BEMUNAT

Bendamustine Hydrochloride For Injection USP, 100 mg/vial
Bendamustine Hydrochloride For Injection USP, 25 mg/vial
(Bendamustine Hydrochloride Lyophilized
Powder for Concentrate for Solution for Infusion)

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

Bendamustine hydrochloride for infusion is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

1.2 Non-Hodgkin's Lymphoma (NHL)

Bendamustine hydrochloride for infusion is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions for CLL

Recommended Dosages

The recommended dose is 100 mg/m^2 administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

Dose Delays. Dose Modifications and Reinitiation of Therapy for CLL:

Bendamustine hydrochloride for infusion administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non -hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved (Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L), Bendamustine hydrochloride for infusion can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. *[See Warnings and Precautions (5.1)]*

Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non- hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle.

Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

2.2 Dosing Instructions for NHL

Recommended Dosages

The recommended dose is 120 mg/m^2 administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Dose Delays. Dose Modifications and Reinitiation of Therapy for NHL:

Bendamustine hydrochloride for infusion administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the bood counts have improved (Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L) Bendamustine hydrochloride for infusion can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. *[See Warnings and Precautions (5.1)]*

Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

Dose modifications for non- hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.

2.3 Reconstitution/Preparation for Intravenous Administration

Bendamustine hydrochloride for infusion is indicated for intravenous administration.

After reconstitution of the solution according to the instructions, Bendamustine hydrochloride for infusion is administered as a short intravenous infusion over 30 - 60 minutes.

To prepare the ready-to-use solution, the contents of a vial of Bendamustine hydrochloride for infusion are dissolved in water for infusions as follows:

First dissolve the vial of Bendamustine hydrochloride for infusion containing 25 mg of Bendamustine hydrochloride in 10 ml by shaking,

First dissolve the vial of Bendamustine hydrochloride for infusion containing 100 mg of Bendamustine hydrochloride in 40 ml by shaking.

As soon as clear solution forms (within 5 minutes) the total Bendamustine hydrochloride for infusion dose is immediately diluted to a final volume of approximately 500 ml with 0.9% sodium chloride solution. If particulate matter is observed, the reconstituted product should not be used.

Apart from isotonic saline solution, Bendamustine hydrochloride for infusion must not be diluted with other base infusion solutions or other infusion solutions.

2.4 Admixture Stability

Store below 30°C in original package.

Protect from light.

Cytotoxic agent – use caution during handling and preparation. Use of gloves and safety glasses is recommended to avoid exposure.

Reconstituted concentrate in the vial
The concentrate should be further processed immediately.

Diluted solution for infusion

The chemical and physical stability of the preparation after reconstitution to form the solution for infusion (water for infusions and isotonic saline solution) was confirmed for 2 hours at 25° C and 2 days at 2 -8° C. From a microbiological point of view, the product 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 24 hours at 2 to 8° C, unless dilution has taken place in controlled and validated aseptic conditions. **If the ready-to -use preparation is not used immediately, the user is responsible for the Storage Period and conditions.**

3 DOSAGE FORMS AND STRENGTHS

1 vial of Bendamustine hydrochloride for infusion contains 25 mg of Bendamustine hydrochloride as lyophilized powder for the preparation of a solution for infusion.

1 vial of Bendamustine hydrochloride for infusion contains 100 mg of Bendamustine hydrochloride as lyophilized powder for the preparation of a solution for infusion.

Excipients: Mannitol

4 CONTRAINDICATIONS

Bendamustine hydrochloride for infusion is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to Bendamustine or mannitol. *(See Warnings and Precautions (5.3))*

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Patients treated with Bendamustine hydrochloride for infusion are likely to experience myelosuppression. In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils closely. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Hematologic nadirs may require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be ≥ 1 x 10^9/L and the platelet count should be ≥ 75 x 10^9/L. *[See Dosage and Administration (2. 1) and (2.2)]*

5.2 Infections

Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, 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. 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. 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. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. 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 diagnostic evaluations should be undertaken and treatment suspended until PML is excluded.

