Biocon

℞

Bendamustine Hydrochloride For Injection

Lyophilised

XNTA™

LYx

XNTA™
Compostion:
Each Vial contains
Bendamustine Hydrochloride 100mg
Reconstitution: Reconstitute with 20ml of Sterile Water for Injection IP.
Shake well to give a clear, colourless to pale yellow solution with a
Bendamustine Hydrochloride concentration of 5mg/ml.
The reconstituted solution must be further diluted before use and must be transferred to the infusion bag within 30 minutes of reconstitution under room temperature.
Discard any unused portion.

DESCRIPTION
Bendamustine Hydrochloride is an alkylating drug with chemical name of 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$ and the molecular weight is 394.7. Bendamustine Hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent.

CLINICAL PHARMACOLOGY
Mechanism of action
Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form 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.

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 proteins 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 (Vss) 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.

Excretion - 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/m² Bendamustine IV over 1-hour the intermediate t½ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination t½ 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.

INDICATIONS AND USAGE
Chronic Lymphocytic Leukemia (CLL)
XNTA™ (Bendamustine Hydrochloride) is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

Non-Hodgkin's Lymphoma (NHL)
XNTA™ (Bendamustine Hydrochloride) 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.

Clinical Studies
Chronic Lymphocytic Leukemia (CLL)
The safety and efficacy of Bendamustine were evaluated in an open-label, randomized, controlled multicenter trial comparing Bendamustine to chlorambucil. The trial was conducted in 301 previously-untreated patients with Binet Stage B or C (Rai Stages I - IV) CLL requiring treatment.Patients were randomly assigned to receive either Bendamustine at 100 mg/m², administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL.

The results of this open-label randomized study demonstrated a higher rate of overall response and a longer progression-free survival for Bendamustine compared to Chlorambucil (see Table 1). Survival data are not mature.
Table 1: Efficacy Data for CLL

	Bendamustine (N=153)	Chlorambucil (N=148)	p-value
Response Rate n(%)			
Overall response rate	90 (59)	38 (26)	< 0.0001
(95% CI)	(51.0, 66.6)	(18.6, 32.7)	
Complete response (CR)*	13 (8)	1 (< 1)	
Nodular partial response (nPR)**	4 (3)	0	
Partial 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 count ≤4.0 x 10910^9/L, neutrophils ≥1.5 x 10910^9/L, platelets > 100 x 10910^9/L, hemoglobin > 110g/L, without transfusions, absence of palpable hepatosplenomegaly, lymph nodes ≤1.5 cm, < 30% lymphocytes without nodularity 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 10910^9/L or 50% improvement over baseline, platelets > 100 x 10910^9/L or 50% improvement over baseline, hemoglobin > 110g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.
†† PFS was defined as time from randomization to progression or death from any cause.

Non-Hodgkin's Lymphoma (NHL) - The efficacy of Bendamustine 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 intravenously at a dose of 120 mg/m², on Days 1 and 2 of a 21-day treatment cycle. Patients were treated for up to 8 cycles.

Efficacy included overall response rate (complete response + complete response unconfirmed + partial response) and duration of response (DR) as summarized in Table 2.
Table 2: Efficacy Data for NHL*

	Bendamustine (N=100)
Response Rate (%)	
Overall response rate (CR+CRu+PR)	74
(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 to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be≥ 20 mm.

CONTRAINDICATIONS
XNTA™ (Bendamustine Hydrochloride) is contraindicated in patients with a known hypersensitivity (e.g.,anaphylactic and anaphylactoid reactions) to Bendamustine or mannitol.

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

Infections - Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with Bendamustine are more susceptible to infections.

Infusion Reactions and Anaphylaxis - Infusion reactions to Bendamustine 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.

Tumor Lysis Syndrome - Tumor lysis syndrome associated with Bendamustine 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 and, without intervention, may lead to acute renal failure and death.

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.

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

Extravasation - There are postmarketing reports of Bendamustine extravasations resulting in hospitalizations from erythema, marked swelling, and pain. Precautions should be taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of Bendamustine.

Use in Pregnancy – Pregnancy category D. Bendamustine 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 resorptions, skeletal and visceral malformations, and decreased fetal body weights. 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 foetus.

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.

Nonclinical Toxicology
Carcinogenesis, Mutagenesis, Impairment of Fertility - Bendamustine was carcinogenic in mice. After intraperitoneal injections at 37.5 mg/m²/day (12.5 mg/kg/day, the lowest dose tested) and 75 mg/m²/day (25 mg/kg/day) for four days, peritoneal sarcomas in female AB/jena mice were produced. Oral administration at 187.5 mg/m²/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/m², 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.

