RH unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

HANDLING AND DISPOSAL:

When handling bendamustine, 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 eyes should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid-impermeable, absorbent disposable foil. Pregnant personnel should be excluded from handling cytostatics.

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

PRESENTATION:

Type I amber glass vials of 20 ml or 50 ml with rubber stopper and an aluminium flip-off overseal.
20 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 vials.

50 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

Not all pack sizes may be marketed.

Product Registration Holder/Importer
Fresenius Kabi Malaysia Sdn Bhd
3-1 & 3-2, Axis Technology Centre,
Lot 13, Jalan 51A/225
46100 Petaling Jaya
Selangor, Malaysia

MANUFACTURER INFORMATION:

Manufactured by:
Fresenius Kabi Oncology Limited
Village Kishanpura, Baddi,
Tehsil Nalagarh
District Solan, IN-174101, India

VERSION NUMBER: MYS/00/2021

DATE OF RELEASE: JULY 2021