5.3 Infusion Reactions and Anaphylaxis

Infusion reactions to Bendamustine hydrochloride for infusion have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome associated with Bendamustine hydrochloride for infusion treatment has been reported in patients in clinical trials and in post-marketing reports. The onset tends to be within the first treatment cycle of Bendamustine hydrochloride for infusion and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of Bendamustine hydrochloride for infusion therapy. However there may be an increased risk of severe skin toxicity when Bendamustine hydrochloride for infusion and allopurinol are administered concomitantly. *[See Warnings and Precautions (5.5)]*

5.5 Skin Reactions

A number of skin reactions have been reported in clinical trials and post -marketing safety reports. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when Bendamustine hydrochloride for infusion was given in combination with other anticancer agents, so the precise relationship to Bendamustine hydrochloride for infusion is uncertain.

In a study of Bendamustine hydrochloride for infusion (90 mg/m9 in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when Bendamustine hydrochloride for infusion was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to Bendamustine hydrochloride for infusion cannot be determined.

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 for infusion should be withheld or discontinued.

5.6 Other Malignancies

There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with Bendamustine hydrochloride for infusion including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with Bendamustine hydrochloride for infusion therapy has not been determined.

5.7 Hepatitis B Virus Reactivation

Administration of Bendamustine hydrochloride for infusion may cause hepatitis due to reactivation of hepatitis B virus. Therefore patients should be tested for hepatitis B infection and undergo appropriate measures prior to administration of Bendamustine hydrochloride for infusion. Regular liver function tests and monitoring of hepatitis virus markers after the start of administration of Bendamustine hydrochloride for infusion must be performed in order to be alerted to signs and/or symptoms of reactivation of hepatitis B virus.

5.8 Use in Pregnancy

Bendamustine hydrochloride for infusion can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of Bendamustine in mice and rats administered during organogenesis caused an increase in resorption, skeletal and visceral malformations, and decreased fetal body weights. *[See Use in Specific Populations (8.1)]*

5.9 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.

6 ADVERSE REACTIONS

The data described below reflect exposure to Bendamustine hydrochloride for infusion in 349 patients who participated in an actively -controlled trial (N=153) for the treatment of CLL and two single-arm studies (N=176) for the treatment of indolent B-cell NHL. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following serious adverse reactions have been associated with Bendamustine hydrochloride for infusion in clinical trials and are discussed in greater detail in other sections of the label.

- Myelosuppression *[See warnings and Precautions (5.1)]*
- Infections *[See Warnings and Precautions (5.2)]*
- Infusion Reactions and Anaphylaxis *[See Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[See Warnings and Precautions (5.4)]*
- Skin Reactions *[See Warnings and Precautions (5.5)]*
- Other Malignancies *[See Warnings and Precautions (5.6)]*
- Hepatitis B Virus Reactivation *[See Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience in CLL

The data described below reflect exposure to Bendamustine hydrochloride for infusion in 153 patients. Bendamustine hydrochloride for infusion was studied in an active- controlled trial. The population was 45-77 years of age, 63% male, 100% white, and had treatment naive CLL. All patients started the study at a dose of 100 mg/m^2 intravenously over 30 minutes on days 1 and 2 every 28 days.

Adverse reactions were reported according to NCI CTC v.2.0. In the randomized CLL clinical study, non-hematologic adverse reactions (any grade) in the Bendamustine hydrochloride for infusion group that occurred with a frequency greater than 15% were pyrexia (24%), nausea pow, and vomiting (16%).

Other adverse reactions seen frequently in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis.

Worsening hypertension was reported in 4 patients treated with Bendamustine hydrochloride for infusion in the randomized CLL clinical study and none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with oral medications and resolved.

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

Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in 5 5% of patients in either treatment group in the randomized CLL clinical study.

