PRODUCT MONOGRAPH

Pr TREANDA®

(bendamustine hydrochloride for injection)

Lyophilized Powder for Injection, for intravenous infusion

25 mg/ vial and 100 mg/ vial

Antineoplastic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
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Date of Revision:
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Manufactured for:
Teva Canada Innovation
Montréal, Quebec
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PrTREANDA®

(bendamustine hydrochloride for injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous injection	Lyophilized powder, 25 mg/ vial and 100 mg/ vial	mannitol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

TREANDA is indicated for treatment of patients with:

Relapsed indolent B-cell non-Hodgkin lymphoma (NHL) who did not respond to or progressed during or shortly following treatment with a rituximab regimen.

> Effectiveness of TREANDA in patients with indolent B-cell NHL is based on overall response rate and duration of response data from a single-arm pivotal study of TREANDA monotherapy in patients who had prior chemotherapy and did not respond to or progressed during or within 6 months of treatment with rituximab or a rituximab-based regimen (see CLINICAL TRIALS).

Symptomatic chronic lymphocytic leukemia (CLL) who have received no prior treatment.

> Approval of TREANDA in CLL is based on a progression-free survival and overall response rate advantage of TREANDA over chlorambucil in a single randomized controlled trial. Prolongation of overall survival or improvement in quality of life was not demonstrated for TREANDA in this study. Efficacy relative to first-line therapies other than chlorambucil has not been established.

TREANDA should be administered under the supervision of a qualified health professional who is experienced in oncology.

Geriatrics (≥ 65 years of age):
In the NHL and CLL populations, there were no clinically significant differences in efficacy and

in the adverse reaction profile between geriatric (≥ 65 years of age) and younger patients.

Pediatrics (< 18 years of age):
There is no indication for the use of TREANDA in the pediatric population. A phase II study did not support efficacy of TREANDA as a monotherapy in the pediatric population (see **CLINICAL TRIALS**).

CONTRAINDICATIONS

TREANDA is contraindicated in patients who are hypersensitive to bendamustine or to any ingredient in the formulation, including mannitol, or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The following are clinically significant adverse events:

- Cardiac failure and myocardial infarction, including fatalities (see Cardiovascular below)
- Myelosuppression (see Hematologic below)
- Infections, including fatalities (see Hematologic below)
- Secondary malignancies (see Carcinogenesis and Mutagenesis below)
- Serious skin reactions [Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)], including fatalities (see Skin below)

TREANDA **should not** be used in patients with:

- Serious infections (see Immune below)

TREANDA should be administered under the supervision of a qualified health professional who is experienced in oncology.

General

TREANDA is not recommended for a subset of relapsed indolent NHL patients with poor tolerance to prior therapies (including other alkylating agents) as they would not be expected to tolerate the 120 mg/m^2 dose administered on days 1 and 2 of a 21-day cycle. The efficacy and safety of other dosing regimens for these patients has not been established.

Extravasation

There are post-marketing 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 TREANDA.

Carcinogenesis and Mutagenesis

Pre-malignant and malignant diseases have developed in patients treated with TREANDA including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. Bendamustine is mutagenic, genotoxic and carcinogenic with cancers reported following subcutaneous and oral delivery of the drug to mice (see **TOXICOLOGY**).

Cardiovascular

Cardiac disorders

Cardiac failure, myocardial infarctions, palpitations, angina pectoris, arrhythmias, pericardial effusion and tachycardia have been reported in patients receiving bendamustine. Some of the reports of congestive heart failure and myocardial infarction were fatal in outcome. Hypokalemia has also been reported in clinical trials. An increase in the excretion fraction of potassium and other electrolytes has been reported in non-clinical studies (see **DETAILED PHARMACOLOGY, Safety Pharmacology**). Serum potassium levels should be closely monitored in patients with cardiac disorders and ECG measurements should be performed where indicated (see **Monitoring and Laboratory Tests**).

ECG Changes, including QTc prolongation

The potential for TREANDA to cause QTc prolongation has been evaluated in a clinical study, and a small increase in QTcF effect was demonstrated (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**). The potential for delayed effects on the QT interval-was not evaluated. Isolated cases of ECG changes (including QT prolongation) have been observed in patients administered TREANDA at a dose higher than recommended for NHL and CLL patients (see **DOSAGE AND ADMINISTRATION,** Overdosage). In preclinical *in vitro* cardiac safety studies, TREANDA inhibited hERG-1 tail current amplitude but had no effect on the cardiac action potential in isolated canine Purkinje fibers (see **DETAILED PHARMACOLOGY, Safety Pharmacology**).

Hypertension

In the phase III CLL study there were 8 reports (5%) of grade 3 or 4 hypertension (3 reported as hypertensive crisis) in the TREANDA treatment group compared to 2 (1%) events (0 reported as hypertensive crisis) in the chlorambucil control arm (see **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions)**. Hypertension should be well-controlled prior to administration of TREANDA.

Endocrine and Metabolism

Tumor Lysis Syndrome

Tumor lysis syndrome associated with TREANDA 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 TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate hydration status, and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of TREANDA therapy. However, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly (see **Skin** below).

Hematologic

Myelosuppression

Patients treated with TREANDA are likely to experience myelosuppression. In the NHL study, 98% of patients had Grade 3-4 myelosuppression (see **ADVERSE REACTIONS**). 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. Hematologic nadirs were observed predominantly in the third week of therapy. In the clinical trials, blood counts were monitored every week initially.

In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb) and neutrophils closely (see **Monitoring and Laboratory Tests**). 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 absolute neutrophil count [ANC] should be $\geq 1 \times 10^9$/L and the platelet count should be $\geq 75 \times 10^9$/L (see **DOSAGE AND ADMINISTRATION**.)

Hepatic

Hepatotoxicity

Fatal and serious cases of liver injury have been reported with TREANDA. Reactivation of hepatitis B was a confounding factor in some patients (see **Immune**, **Infections**). Most cases were reported within the first three months of starting therapy.

Grade 3 or 4 increases in bilirubin occurred in 3% of TREANDA treated patients in the CLL study. Grade 3 or 4 increases in aspartate transaminase [AST] and alanine transaminase [ALT] were reported for 1% and 3% of CLL patients in the TREANDA treatment arm, respectively. One patient in the TREANDA arm of the study discontinued due to hepatotoxicity.

Monitor liver chemistry tests prior to and during bendamustine therapy (see **Monitoring and Laboratory Tests**

Immune

Infections

TREANDA should not be administered to patients with serious infections, including patients with HIV. Infections, including hepatitis, pneumonia and sepsis have been reported in patients in clinical trials and in post-marketing reports. Infections have been associated with hospitalization, septic shock and death. Patients and physicians should closely monitor for signs of infection (see **Monitoring and Laboratory Tests**). Patients with myelosuppression following treatment with TREANDA are more susceptible to infections and should be advised to contact a physician if they have symptoms or signs of infection. The use of live attenuated vaccines should be avoided.

Cytomegalovirus (CMV) infections were reported in 5% of patients in the NHL study and were responsible for at least one death. CMV testing should be considered in patients with fever of unknown origin.

Herpes zoster was reported in 12% of patients in the NHL study (Grade 3: 4%; Grade 4; 0%). Patients should be informed about early signs and symptoms of herpes zoster and should seek treatment as early as possible.

Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after treatment with bendamustine, with some cases resulting in acute hepatic failure or fulminant hepatitis leading to fatal outcome.

Patients should be monitored for reactivation of infections including (but not limited to) Hepatitis B, Cytomegalovirus, Mycobacterium tuberculosis, and Herpes zoster. Patients should undergo appropriate measures (including clinical and laboratory monitoring, prophylaxis, and/or treatment) for infection and/or infection reactivation prior to administration, throughout therapy, and several months following termination.

Sensitivity/Resistance

Infusion Reactions and Anaphylaxis

Infusion reactions to TREANDA 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.

Sexual Function and Reproduction

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.

Skin

Fatal and serious skin reactions have been reported with TREANDA treatment in clinical trials and post marketing safety reports, including toxic skin reactions [Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS)], bullous exanthema, and rash. Events occurred when TREANDA was given as a single agent and in combination with other anticancer agents or allopurinol.

There may be an increased risk of severe skin toxicity when these agents are administered concomitantly.

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, TREANDA should be withheld or discontinued.

Special Populations

Pregnant Women: TREANDA can cause fetal harm when administered to a pregnant woman. Toxicology studies in mice and rats demonstrated that bendamustine is embryotoxic and teratogenic (see **TOXICOLOGY**). There are no adequate and well-controlled studies in pregnant women.

TREANDA is not recommended during pregnancy. 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.

Nursing Women: 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.

Women or Men of Childbearing Potential: Women or men of childbearing potential should be advised to start using an effective method of contraception 2 weeks before receiving TREANDA until at least 4 weeks after the last dose of the study medication.

Pediatrics (< 18 years of age):
In a single arm phase I/II trial conducted in pediatric patients with leukemia, adverse events of anemia, abdominal pain, pyrexia, febrile neutropenia, hypokalemia, hypomagnesemia,

hypertension, hypotension, and grade 3/4 hematologic toxicity were more common in pediatric patients than observed in adults with NHL. No new adverse drug reactions were identified (see ADVERSE REACTIONS).

Higher mean exposures to bendamustine (1.3-2-fold) were observed in pediatric patients following a 120 mg/m^2 intravenous infusion over 60 minutes compared to adult patients following the same dose (see ACTION AND CLINICAL PHARMACOLOGY).

Geriatrics (≥ 65 years of age): 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.

Renal Impairment: No studies assessing the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with creatinine clearance (CrCL) between 40-80 mL/min. TREANDA should not be used in patients with CrCL < 40 mL/min (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**).

Hepatic Impairment: No studies assessing the impact of hepatic impairment on the pharmacokinetics of bendamustine have been conducted. TREANDA should be used with caution in patients with mild hepatic impairment (total bilirubin > ULN – 1.5X ULN or AST or ALT or ALP > ULN – 2.5 X ULN). TREANDA should not be used in patients with moderate or severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations**). Patients with non-clinically significant elevations of bilirubin due to Gilbert's disease were eligible for clinical studies with TREANDA.

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

Monitoring and Laboratory Tests

Prior to initiating treatment with TREANDA, complete blood counts (CBC), renal (creatinine) and liver (AST, ALT, bilirubin and ALP) function tests, electrolytes, blood pressure and hepatitis B testing should be performed and/ or measured.

During treatment with TREANDA, CBC and electrolytes should be measured at regular intervals and CBC more frequently in patients who develop cytopenias (see **ADVERSE REACTIONS**). Patients and physicians should closely monitor for signs of infection and in the case of fever of unknown origin CMV testing should be performed. Signs of tumor lysis syndrome should be monitored where warranted. Periodic ECG monitoring should be performed in patients with cardiac disorders, particularly in the event of electrolyte imbalances. Monitoring of liver and renal functions, blood pressure and blood sugar should also be performed periodically.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Patients with B-cell indolent NHL received a higher and more frequent dose of bendamustine compared to CLL patients in the pivotal clinical trials. The adverse event profile for indolent B-cell lymphoma patients follows administration of a 120 mg/m^2 dose of bendamustine on days 1 and 2 of a 21-day cycle for up to a total of 8 cycles. Patients with CLL were administered a 100 mg/m^2 dose of bendamustine on days 1 and 2 of a 28-day cycle for a maximum of 6 cycles. Patients with small lymphocytic lymphoma (SLL) were enrolled into both the NHL and CLL clinical trials.

In the NHL study, the median total dose was 1410 mg/m^2 with a median duration of treatment of 107 days (range 2 – 233). In the CLL study, the median total dose was 1010 mg/m^2 with a median duration of treatment of 142 days (range 2-211).

Twenty-one of the 100 treated patients (21%) in the NHL study had SLL while 10 of 161 patients (6.2%) in the CLL study had SLL. There were 4 on-treatment deaths in the SLL subpopulation in the NHL study compared to none for the SLL subpopulation of the CLL study.

Hematologic laboratory abnormalities (see Tables 2 and 4) were more commonly identified as adverse events following administration of bendamustine in the NHL study compared to the CLL trial (see Tables 1 and 3). In both trials the most common hematological adverse events were neutropenia, thrombocytopenia, anemia and leukopenia.

The most common non-hematologic adverse events (≥30%) occurring in the NHL study were nausea (77%), fatigue (64%), diarrhea (42%), vomiting (40%), pyrexia (36%) and constipation (31%). The most common non-hematologic Grade 3 or 4 adverse events (≥5%) were fatigue (14%), febrile neutropenia, hypokalemia and dehydration, each reported in 6% of patients, and pneumonia and diarrhea , each reported in 5% of patients. Antiemetics were concomitantly administered to 96% of patients.

Serious adverse events, regardless of causality, were reported in 39% of NHL patients receiving TREANDA. The most common serious adverse events occurring in ≥5% of patients were febrile neutropenia and pneumonia. Other important serious adverse events reported were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome.

Non-hematologic adverse events in the CLL study that occurred with a frequency greater than 15% in the TREANDA group were pyrexia (25%), nausea (19%), and vomiting (16%). Antiemetics were taken concomitantly by 37% of patients in the bendamustine treatment group compared to only 4% in the chlorambucil control group.

The most common Grade 3 or 4 non-hematological adverse events reported for the bendamustine treatment group in CLL were pyrexia, pneumonia, infection, hyperuricemia, rash, hypertensive crisis (all each 2%) and hypertension (3%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Non-Hodgkin Lymphoma (NHL)

The data described below reflect exposure to TREANDA in 100 patients with indolent B-cell NHL treated in a single-arm pivotal study. These patients received TREANDA at a dose of 120 mg/m^2 intravenously (i.v.) over 60 minutes on Days 1 and 2 for up to 8 21-day cycles.

Sixty-eight patients (68%) had adverse events causing dose reduction, interruption or discontinuation. The most common reason for dose delay was neutropenia. Thirty-one patients had adverse events with reported outcomes of discontinuation of study drug treatment. The most common events with this outcome were thrombocytopenia (9%), fatigue (6%) and neutropenia (4%).

The treatment-emergent adverse events occurring in at least 5% of the NHL patients, regardless of severity and causality, are shown in Table 1.

Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA).