SIDE EFFECTS
Clinical Trials Experience in CLL - The data described below reflect exposure to Bendamustine in 153 patients. Bendamustine was studied in an active-controlled trial. The population was 45-77 years of age, 63% male, 100% white, and had treatment naïve CLL. All patients started the study at a dose of 100 mg/m² intravenously over 30 minutes on Days 1 and 2 every 28 days.

The most frequent adverse reactions leading to study withdrawal for patients receiving Bendamustine were hypersensitivity (2%) and pyrexia (1%).
Table 3 contains the treatment emergent adverse reactions, regardless of attribution, that were reported in ≥5% of patients in either treatment group in the randomized CLL clinical study.
Table 3: Non-Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

System organ class Preferred term	Number (%) of patients			
	Bendamustine (N=153)		Chlorambucil (N=143)	
	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 NUTRITIONAL 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

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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.

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

Table 4: Incidence of Hematology Laboratory Abnormalities in Patients Who Received Bendamustine or Chlorambucil in the Randomized CLL Clinical Study

Laboratory Abnormality	Bendamustine N=150		Chlorambucil N=141	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hemoglobin 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 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.

Clinical Trials Experience in NHL - The data described below reflect exposure to Bendamustine 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 at a dose of 120 mg/m² intravenously on Days 1 and 2 of a 21-day cycle, upto 8 cycles.

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

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

System organ class Preferred term	Number (%) of patients*	
	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)
Diarrhea	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		
Headache	36 (21)	0
Dizziness	25 (14)	0
Dysgeusia	13 (7)	0
PSYCHIATRIC DISORDERS		
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)	1 (< 1)
Pruritus	11 (6)	0
Dry skin	9 (5)	0
Night sweats	9 (5)	0
Hyperhidrosis	8 (5)	0
VASCULAR DISORDERS		
Hypotension	10 (6)	2 (1)

*Patients may have reported more than 1 adverse reaction. NOTE: Patients counted only once in each preferred term category and once in each system organ class category.

Hematologic toxicities, based on laboratory values and CTC grade, in NHL patients treated in both single arm studies combined are described in Table 6.

Table 6: Incidence of Hematology Laboratory Abnormalities in Patients Who Received Bendamustine in the NHL Studies

Hematology variable	Percent of patients	
	All Grades	Grades 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. 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. Adverse reactions occurring less frequently but possibly related to Bendamustine treatment were hemolysis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and skin necrosis.

DRUG INTERACTIONS

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.

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.

DOSAGE AND ADMINISTRATION

Recommended Dosage for CLL - The recommended dose is 100 mg/m² administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles.

Recommended Dosage for NHL - The recommended dose is 120 mg/m² 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 - Bendamustine 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 blood counts have improved [Absolute Neutrophil Count (ANC) ≥1 x 10910^9/L, platelets ≥75 x 10910^9/L], Bendamustine can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted.

Reconstitution/Preparation for Intravenous Administration

- Aseptically reconstitute each vial as follows:
  - 100 mg XNTA™ vial: Add 20 mL of only Sterile Water for Injection, USP. Shake well to yield a clear, colourless to a pale yellow solution with a Bendamustine HCl concentration of 5 mg/mL. The lyophilized powder should completely dissolve in 5 minutes. If particulate matter is observed, the reconstituted product should not be used.
- Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of Bendamustine HCl in the infusion bag should be within 0.2 – 0.6 mg/mL. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colourless to slightly yellow solution.

Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined above. No other diluents have been shown to be compatible.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Any unused solution should be discarded according to institutional procedures for antineoplastics.

OVERDOSAGE

The intravenous LD_{50} of Bendamustine HCl is 240 mg/m² 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/m². 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 overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

PRESENTATION

XNTA™ is available in sterile single dose vial containing 100 mg of Bendamustine.

INFORMATION FOR PATIENTS

- 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 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 can cause fetal harm. Women should avoid becoming pregnant throughout treatment and for 3 months after Bendamustine therapy has stopped. Men receiving Bendamustine should use reliable contraception for the same time period. Pregnancy should be reported immediately. Nursing should be avoided while receiving Bendamustine.
- Fatigue - Bendamustine may cause tiredness and driving any vehicle or operating any dangerous tools or machinery if they experience this side effect should be avoided.
- Nausea and Vomiting - Bendamustine may cause nausea and/or vomiting. Patients should report nausea and vomiting so that symptomatic treatment may be provided.
- Diarrhea - Bendamustine may cause diarrhea. Patients should report diarrhea to the physician so that symptomatic treatment may be provided.
- Rash - Mild rash or itching may occur during treatment with Bendamustine. Patients should immediately report severe or worsening rash or itching.

Storage : Store below 25 ℃, do not freeze. Protect from light.
Keep out of reach of children.

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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