Table 1: Non-Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

	Number (%) of patients			
	Bendamustine hydrochloride for infusion (N=153)		Chlorambucil (N=143)	
System organ class Preferred term	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Total number of patients with at least 1 adverse reaction	121 (79)	52 (34)	96 (67)	25 (17)
Gastrointestinal disorders				
Nausea	31 (20)	1 (<1)	21 (15)	1 (<1)
Vomiting	24 (16)	1 (<1)	9 (6)	0
Diarrhea	14 (9)	2 (1)	5 (3)	0
General disorders and administration site conditions				
Pyrexia	36 (24)	6 (4)	8 (6)	2 (1)
Fatigue	14 (9)	2 (1)	8 (6)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	1 (<1)	0
Immune system disorders				
Hypersensitivity	7 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	10(7)	0	12 (8)	0
Infection	9(6)	3(2)	1 (<1)	1 (<1)
Herpes simplex	5(3)	0	7 (5)	0
Investigations				
Weight decreased	11(7)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	11(7)	3(2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	1 (<1)	7 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
rash	12(8)	4 (3)	7 (5)	3 (2)
Pruritus	8 (5)	0	2 (1)	0

The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2. These findings confirm the myelosuppressive effects seen in patients treated with Bendamustine hydrochloride for infusion. Red bood cell transfusions were administered to 20% of patients receiving Bendamustine hydrochloride for infusion compared with 6% of patients receiving chlorambucil.

Table 2: Incidence of Hematology Laboratory Abnormalities in Patients Who Received Bendamustine hydrochloride for infusion and Chlorambucil in the Randomized CLL Clinical Study

	Bendamustine hydrochloride for infusion (N=150)		Chlorambucil (N=141)	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Haemoglobin Decreased	134 (89)	20 (13)	115 (82)	12 (9)
Platelets Decreased	116 (77)	16 (11)	110 (78)	14 (10)
Leukocytes Decreased	92 (61)	42 (28)	26 (18)	4 (3)
Lymphocytes Decreased	102 (68)	70 (47)	27 (19)	6 (4)
Neutrophils Decreased	113 (75)	65 (43)	86 (61)	30 (21)

In the randomized CLL clinical study, 34% of patients had bilirubin elevations, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of Grade 3 or 4 were limited to 1% and 3% of patients, respectively. Patients treated with Bendamustine hydrochloride for infusion may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that significant deterioration does not occur.

6.2 Clinical Trials Experience in NHL

The data described below reflect exposure to Bendamustine hydrochloride for infusion in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31-84 years of age, 60% male, and 40% female. The race distribution was 89% White, 7% Black, 3% Hispanic, 1% other, and < 1% Asian. These patients received Bendamustine hydrochloride for infusion at a dose of 120 mg/m^2 intravenously on Days 1 and 2 for up to 8 21-day cycles.

The adverse reactions occurring in at least 5% of the NHL patients, regardless of severity, are shown in Table 3. The most common non-hematologic adverse reactions (≥ 30%) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%) and pyrexia (34%). The most common non-hematologic Grade 3 or 4 adverse reactions (≥ 5%) were fatigue (11%), febrile neutropenia (6%), and pneumonia, hypokalemia and dehydration, each reported in 5% of patients.

Table 3: Non- Hematologic Adverse Reactions Occurring in at Least 5% of NHL Patients Treated with Bendamustine hydrochloride for infusion by System Organ Class and Preferred Term (N=176)