Table 1: Adverse Events Occurring in at Least 5% of NHL Patients Treated with TREANDA by System Organ Class and Preferred Term

System organ class Preferred term	Number (%) of patients*	
	All Grades	**Grade 3/4**
Total number of patients with at least 1 adverse event	100 (100)	77 (77)
Blood and lymphatic systems disorders		
Neutropenia	45 (45)	42 (42)
Anemia	37 (37)	10 (10)
Thrombocytopenia	36 (36)	16 (16)
Leukopenia	16 (16)	12 (12)
Cardiac disorders		
Tachycardia	5 (5)	0
Gastrointestinal disorders		
Nausea	77(77)	4 (4)
Diarrhea	42 (42)	5 (5)
Vomiting	40 (40)	2 (2)
Constipation	31 (31)	0
Stomatitis	21 (21)	0
Abdominal pain	14 (14)	1 (1)
Dyspepsia	14 (14)	0

System organ class Preferred term	Number (%) of patients*	
	All Grades	Grade 3/4
Gastroesophageal reflux disease	11 (11)	0
Dry mouth	9 (9)	0
Abdominal pain upper	5 (5)	0
General disorders and administration site conditions		
Fatigue	64 (64)	14 (14)
Pyrexia	36 (36)	1 (1)
Chills	14 (14)	0
Edema peripheral	14 (14)	0
Asthenia	13 (13)	4 (4)
Infusion site pain	7 (7)	0
Pain	9 (9)	0
Thirst	6 (6)	0
Catheter site pain	5 (5)	0
Infections and infestations		
Herpes zoster	12 (12)	4 (4)
Urinary tract infection	11 (11)	3 (3)
Upper respiratory tract infection	9 (9)	0
Pneumonia	9 (9)	5 (5)
Nasopharyngitis	9 (9)	0
Sinusitis	8 (8)	0
Febrile neutropenia	6 (6)	6 (6)
Herpes simplex	6 (6)	0
Oral candidiasis	6 (6)	0
Cytomegalovirus infection	5 (5)	3 (3)
Investigations		
Weight decreased	20 (20)	3 (3)
Blood creatinine increased	5 (5)	1 (1)
Metabolism and nutrition disorders		
Anorexia	24 (24)	3 (3)
Dehydration	15 (15)	6 (6)
Decreased appetite	12 (12)	1 (1)
Hypokalemia	11 (11)	6 (6)
Hypomagnesaemia	5 (5)	2 (2)
Musculoskeletal and connective tissue disorders		
Back pain	13 (13)	3 (3)
Arthralgia	6 (6)	0
Pain in extremity	6 (6)	2 (2)
Bone pain	5 (5)	0
Myalgia	5 (5)	0
Nervous system disorders		
Headache	21 (21)	0
Dizziness	15 (15)	0
Dysgeusia	11 (11)	0
Psychiatric disorders		
Insomnia	15 (15)	0
Anxiety	8 (8)	0
Depression	5 (5)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	17 (17)	2 (2)
Cough	16 (16)	1 (1)

System organ class Preferred term	Number (%) of patients*	
	All Grades	Grade 3/4
Pharyngolaryngeal pain	10 (10)	1 (1)
Nasal congestion	5 (5)	0
Skin and subcutaneous tissue disorders		
Rash	15 (15)	1 (1)
Dry skin	7 (7)	0
Pruritus	6 (6)	0
Hyperhidrosis	5 (5)	0
Vascular disorders		
Hypotension	8 (8)	2 (2)

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

The following clinically relevant adverse events were reported in < 5% of the patients treated with TREANDA:

Cardiac disorders: myocardial infarction (3%), cardiorespiratory arrest (2%), sinus tachycardia (2%)

General disorders and administration site conditions: infusion-related reaction (2%)

Infections and infestations: cytomegalovirus infection (3%), sepsis/septic shock (2%)

Metabolism and nutrition disorders: tumour lysis syndrome (2%), hyperkalemia (2%), hypoglycemia (3%), hyponatremia (3%)

Neoplasms benign, malignant and unspecified: myelodysplastic syndrome (1%), anaplastic large T-cell lymphoma (1%), squamous cell carcinoma (1%)

Renal and urinary disorders: acute renal failure (1%)

Respiratory, thoracic and mediastinal disorders: respiratory failure (2%).

Chronic Lymphocytic Leukemia (CLL)

The data described below reflect exposure to TREANDA in 161 patients. TREANDA was studied in an active-controlled trial. All patients started the study at a dose of 100 mg/m^2 intravenously over 30 minutes on Days 1 and 2 for up to 6 28-day cycles.

Table 2 contains the treatment emergent adverse events, regardless of attribution, that were reported in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA).

Worsening hypertension was reported in 4 patients treated with TREANDA in the randomized CLL clinical study and none treated with chlorambucil. Three of these 4 adverse events were described as a hypertensive crisis and were managed with oral medications and resolved. The most frequent adverse events leading to study withdrawal for patients receiving TREANDA were hypersensitivity (2%), pyrexia (1%) and rash (1%).

Table 2: Adverse Events Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

	Number (%) of patients			
	TREANDA (N=161)		Chlorambucil (N=151)	
System Organ Class Preferred term	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Total number of patients with at least 1 adverse event	**143 (89)**	**88 (55)**	**123 (81)**	**49 (32)**
Blood and lymphatic system disorders				
Neutropenia	**44 (27)**	**37 (23)**	**21 (14)**	**14 (9)**
Thrombocytopenia	**37 (23)**	**19 (12)**	**31 (21)**	**12 (8)**
Anemia	**30 (19)**	**4 (2)**	**19 (13)**	**0**
Leukopenia	**28 (17)**	**23 (14)**	**5 (3)**	**2 (1)**
Lymphopenia	**10 (6)**	**10 (6)**	**1 (<1)**	**0**
Gastrointestinal disorders				
Nausea	31 (19)	1 (<1)	21 (14)	1 (<1)
Vomiting	25 (16)	2 (1)	10 (7)	0
Diarrhea	16 (10)	2 (1)	6 (4)	0
General disorders and administration site conditions				
Pyrexia	40 (25)	4 (2)	8 (5)	2 (1)
Fatigue	14 (9)	2 (1)	8 (5)	0
Asthenia	13 (8)	0	6 (4)	0
Chills	9 (6)	0	2 (1)	0
Immune system disorders				
Hypersensitivity	8 (5)	2 (1)	3 (2)	0
Infections and infestations				
Nasopharyngitis	11 (7)	0	12 (8)	0
Infection	10 (6)	3 (2)	2 (1)	1 (<1)
Herpes simplex	5 (3)	0	7 (5)	0
Investigations				
Weight decreased	10 (6)	0	5 (3)	0
Metabolism and nutrition disorders				
Hyperuricemia	12 (7)	3 (2)	2 (1)	0
Respiratory, thoracic and mediastinal disorders				
Cough	10 (6)	1 (<1)	8 (5)	1 (<1)
Skin and subcutaneous tissue disorders				
Rash	15 (9)	4 (2)	7 (5)	3 (2)
Pruritus	8 (5)	0	4 (3)	0

The following clinically relevant adverse events were reported in <5% of the patients treated with TREANDA in the Phase III randomized controlled trial:

Cardiac disorders: myocardial infarction (<1%), supraventricular arrhythmia (<1%)

Hepatobiliary disorders: hepatotoxicity (2%)

Infections and infestations: sepsis/pseudomonal sepsis (1%)

Investigations: bilirubin increased (2%)

Metabolism and nutrition disorders: tumour lysis syndrome (1%), hyperglycemia (<1%), hyperkalemia (<1%), hypokalemia (<1%)

Neoplasms benign, malignant and unspecified: bronchial carcinoma (<1%), lung neoplasm (<1%)

Renal and urinary disorders: renal impairment (1%), acute renal failure (<1%)

Respiratory, thoracic and mediastinal disorders: dyspnoea (2%), respiratory failure (<1%)

Vascular disorders: hypertension (3%), hypertensive crisis (2%).

Abnormal Hematologic and Clinical Chemistry Findings

Non-Hodgkin Lymphoma (NHL)

Hematologic toxicities, based on laboratory values and CTC grade, in the NHL study patients are described in Table 3. 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 were hypokalemia (6%), hyperglycemia (5%), elevated creatinine (3%), hypocalcemia (3%), hyponatremia (2%) and elevated albumin (2%).

Table 3: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA in the NHL Study

Hematology Variable	Percent of patients	
	All Grades	Grades 3/4
Lymphocytes Decreased	96	94
Leukocytes Decreased	92	56
Hemoglobin Decreased	94	10
Neutrophils Decreased	83	61
Platelets Decreased	88	25

Chronic Lymphocytic Leukemia (CLL)

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 TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

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

	TREANDA (N=158)		Chlorambucil (N=149)	
Laboratory Abnormality	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Hemoglobin Decreased	141 (89)	21 (13)	124 (83)	12 (8)
Platelets Decreased	122 (77)	18 (11)	115 (77)	14 (9)
Leukocytes Decreased	98 (62)	44 (28)	32 (21)	4 (3)
Lymphocytes Decreased	109 (69)	77 (49)	31 (21)	6 (4)
Neutrophils Decreased	119 (75)	67 (42)	95 (64)	31 (21)

In the randomized CLL clinical study, 34% of TREANDA-treated 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 TREANDA may also have changes in their creatinine levels.

Pediatric patients with acute leukemia

In a single arm phase I/II trial conducted in pediatric patients with leukemia, adverse events of anemia (66%), abdominal pain (21%), pyrexia (53%), febrile neutropenia (39%), hypokalemia (18%), hypomagnesemia (18%), hypertension (29%), hypotension (18%), and grade 3/4 hematologic toxicity as assessed by routine laboratory tests of platelets (85%), neutrophils (79%), hemoglobin (47%), and leukocytes (71%) were reported.

Post-Market Adverse Drug Reactions

The following adverse events have been identified during post-approval use of TREANDA. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency: Pneumocystis jiroveci pneumonia, acute respiratory distress syndrome, anaphylaxis, and injection or infusion site reactions including phlebitis, pruritus, irritation, pain, and swelling, atrial fibrillation, congestive heart failure, myocardial infarction, palpitations and pancytopenia. Some cases of congestive heart failure and myocardial infarction were fatal.

Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications. (See **WARNINGS AND PRECAUTIONS**)

DRUG INTERACTIONS

Overview

No clinical assessments of pharmacokinetic drug-drug interactions between TREANDA 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. There is a potential for CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin) or inducers (e.g., omeprazole, smoking) to affect the circulating levels of bendamustine and its active metabolites. However, it is unknown if this will significantly impact the activity of bendamustine in patients. 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 such as P-glycoprotein (Pgp), breast cancer resistance protein (BCRP) and other transporters has not been evaluated. *In vitro* data suggest that bendamustine may be a substrate for P-glycoprotein.

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.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

TREANDA 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 [ANC ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician at a reduced dose according to the dose modification schemes for NHL and CLL discussed below.

Recommended Dose and Dosage Adjustment

Dosing Instructions for NHL

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

Dose Modifications for NHL:
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.

Dosing Instructions for CLL

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

Dose Modifications and Reinitiation of Therapy for CLL:
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.

Administration

Reconstitution:

Parenteral Products:

Aseptically reconstitute each single-use TREANDA vial as follows:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
25 mg	5 mL of **only Sterile Water for Injection, USP**	5 mL	5 mg/mL
100 mg	20 mL of **only Sterile Water for Injection, USP**	20 mL	5 mg/mL

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. Both polyvinyl chloride (PVC) and polyethylene (PE) lined PVC infusion bags may be used. 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 colorless 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.

Admixture Stability
TREANDA vial contains no antimicrobial preservative and is intended for single-use only. The admixture should be prepared as close as possible to the time of patient administration.

Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture can be used within 24 hours when stored refrigerated (2-8°C) or within 3 hours when stored at room temperature (15-30°C) and room light. Administration of TREANDA must be completed within this period.

OVERDOSAGE

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 TREANDA overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TREANDA contains bendamustine hydrochloride (bendamustine HCl), an alkylating agent, as the active ingredient. 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 and role of the benzimidazole ring has not been fully defined.

Pharmacodynamics

The cytotoxic activity of bendamustine was evaluated against a range of human solid and leukemic cell lines. Two assays were performed to assess cell viability. For adherent cell lines, assays of total cellular protein by the bicinchoninic acid (BCA) method were used as a measure of cell survival. For cells grown in suspension, changes in the number of metabolically active cells were measured by the WST-1 tetrazolium assay.

Bendamustine showed a wide range of half-maximal inhibitory concentration (IC_{50}) values in the tumor cell lines tested. The greatest potency was observed for the 2 small cell lung cancer lines NCI-H69 (IC_{50}=4 μM) and NCI-H146 (IC_{50}=6 μM). IC_{50} values at or below 20 μM were also determined for the T47D and MDA-MB-453 breast cancer cell lines, the CCRF-SB B-cell acute lymphoblastic leukemia cell line, the KG-1 acute myeloid leukemia cell line and the Namalwa NHL cell line.

In the NHL study, bendamustine exposure ($AUC_{0-\infty}$ and C_{max}) was not influenced by the covariates analyzed (age, sex, weight, etc.) and was not a significant predictor of responder status, duration of response or progression-free survival. The pharmacokinetic/pharmacodynamic analyses were also unable to establish a relationship between exposure and treatment emergent adverse events with the exception of nausea. There was a positive correlation between nausea and bendamustine C_{max} but not $AUC_{0-\infty}$.

Electrocardiography

A multicentre, open-label, uncontrolled single arm ECG assessment study was performed in 53 patients, 80% of whom had indolent NHL. On day 1 of Cycle 1, patients were administered a rituximab IV infusion followed by a 30 minute 90 mg/m^2 IV infusion of bendamustine. Triplicate ECG recordings were assessed at baseline prior to Day 2 bendamustine dosing of 90 mg/m^2, at the end infusion, and 1 hour after infusion. The mean change from baseline for QTcF interval duration showed a change of +6.7 ms (90% CI 4.3, 9.1) and +4.1 ms (90% CI 1.8, 6.3) for the end of infusion and 1 hour time points after administration of bendamustine respectively.

Pharmacokinetics

The pharmacokinetic profile of bendamustine for a subgroup of patients of the NHL study is provided in Table 5. The majority (93%) of the infused bendamustine dose was cleared from the plasma within 7 hours.