	Number (%) of patients*	
System organ class Preferred term	**All Grades**	**Grade 3/4**
Total number of patients with at least 1 adverse reaction	176 (100)	94 (53)
Cardiac disorders		
Tachycardia	13 (7)	0
Gastrointestinal disorders		
Nausea	132 (75)	7 (4)
Vomiting	71 (40)	5 (3)
Diarrhoea	65 (37)	6 (3)
Constipation	51 (29)	1 (<1)
Stomatitis	27 (15)	1 (<1)
Abdominal pain	22 (13)	2 (1)
Dyspepsia	20 (11)	0
Gastroesophageal reflux disease	18 (10)	0
Dry mouth	15 (9)	1 (<1)
Abdominal pain upper	8 (5)	0
Abdominal distension	8 (5)	0
General disorders and administration site conditions		
Fatigue	101 (57)	19 (11)
Pyrexia	59 (34)	3 (2)
Chills	24 (14)	0
Edema peripheral	23 (13)	1 (<1)
Asthenia	19 (11)	4 (2)
Chest pain	11 (6)	1 (<1)
Infusion site pain	11 (6)	0
Pain	10 (6)	0
Catheter site pain	8 (5)	0
Infections and infestations		
Herpes zoster	18 (10)	5 (3)
Upper respiratory tract infection	18 (10)	0
Urinary tract infection	17 (10)	4(2)
Sinusitis	15 (9)	0
Pneumonia	14 (8)	9 (5)
Febrile Neutropenia	11 (6)	11 (6)
Oral candidiasis	11 (6)	2 (1)
Nasopharyngitis	11 (6)	0
Investigations		
Weight decreased	31 (18)	3 (2)
Metabolism and nutrition disorders		
Anorexia	40 (23)	3(2)
Dehydration	24 (14)	8 (5)
Decreased appetite	22 (13)	1 (<1)
Hypokalemia	15 (9)	9 (5)
Musculoskeletal and connective tissue disorders		
Back pain	25 (14)	5 (3)
Arthralgia	11 (6)	0
Pain in extremity	8 (5)	2 (1)
Bone pain	8 (5)	0
Nervous system disorders		1 (<1)
Headache	36 (21)	0
Dizziness	25 (14)	0
Dysgeusia	13 (7)	0
Psychiatric disorders		1 (<1)
Insomnia	23 (13)	0
Anxiety	14 (8)	1 (<1)
Depression	10 (6)	0
Respiratory, thoracic and mediastinal disorders		
Cough	38 (22)	1 (<1)
Dyspnea	28 (16)	3(2)
Pharyngolaryngeal pain	14 (8)	1 (<1)
Wheezing	8 (5)	0
Nasal congestion	8 (5)	0
Skin and subcutaneous tissue disorders		
Rash	28 (16)	
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8(5)	0
Vascular disorders		
Hypotension	10 (6)	2 (1)

*Patients may have reported more than 1 adverse reaction.

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

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

Table 4: Incidence of Hematology Laboratory Abnormalities in Patients Who Received Bendamustine hydrochloride for infusion in the NHL Studies

Hematology variable	**Percent of patients**	
	All Grades	**Grade 3/4**
Lymphocytes Decreased	99	94
Leukocytes Decreased	94	56
Hemoglobin Decreased	88	11
Neutrophils Decreased	86	60
Platelets Decreased	86	25

In both studies, serious adverse reactions, regardless of causality, were reported in 37% of patients receiving Bendamustine hydrochloride for infusion. The most common serious adverse reactions occurring in ≥ 5% of patients were febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or post-marketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

Serious drug-related adverse reactions reported in clinical trials included myelosuppression, infection, pneumonia, tumor lysis syndrome and infusion reactions *(see Warnings and Precautions (5))*. Adverse reactions occurring less frequently but possibly related to Bendamustine hydrochloride for infusion treatment were hemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Bendamustine hydrochloride for infusion. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: anaphylaxis; and infusion or infusion site reactions including pruritus, irritation, pain, and swelling.

Skin reactions including SJS and TEN have occurred when B was administered concomitantly with allopurinol and other medications known to cause these syndromes. *[See Warnings and Precautions (5.5)]*.

Hepatitis due to reactivation of hepatitis B virus may occur. *[See Warnings and Precautions (5.7)]*.

7 DRUG INTERACTIONS

No formal clinical assessments of pharmacokinetic drug-drug interactions between Bendamustine hydrochloride for infusion and other drugs have been conducted.

Bendamustine's active metabolites, gamma-hydroxy Bendamustine (M3) and N-desmethyl-Bendamustine (m4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of Bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of Bendamustine and increase plasma Concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

The role of active transport systems in Bendamustine distribution has not been fully evaluated. *In vitro* data suggest that P-glycoprotein, breast cancer resistance protein (BCRP), and/ or other efflux transporters may have a role in Bendamustine transport

Based on *in vitro* data, Bendamustine is not likely to inhibit metabolism via human CYP isoenzymes CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category *[See Warning and Precautions (5.8)]*. Bendamustine hydrochloride for infusion can cause fetal harm when administered to a pregnant woman. Single intraperitoneal doses of Bendamustine from 210 mg/m^2 (70 mg/kg) in mice administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities) and deceased fetal body weights. This dose did not appear to be maternally toxic and lower doses were not evaluated. Repeat intraperitoneal dosing in mice on gestation days 7-11 resulted in an increase in resorption from 75 mg/m^2 (25 mg/kg) and an increase in abnormalities from 112.5 mg/m^2 (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of Bendamustine from 120 mg/m^2 (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, or 13 caused embryo and fetal lethality as indicated by increased resorption and a decrease in live fetuses. A significant increase in external [effect on tail, head, and herniation of external organs (exomphalos)] and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.2 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for Bendamustine in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Pediatric Use

The safety and effectiveness of Bendamustine hydrochloride for infusion in pediatric patients have not been established.

8.4 Geriatric Use

In CLL and NHL studies, there were no clinically significant differences in the adverse reaction profile between geriatric (≥65 years of age) and younger patients.

Chronic Lymphocytic Lymphoma

In the randomized CLL clinical study, 153 patients received Bendamustine hydrochloride for infusion. The overall response rate for patients younger than 65 years of age was 70% (1,82) for Bendamustine hydrochloride for infusion and 30% (n=69) for chlorambucil. The overall response rate for patients 65 years or older was 47% (n=71) for Bendamustine hydrochloride for infusion and 22% (n=79) for chlorambucil. In patients younger than 65 years of age, the median progression-free survival was 19 months in the Bendamustine hydrochloride for infusion group and 8 months in the chlorambucil group. In patients 65 years or older, the median progression-free survival was 12 months in the Bendamustine hydrochloride for infusion group and 8 months in the chlorambucil group.

Non-Hodgkin's Lymphoma

Efficacy (Overall Response Rate and Duration of Response) was similar in patients < 65 years of age and patients to 65 years. Irrespective of age, all of the 176 patients experienced at least one adverse reaction.

8.5 Renal Impairment

No formal studies assessing the impact of renal impairment on the pharmacokinetics of Bendamustine have been conducted. Bendamustine hydrochloride for infusion should be used with caution in patients with mild or moderate renal impairment. Bendamustine hydrochloride for infusion should not be used in patients with CrCL < 40 mL/min. *[See Clinical Pharmacology (12.3)]*

8.6 Hepatic Impairment

No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of Bendamustine have been conducted. Bendamustine hydrochloride for infusion should be used with caution in patients with mild hepatic impairment. Bendamustine hydrochloride for infusion should not be used in patients with moderate (AST or ALT 2.5-10 X ULN and total bilirubin 1.5-3 X ULN) or severe (total bilirubin > 3 X ULN) hepatic impairment. *[See Clinical Pharmacology (12.3)]*

8.7 Effect of Gender

No clinically significant differences between genders were seen in the overall incidences of adverse reactions in either CLL or NHL studies.

Chronic Lymphocytic Leukemia

In the randomized CLL clinical study, the overall response rate (ORR) for men (n=97) and women (n=56) in the Bendamustine hydrochloride for infusion group was 60% and 57%, respectively. The ORR for men (n=90) and women (n=58) in the chlorambucil group was 24% and 28%, respectively. In this study, the median progression-free survival for men was 19 months in the Bendamustine hydrochloride for infusion treatment group and 6 months in the chlorambucil treatment group. For women, the median progression-free survival was 13 months in the Bendamustine hydrochloride for infusion treatment group and 8 months in the chlorambucil treatment group.

Non-Hodgkin's Lymphoma

The pharmacokinetics of Bendamustine were similar in male and female patients with indolent NHL. No clinically-relevant differences between genders were seen in efficacy (ORR and DR).

9 OVERDOSAGE

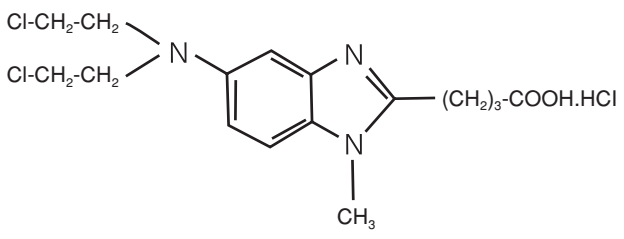
The intravenous LD. of Bendamustine HCl is 240 mg/m^2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress.