Table 5: Mean Pharmacokinetic Parameters with Standard Error for Bendamustine Following a Single Dose of 120 mg/m^2 of Bendamustine Hydrochloride During Cycle 1

Parameter	Mean (n =11)	S.E.
C_{max} (ng/mL)	5605	2427
t_{max} (hr)	0.99	NA
AUC_{0-7} (ng.hr/mL)	6633	3604
$AUC_{0-\infty}$ (ng.hr/mL)	7162	3785
$t_{1/2\ elimination}$ (hr)	0.72	0.30

NA = non-applicable

Absorption: Following a single i.v. dose of bendamustine hydrochloride C_{max} typically occurred at the end of the infusion. The dose proportionality of bendamustine has not been established in humans, although in animal studies plasma concentrations were often greater than dose proportional.

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. Blood to plasma concentration ratios suggest that bendamustine does not bind to erythrocytes. In mice and rats, the majority of [^{14}C]-bendamustine distributed to the kidneys and liver with no evidence of melanin associated binding (pigmented skin or uveal tract) or of significant uptake across the blood-brain barrier.

In a human mass balance study, levels of radioactivity were sustained in the plasma as compared with plasma concentrations of bendamustine, M3 and M4, suggesting that, despite the rapid clearance of bendamustine and its active metabolites, 1 or more longer-lived [^{14}C]-bendamustine-derived materials remain in the plasma. The mean steady-state volume of distribution (V_{ss}) of bendamustine was approximately 20 L. Steady-state volume of distribution for total radioactivity was approximately 50 L, indicating that neither bendamustine nor total radioactivity is extensively distributed into the tissues.

Metabolism: *In vitro* data indicate that bendamustine is readily hydrolyzed to inactive monohydroxy and dihydroxy-bendamustine metabolites, HP1 and HP2 respectively. Two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. Concentrations of these metabolites in plasma are 1/10th and 1/100th that of the parent compound, respectively, suggesting that the cytotoxic activity is primarily due to bendamustine. Results of a human mass balance study indicate that bendamustine is extensively metabolized via hydrolytic, oxidative, and conjugative pathways and very little unmodified bendamustine is excreted in feces and urine

(see **Excretion** below).

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: Mean recovery of total radioactivity in cancer patients following intravenous infusion of [^{14}C]-bendamustine hydrochloride was approximately 76% of the radiochemical dose when collected up to day 8 (168 hrs post-dose). Approximately half (45.5%) of the dose was recovered in the urine and approximately a quarter (25.2%) of the dose was recovered in the feces. Urinary excretion was confirmed as a relatively minor pathway of elimination of unmodified bendamustine, with only approximately 3.3% of the dose recovered in the urine as the parent compound. Less than 1% of the dose was recovered in the urine as M3 and M4, and less than 5% of the dose was recovered in the urine as HP2.

Bendamustine clearance in humans is approximately 700 mL/minute. After a single dose of 120 mg/m^2 bendamustine i.v. over 1 hour, the mean apparent terminal elimination half-life ($t_{½}$) of the parent compound is approximately 40 minutes. The mean apparent $t_{½}$ of M3 and M4 are approximately 3 hours and 40 minutes, respectively. Little or no accumulation in plasma is expected for bendamustine administered on days 1 and 2 of a 21-day cycle.

Special Populations and Conditions

Pediatrics: Bendamustine pharmacokinetics were evaluated in 42 pediatric patients with leukemia aged 1 to 19 in a single Phase I/II trial that administered TREANDA at 90 and 120 mg/m^2 doses as an intravenous infusion over 60 minutes (see CLINICAL TRIALS). The geometric mean body surface adjusted clearance of bendamustine was 14.2 L/h/m^2. The results of this study showed that the pharmacokinetic profile of bendamustine was similar across the pediatric population.

A comparison of the systemic exposure in pediatric patients at 120 mg/m^2 to that obtained in adult cancer patients at that same dose, indicated that mean C_{max} and AUC_{0-t} in pediatric patients were approximately 1.3- and 2-fold higher, respectively, than those in adults. C_{max} ranged from 997ng/mL to 16378 ng/mL in pediatric patients and from 1972 ng/mL to 10593 ng/mL in adult patients; AUC_{0-t} ranged from 1999 ng•hr/mL to 33307 ng•hr/mL in pediatric patients and from 1599 ng•hr/mL to 13496 ng•hr/mL in adult patients.

Geriatrics: Bendamustine exposure (as measured by AUC and C_{max}) has been studied in patients aged 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 **WARNINGS AND PRECAUTIONS, Special populations, Geriatrics**)

Gender: The pharmacokinetics of bendamustine were similar in male and female patients.

Race: The effect of race on the safety, and/or efficacy of TREANDA has not been established. A small study in Japanese patients (n =6) suggest that the pharmacokinetics of bendamustine

following intravenous administration of bendamustine are not affected by race.

Hepatic Insufficiency: In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin > ULN – 1.5 X ULN or AST or ALT or ALP > ULN – 2.5 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 (or severe) hepatic impairment (see **WARNINGS AND PRECAUTIONS, Special populations, Hepatic Impairment**).

Renal Insufficiency: In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no 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 CrCL between 40-80 mL/min. Bendamustine should not be used in patients with CrCL <40 mL/min (see **WARNINGS AND PRECAUTIONS, Special populations, Renal Impairment**).

STORAGE AND STABILITY

TREANDA may be stored at 2-25°C, with excursions permitted up to 30°C. Retain in original package until time of use to protect from light.

SPECIAL HANDLING INSTRUCTIONS

As with other toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from TREANDA. 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 TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TREANDA contains 25 mg or 100 mg bendamustine hydrochloride. Non-medicinal ingredients: mannitol.

TREANDA is supplied as a sterile lyophilized powder for injection as 25 mg in 8 mL amber single-use vials and 100 mg in 20 mL amber single-use vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: bendamustine hydrochloride

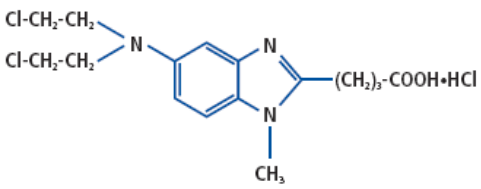
Chemical name:

1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride

Molecular formula and molecular mass:

$C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$, 394.7 g/mole

Structural formula:



Physicochemical properties:

Bendamustine hydrochloride is a white to off-white powder with amphoteric properties due to the nitrogen mustard group and the butyric acid side chain. It has a pH of 2.7 in a 1% w/v solution. Bendamustine hydrochloride is soluble over the physiological pH range.

CLINICAL TRIALS

Non-Hodgkin Lymphoma (NHL)

The safety and efficacy of TREANDA was evaluated in a single-arm pivotal trial (SDX-105-03) of patients with indolent B-cell non-Hodgkin lymphoma (NHL) who did not respond to treatment with or progressed within 6 months of a rituximab regimen. Patients received TREANDA intravenously at a dose of 120 mg/m^2, on Days 1 and 2 of a 21-day treatment cycle for a maximum of 8 cycles.