Across all clinical experience, the reported maximum single dose received was 280 mg/m^2. Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients.

No specific antidote for Bendamustine hydrochloride for infusion overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

10 DESCRIPTION

Bendamustine hydrochloride for infusion contains Bendamustine hydrochloride, an alkylating drug, as the active ingredient. The chemical name of Bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2$ .HCl, and the molecular weight is 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:



Bendamustine hydrochloride for infusion is indicated for intravenous administration. After reconstitution of the solution according to the instructions, Bendamustine hydrochloride for infusion is administered as a short intravenous infusion over 30 - 60 minutes.

To prepare the ready-to-use solution, the contents of a vial of Bendamustine hydrochloride for infusion are dissolved in water for infusions as follows:

First dissolve the vial of Bendamustine hydrochloride for infusion containing 25 mg of Bendamustine hydrochloride in 10 ml by shaking,

First dissolve the vial of Bendamustine hydrochloride for infusion containing 100 mg of Bendamustine hydrochloride in 40 ml by shaking.

As soon as clear solution forms (within 5 minutes) the total Bendamustine hydrochloride for infusion dose is immediately diluted to a final volume of approximately 500m1 with 0.9% sodium chloride solution. If particulate matter is observed, the reconstituted product should not be used.

Apart from isotonic saline solution, Bendamustine hydrochloride for infusion must not be diluted with other base infusion solutions or other infusion solutions.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives for electrophilic alkyl groups. These groups for covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of Bendamustine remains unknown.

11.2 Pharmacokinetics

Absorption

Following a single IV dose of Bendamustine hydrochloride C_{max} typically occurred at the end of infusion. The dose proportionality of Bendamustine has not been studied.

Distribution

In vitro, the binding of Bendamustine to human serum plasma protein ranged from 94-96% and was concentration independent from 1-50 µg/mL. Data suggest that Bendamustine is not likely to displace or to be displaced by highly protein- bound drugs. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 µg/mL indicating that Bendamustine distributes freely in human red blood cells. In humans, the mean steady state volume of distribution (V_{ss}) was approximately 25 L.

Metabolism

In vitro data indicate that Bendamustine is primarily metabolized via hydrolysis to metabolites with low cytotoxic activity. *In vitro,* studies indicate that two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are 1/10 and 1/100 that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to Bendamustine.

In vitro studies using human liver microsomes indicate that Bendamustine does not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes in primary cultures of human hepatocytes.

Elimination

No mass balance study has been undertaken in humans. Preclinical radiolabeled Bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces.

Bendamustine clearance in humans is approximately 700 mL /minute. After a single dose of 120 mg/m^2 Bendamustine IV over 1- hour the intermediate $t_{1/2}$ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination $t_{1/2}$ of M3 and M4 are approximately 3 hours and 30 minutes respectively. Little or no accumulation in plasma is expected for Bendamustine administered on Days 1 and 2 of a 28-day cycle.

Renal Impairment

In a population pharmacokinetic analysis of Bendamustine in patients receiving 120 mg/m^2 there was to meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of Bendamustine. Bendamustine has not been studied in patients with CrCL <40 mL/min.

These results are however limited, and therefore Bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 mL/min. *[See Use in Specific Populations (8.6)]*

Hepatic impairment

In a population pharmacokinetic analysis of Bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin 5 ULN, AST to ULN to 2.5 x ULN, and/ or ALP to ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of Bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment.

These results are however limited, and therefore Bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5 -10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment. *[See Use in Specific Populations (8.7)]*

Effect of Age

Bendamustine exposure (as measured by AUC and C_{max}) has been studied in patients ages 31 through 84 years. The pharmacokinetics of Bendamustine (AUC and C_{max}) were not significantly different between patients less than or greater than/ equal to 65 years of age. *[See Use in Specific Populations (8.4, 8.5)]*

Effect of Gender

The pharmacokinetics of Bendamustine were similar in male and female patients. *[See Use in Specific Populations (8.8)]*

Effect of Race

The effect of race on the safety, and/or efficacy of Bendamustine hydrochloride for infusion has not been established. Based on a cross-study comparison, Japanese subjects (n=6) had on average exposures that were 40% higher than non-Japanese subjects receiving the same dose. The significance of this difference on the safety and efficacy of Bendamustine hydrochloride for infusion in Japanese subjects has not been established.