Study demographics and trial design

The study was conducted at 24 centers in the United States (US) and 4 centers in Canada, by 28 investigators. The primary objectives were to determine the overall response rate (ORR) and duration of response (DR) in patients with indolent B-cell NHL treated with bendamustine. In addition to prior rituximab treatment, patients were required to have received at least 1 prior chemotherapy, with a maximum of 3 prior chemotherapy regimens.

Efficacy was based on the assessments by a blinded independent review committee (IRC) and included ORR (complete response + complete response unconfirmed + partial response) and DR. The study was designed to rule out an ORR of <40% and a duration of response of <4 months (null hypothesis). Tumor assessments were performed every 6 weeks for the first two tumor assessments and every 12 weeks thereafter until the patient completed treatment.

In this study, the mean age was 59.3 years, 65% were male, and 95% of the patients 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.

Study results

As summarized in Table 6, the results for the primary efficacy endpoints of ORR of 75% (p<0.0001) and median DR of 40 weeks by IRC assessment were statistically significant.

Table 6: Results of Study SDX-105-03 [*a]

TREANDA	**Study SDX-105-03 IRC (N=100)**
Response Rate (%)	
Overall response rate (CR + Cru + PR)	75
(95% CI)	(65.3, 83.1)
p-value[*b]	< 0.0001
Complete response (CR)	14
Complete response unconfirmed (CRu)	3
Partial response (PR)	58
Duration of Response (DR)	
Median, weeks (95% CI)	40.1 (31.0, 46.9)

CI = confidence interval

[*a] IRC assessment was based on modified International Working Group response criteria (IWG-RC) 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.

[*b] based on the null hypothesis of an ORR of <40%.

The overall response rate and median duration of response for patients who responded to bendamustine treatment after receiving previous chemotherapy are presented in Table 7. Responses were seen in patients who previously received an alkylating agent (74%), in patients with disease refractory to prior alkylating agent therapy (60%), in patients with disease refractory

to their last chemotherapy (64%), and in patients with prior radioimmunotherapy (63%). Durable responses were seen across all patient groups defined by baseline characteristics.

Table 7: Overall Response Rate (ORR) and Duration of Response (DR) in Patients that Received Previous Therapies

VARIABLE	Number of Patients (%)	ORR (Cr + Cru + PR) (IRC)	Median DR *[a] (weeks) (IRC)
TYPE OF PREVIOUS THERAPY	100 (100)	75% (CI 65.34, 83.12) (p<0.0001)	40.1 (CI 31.0, 45.3)
PREVIOUS CHEMOTHERAPY REGIMENS	99 (99)		
Alkylator containing chemotherapy (CVP, CHOP)	91 (91)	74% (CI 63.35, 82.31)	36.6 (CI 28.9, 46.9)
Disease refractory *[b] to the last Alkylator containing chemotherapy	30 (30)	60% (CI 40.60, 77.34)	33.3 (CI 21.4, NA)
Disease refractory to the last chemotherapy	36 (36)	64% (CI 46.22, 79.18)	27.3 (CI 21.4, NA)
Radioimmunotherapy (RIT)	24 (24)	63% (CI 40.59, 81.20)	47.4 (CI 30.1, 66.1)
NUMBER OF PRIOR CHEMOTHERAPY REGIMENS			
Any	99 (99)		
1	41(41)	75% (CI 64.89, 83.45)	40.3 (CI 33.3, 47.4)
2	36 (36)		
3	14 (14)		
>3	8 (8)	75% (CI 34.91, 96.81)	19.7 (CI 18.3, 30.1)

*[a] Patients who are progression-free at the time of data analysis were censored at the time of their last assessment of tumor response.
*[b] Fail to respond or progress during treatment with chemotherapy.

There were no clinically relevant differences on overall response rate and duration of response between genders.

Chronic Lymphocytic Leukemia (CLL)

The safety and efficacy of TREANDA in the treatment of CLL were evaluated in an open-label, randomized, controlled multicenter trial comparing TREANDA to chlorambucil (study 02CLLIII). The trial was conducted in 319 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.

Patients were randomly assigned 1:1 to treatment with TREANDA or chlorambucil stratified by study center and Binet stage (B or C) CLL. Patients received either TREANDA 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 [height in cm -100 to give weight in kg]) administered orally on Days 1 and 15 of each 28-day cycle.

Study demographics and trial design

The study was conducted at 45 centers in 8 countries. The majority of patients were enrolled in study centers in Germany (40%) and Bulgaria (37%). The 6 countries accounting for the remaining 23% of study patients were Italy (10%), Spain (6%), France (5%), Sweden (1%), Austria (1%) and England (<1%).

The patient populations in the TREANDA and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age and gender (Table 8), Binet stage (72% vs. 71% Binet B), lymphadenopathy (79% vs. 80%), enlarged spleen (77% vs. 78%), enlarged liver (49% vs. 45%), hypercellular bone marrow (80% vs. 72%), "B" symptoms (50% vs. 50%), lymphocyte count (mean 69.3 x10^9/L vs. 63.2 x10^9/L) and serum lactate dehydrogenase concentration (mean 369.4 vs. 385.4 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).

The two primary endpoints of this study were overall response rate (ORR) and progression-free survival (PFS). Important secondary endpoints were overall survival and quality of life.

An Independent Response Assessment Committee (ICRA) was established during the conduct of the study to ensure that the response evaluations in this open-label study were consistently managed. The ICRA performed a blinded review of the data based on assessments conducted every 12 weeks and determined a best overall response for each patient and a date of progression when indicated.

A calculated response analysis based on the ICRA adjudicated data is reported as the final efficacy measures for ORR and PFS. In this analysis, the National Cancer Institute-sponsored Working Group (NCI-WG) criteria were applied programmatically to the data using the variables of lymph node measurements, records of B-symptoms, hematology laboratory data, and records of transfusions and new anticancer treatments. In the calculated response analysis, patients were censored if they had a transfusion or started a new anticancer treatment before documented progression. Patients were also required to have a confirmed normocellular bone marrow within 56 days of the initial clinical assessment to be classified as complete responders (CR). Patients that met all other requirements for a CR (see Table 9), but did not have a complete bone marrow assessment were considered to have a partial response (PR).

Table 8: Summary of Patient Demographics for Study 02CLLIII in CLL

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
02CLLIII	Phase III, randomized, open-label, parallel-group, multicenter study to compare the efficacy and safety of bendamustine and chlorambucil	Bendamustine: 100 mg/m^2/d intravenously on Days 1 to 2, or Chlorambucil: 0.8 mg/kg orally on Days 1 and 15; treatment cycles were repeated every 4 weeks for a maximum of six cycles.	N = 319	63.3 (35.0-78.0 years)	62% male 38% female

Study results

The results of the study demonstrated a higher ORR and a longer PFS for TREANDA compared to chlorambucil (Table 9). Superiority of bendamustine was evident in both primary efficacy measures. ORR was 68% in the bendamustine treatment group compared with 33% in the chlorambucil treatment group (p<0.0001) based on calculated responses. The median PFS was 21 months in the bendamustine treatment group, compared to 9 months in the chlorambucil treatment group; hazard ratio 0.26. There were no significant differences in ORR and PFS between genders, in either treatment arm.