11.3 Pharmacokinetics/Pharmacodynamics

Based on the pharmacokinetics/pharmacodynamics analyses of data from NHL patients, a correlation was observed between nausea and Bendamustine C_{max}.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bendamustine was carcinogenic in mice. After intraperitoneal infusions at 37.5 mg/m^2/day (12.5 mg/kg/day, the lowest dose tested) and 75 mg/m^2/day (25 mg/kg/day) for four days, peritoneal sarcomas in female AB/jena mice were produced. Oral administration at 187.5 mg/m^2/day (62.5 mg/kg/day, the only dose tested) for four days induced mammary carcinomas and pulmonary adenomas.

Bendamustine is a mutagen and clastogen. In a reverse bacterial mutation assay (Ames assay), Bendamustine was shown to increase revertant frequency in the absence and presence of metabolic activation. Bendamustine was clastogenic in human lymphocytes *in vitro*, and in rat bone marrow cells *in vivo* (increase in micronucleated polychromatic erythrocytes) from 37.5 mg/m^2, the lowest dose tested.

Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacities.

13 CLINICAL STUDIES

13.1 Chronic Lymphocytic Leukemia (CLL)

The safety and efficacy of Bendamustine hydrochloride for infusion were evaluated in an open-label, randomized, controlled multicenter trial comparing Bendamustine hydrochloride for infusion to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment. Need-to-treat criteria included hematopoietic insufficiency, B-symptoms, rapidly progressive disease or risk of complications from bulky lymphadenopathy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, Richter's syndrome, or transformation to prolymphocytic leukemia were excluded from the study.

The patient populations in the Bendamustine hydrochloride for infusion and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (79% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), "B" symptoms (51% vs. 53%), lymphocyte count (mean 65.7x10^9./L vs. 65.1x10^9./L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotypic confirmation of CLL (CD5, CD23 and either CD19 or CD20 or both).

Patients were randomly assigned to receive either Bendamustine hydrochloride for infusion at 100 mg/m^2, administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL.

The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for bendamustine hydrochloride for infusion compared to chlorambucil (see Table 5). Survival data are not mature.

Table 5: Efficacy Data for CLL

	Bendamustine hydrochloride for infusion (N=153)	Chlorambucil (N=148)	p-value
Response Rate n (%)			
Overall response rate (95% CI)	90 (59) (51.0, 66.6)	38 (26) (18.6, 32.7)	<0.0001
Complete response (CR)*	13(8)	1(<1)	
Nodular partial response (nPR)**	4(3)	0	
Patial response (PR)+	73(48)	37(25)	
Progression-Free Survival++			
Median, months (95% CI)	18 (11.7,23.5)	6 (5.6,8.6)	
Hazard ratio (95% CI)	0.27 (0.17, 0.43)		<0.0001

CI = Confidence interval

*CR was defined as peripheral lymphocyte counts ≤ 4.0 x 10^9/L, neucephils ≥ 1.5 x 10^9/L, platelets >100 x 10^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepatosplenomegaly , lymph nodes ≤ 1.5 cm, <30% lymphocytes without modularity in at least a normocellular bone marrow and absence of "B" symptoms. The clinical and laboratory criteria were required to be maintained for a period of at least 56 days.

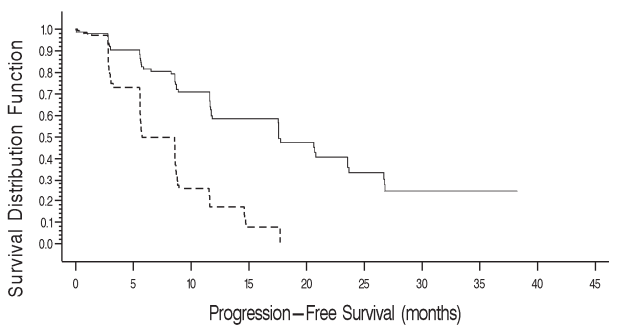
**nPR was defined as described for CR with the exception that the bone marrow biopsy shows persistent nodules.