Table 9: Results[a] of Study 02CLLIII in CLL

	TREANDA (N=162)	Chlorambucil (N=157)	p-value
Response Rate n(%)			
Overall response rate	110 (68)	51 (33)	<0.0001
(95% CI)	(60.7, 75.1)	(25.2, 39.8)	
Complete response (CR)*	14 (9)	1 (<1)	
Nodal partial response (nPR)**	6 (4)	0	
Partial response (PR)†	90 (56)	50 (32)	
Progression-Free Survival††			
Median, months (95% CI)	20.7 (17.5, 26.7)	8.6 (5.7, 8.7)	
Hazard ratio (95% CI)	0.26 (0.17, 0.38)		<0.0001

CI = confidence interval

a Results are based on calculated responses (see above)

* CR was defined as peripheral lymphocyte count ≤ 4.0 x 10^9/L, neutrophils ≥ 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 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 10^9/L or 50% improvement over baseline, platelets >100 x 10^9/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.

Kaplan-Meier estimates of progression-free survival comparing TREANDA with chlorambucil are shown in Figure 1.

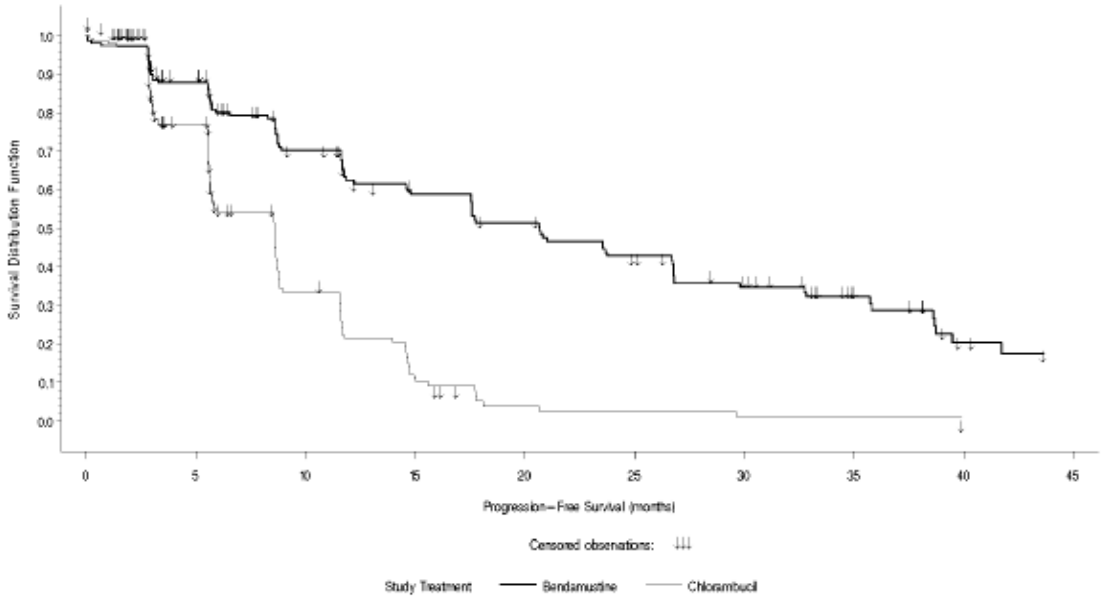


Figure 1: Progression-Free Survival in CLL

For patients in the ITT analysis set with calculated responses of CR, nPR, or PR, the median duration of response was 23 months for the 110 responders in the bendamustine treatment group and 8 months for the 52 responders in the chlorambucil treatment group.

Overall Survival

The total number of deaths reported during the study was 19% of patients in the bendamustine treatment group and 26% of patients in the chlorambucil treatment group. The hazard ratio is 1.38 (95% CI, 0.78, 2.46, P=0.18).

Quality of Life

There were no significant differences in the overall quality of life between the bendamustine and chlorambucil treatment groups as measured by global health status.

Pediatrics (< 18 years of age):

TREANDA was evaluated in a Phase I/II trial that included pediatric patients from 1-19 years of age with relapsed or refractory acute leukemia, including 27 patients with acute lymphocytic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). TREANDA was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21 day cycle**.** The Phase I portion (n=11) was a dose-escalation study designed to determine the recommended Phase II dose, with doses of 90 and 120 mg/m^2 evaluated. The recommended Phase II dose of TREANDA in pediatric patients was determined to be 120 mg/m^2. The Phase II portion of the study (n=32) was designed to evaluate the efficacy and safety of the recommended dose from the Phase I portion of the study (120 mg/m^2). The primary efficacy variable was Objective Response Rate (ORR), defined as the proportion of patients who achieved Complete Response (CR) or CR without platelet recovery (CRp) during treatment as determined by hematology laboratory results and bone marrow evaluation. There was no treatment response (CR+ CRp) in any patient during the Phase II portion of this study.

DETAILED PHARMACOLOGY

Non-Clinical

Pharmacodynamics

Bendamustine is an alkylating agent that contains a bifunctional mechlorethamine group and a benzimidazole heterocyclic ring. Bendamustine showed greatest *in vitro* cytotoxic activity in cell lines derived from breast cancer, small cell lung cancer, and B-cell lymphomas. (see **ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action**).

In xenograft models of lymphoma, bendamustine treatment inhibited tumor growth. Bendamustine also demonstrated activity in xenograft models of human lung and breast cancer.

Pharmacokinetics

ADME studies were performed in rat, mouse and dog. Bendamustine undergoes rapid dehalogenation in buffered solutions at physiological pH. Bendamustine is stabilized in the circulation through its association with plasma proteins; primarily albumin (>95% protein bound). Bendamustine was rapidly distributed (5 min) to the kidneys and liver of rats with the majority of radioactivity eliminated from the plasma within the first hour. Extensive distribution to other tissues is limited, which is consistent with the small volume of distribution determined in humans (see **ACTION and CLINICAL PHARMACOLOGY, Pharmacokinetics**). In contrast to human studies, more radioactive material was excreted in feces (54-66%) and less in the urine (20-25%) following administration of ^{14}C-bendamustine to the rat and dog. In the pigmented rat, there was no evidence of melanin associated binding (pigmented skin or uveal tract of eye) or of significant uptake into testes and brain.

One major metabolite in the rat bile, labeled M19, accounted for 60% of the radioactive peaks from the LC-MS/MS/MS analysis. It is proposed that glutathione conjugation followed proteolytic cleavage and the formation of N-acetylcysteine facilitated biliary excretion of bendamustine. The M19 metabolite is also found in the urine but the most abundantly excreted urine metabolite was identified as M5. This metabolite is made much more water soluble following dehalogenation, N-dealkylations and oxidation. Therefore, phase II conjugation reactions appear to be important in efficient elimination of bendamustine in bile and urine although the pathways and enzymes responsible for phase II conversions have not been elucidated.

Safety Pharmacology

Bendamustine was evaluated for effects on hERG current in human Embryonic Kidney (HEK) 293 cells. At bendamustine concentrations of 20 and 200 μM, dose-dependent inhibitions of hERG current of 20% and 65%, respectively, were observed. In contrast, bendamustine had no effect on the cardiac action potential in isolated canine Purkinje fibers. The treatment showed no effect on action potential duration, APD50, APD70, or APD90, under normal (60 pulses per minute) or low (20 pulses per minute) stimulation rates over a concentration range of 1.5 to 7.5 μg/mL.