+PR was defined as ≥ 50% decrease in peripheral lymphocyte count from the pretreatment baseline value, and either ≥ 50% reduction in lymphadenopathy, or ≥ 50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10^9/L or 50% improvement over baseline, platelets > 100 x10^9/L or 50% Improvement over baseline, hemoglobin >110gL or 50% improvement over baseline without transfusions, for a period of 56 days.

++PFS was defined as time from randomization to progression or death from any cause.

Kaplan-Meier estimates of progression-free survival comparing bendamustine hydrochloride for infusion with chlorambucil are shown in figure 1.

Figure 1 . Progression-Free Survival



Study Treatment –Bendamustine Hydrochloride for Infusion --Chlorambucil

13.2 Non-Hodgkin`s Lymphoma (NHL)

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

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

Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table 6.

Table 6: Efficacy Data for NHL*

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

CI = confidence interval

*IRC assessment was based on modified International Working group response criteria (IWG-RC)[2]. Modifications of IWG- RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥ 20 mm.

14 REFERENCES

1. Cheson et al. National Cancer Institute - sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia. Blood Vol 87 1996:pp 4990.
2. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. J Clin Oncol. 1999;17: 1244-1253.
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4. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm-vi/otm-vi-2.html
5. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm*. 2006; 63:1172-1193.
6. Polovich, M., White, J. M., & Kelleher, LO. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, Pk. Oncology Nursing Society.

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 Safe Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from Bendamustine hydrochloride for infusion .The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of Bendamustine hydrochloride for infusion contacts the skin, wash the skin immediately and thoroughly with soap and water. If Bendamustine hydrochloride for infusion contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

15.2 How Supplied

Bendamustine hydrochloride for infusion (with 25 mg Bendamustine hydrochloride): 20 ml, type I amber vial with double rubber stopper and flip off blue seal for single use.

Bendamustine hydrochloride for infusion (with 100 mg Bendamustine hydrochloride): 50 ml, type I amber vial with double rubber stopper and flip off blue seal for single use.

15.3 Storage

Store below 30°C in original package.

Protect from light.

Cytotoxic agent – use caution during handling and preparation. Use of gloves and safety glasses is recommended to avoid exposure.

16 PATIENT COUNSELING INFORMATION

- Allergic (Hypersensitivity Reactions

Patients should be informed of the possibility of mild or serious allergic reactions and to immediately report rash, facial swelling, or difficulty breathing during or soon after infusion.

- Myelosuppression

Patients should be informed of the likelihood that Bendamustine hydrochloride for infusion will cause a decrease in white blood cells, platelets, and red blood cells. They will need frequent monitoring of these parameters. They should be instructed to report shortness of breath, significant fatigue, bleeding, fever, or other signs of infection.

- Pregnancy and Nursing

Bendamustine hydrochloride for infusion can cause fetal harm. Women should be advised to avoid becoming pregnant throughout treatment and for 3 months after Bendamustine hydrochloride for infusion therapy has stopped. Men receiving Bendamustine hydrochloride for infusion should use reliable contraception for the same time period. Advise patients to report pregnancy immediately. Advice patients to avoid nursing while receiving Bendamustine hydrochloride for infusion.

- Fatigue

Advise patients that Bendamustine hydrochloride for infusion may cause tiredness and to avoid driving any vehicle or operating any dangerous tools or machinery if they experience this side effect.

- Nausea and Vomiting

Advise patients that Bendamustine hydrochloride for infusion may cause nausea and/or vomiting. Patients should report nausea and vomiting so that symptomatic treatment may be provided.

- Diarrhea

Advise patients that Bendamustine hydrochloride for infusion may cause diarrhea. Patients should report diarrhea to the physician so that symptomatic treatment may be provided.

- Rash

Advise patients that a mild rash or itching may occur during treatment with Bendamustine hydrochloride for infusion. Advise patients to immediately report severe or worsening rash or itching.

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