The effect of bendamustine on measured ECG intervals in animals was not evaluated. Heart rates of dogs were reduced in a repeat-dose toxicology study following administration of bendamustine for 4 consecutive days at 132 mg/m^2/day for up to 4 31-day cycles (see **TOXICOLOGY**).

Bendamustine infused over a period of 40 minutes at a dose of 25 mg/kg (approximately 150 mg/m^2) to rats for 2 days caused a significant increase in the excretion fraction of sodium (3.5-fold increase), potassium (4.2-fold) and chloride (3.5-fold increase). Compared to controls, animals treated with 150 mg/m^2 bendamustine had a significant decrease (2.5-fold) in the glomerular filtration rate compared to control saline injected rates. The results are consistent with reports of electrolyte imbalances in patients enrolled in clinical studies.

No specific studies were performed to address the impact of bendamustine on the central nervous, cardiovascular or respiratory systems in animals.

Clinical

Pharmacokinetics / Pharmacodynamics

Bendamustine is the major active moiety *in vivo*. The primary circulating metabolites in humans have been identified as M3 and M4. These metabolites are less abundant than parent compound in plasma with the respective area under the plasma concentration time curve (AUC) being 1/10th and 1/100th that of bendamustine, respectively. The cytotoxic activity of M3 (against various lymphoma cells and healthy lymphocytes) is similar to that of parent compound, but M4 is 5- to 10-fold less active. In addition, 2 hydrolysis products are formed, mono-hydroxy [HP1] and di-hydroxy [HP2] bendamustine, which have little cytotoxic activity (HP1 is 10-fold less active, HP2 is 15-fold less active).

TOXICOLOGY

Single-Dose Toxicity

High doses of bendamustine HCl to mice and rats induced sedation, tremors, ataxia, convulsions, body weight loss and respiratory distress quickly (1-2 hours) after administration. This was accompanied by macroscopic findings of atrophy of the thymus, spleen and testes. The maximum tolerated dose (MTD) for an i.v. administration was 150 mg/m^2 and 180 mg/m^2 for the mouse and rat, respectively. An i.v. dose of 240 mg/m^2 was lethal in 50% of mice and rats (LD_{50} dose).

Repeat-Dose Toxicity

Repeat i.v. dose studies with bendamustine HCl of up to 15 weeks in rats and dogs were conducted.

In a 15-week intermittent i.v. infusion toxicity and toxicokinetic study in rats, bendamustine HCl was administered over 5 dose cycles via i.v. infusion to groups of rats to assess the toxicological profile and reversibility of any effects during a 4-week recovery period. Each dose cycle consisted of a 30-minute infusion once daily for 3 consecutive days, followed by an 18-day nondosing period (21-day cycle). Doses evaluated were 0 (saline), 5, 10 or 15 mg/kg/day which is equivalent to 0, 30, 60 and 90 mg/m^2/day. Standard toxicological parameters were evaluated during the study.

Hematologic evaluations showed a dose-related decrease in white blood cell count, primarily due to a decreased absolute lymphocyte count, at all dose levels. In general, mean body weights were lower for the all active-drug–treated male groups and the 60- and 90-mg/m^2/dose female groups. In addition, several rats from all bendamustine treatment groups were euthanized due to general debilitation. Possible bendamustine HCl treatment-related deaths were due to infections (pyelonephritis), glomerulopathy and lung thrombosis. Microscopic aberrations were found in the kidneys (tubular degeneration/necrosis and karymegoly) and bone (hyperplasia of bone marrow in femur and sternum). Bone marrow hyperplasia was not dose related but both tubular degeneration and karymegoly were considered treatment related. Cardiomyopathy (focal/multifocal) was observed in male rats receiving the highest dose. Toxicokinetic measurements indicated exposure was not dose proportional and exposures were similar to (90 mg/m^2 dose) or less than (30 and 60 mg/m^2) exposure reported in NHL patients administered the recommended 120 mg/m^2 dose. The no-observed adverse event level (NOAEL) was not determined but is <30 mg/m^2 in rats.

In a 15-week (three cycles of 35 days) intermittent i.v. infusion study in beagle dogs, bendamustine HCl was administered via i.v. infusion to groups of dogs to assess the toxicological profile and reversibility of any effects during a 31-day recovery period following each dosing cycle. Each dosing cycle consisted of a 30 minute infusion once daily for 4 consecutive days, followed by a 31-day non-dosing period (35-day cycle). Four groups of 3 males and 3 females each, were given i.v. infusion doses of 0 (water for injection: 0.9% sodium chloride 1:1), 1.65, 3.3, or 6.6 mg/kg/dose, which is equivalent to 0, 33, 66 and 132 mg/m^2/dose,

respectively. Standard toxicological parameters, including ophthalmoscopy, were evaluated during the study.

Bendamustine HCl clearly disrupted cellular turnover in the gastrointestinal tract, immune system, and testes, where rapid cell division occurs. At the highest dose level of 132 mg/m^2/dose the effects were cumulative and resulted in significant toxicity and moribundity over 2 treatment cycles and no animals continued to the third cycle. There were signs of significant immunosuppression in these high dose animals including bone marrow suppression (decreased myeloid cells) and moderate to severe involution in the thymus and absence of germinal centres in the spleen and mesenteric lymph nodes. In addition, the mean baseline heart rate of 130 beats/min decreased to 93 beats/min during cycle 2 at this high dose. The dose levels of 1.65 and 3.3 mg/kg/dose were tolerated over the 3 dosing cycles, with changes in lymphoid tissue and testes being observed. The kidney was also identified as a target organ in the dog, with basophilic tubules with enlarged nuclei being observed in dogs from all 3 treatment groups. Systemic exposure was demonstrated at all 3 dose levels and was considered slightly greater than dose proportional in cycle 1 and dose proportional in cycle 3. Female dogs appeared to have a slightly higher exposure than male dogs. Based upon the findings in the lymphoid tissues, testes, and kidneys, the NOAEL in this study was not determined but it is less than 33 mg/m^2/dose.

Genotoxicity

The genetic toxicology potential of bendamustine was evaluated in a standard test battery consisting of an *in vitro* bacterial reverse mutation assay, an *in vitro* chromosome aberration assay in human peripheral blood lymphocytes and an *in vivo* rat bone marrow micronucleus assay. The results described below demonstrate that bendamustine HCl is both mutagenic and clastogenic.

In the *in vitro* bacterial mutation assay, bendamustine HCl showed clear evidence of mutagenic activity in tester strain TA98 in the presence of metabolic activation, and in tester strainWP2*uvrA* in the presence and absence of metabolic activation.

In the *in vitro* chromosome aberration assay using human lymphocytes, bendamustine HCl was shown to produce a statistically significant increase in the proportion of cells with chromosome aberrations, both in the presence and absence of metabolic activation.

In the *in vivo* mammalian erythrocyte micronucleus study, bendamustine HCl was shown to produce a significant increase in the incidence of micronucleated polychromatic erythrocytes at both the 24 and 48 hour intervals, when compared to the vehicle control groups, following single i.v. doses of 6.25, 12.5, and 25 mg/kg, which is approximately 18.8, 37.5 and 75 mg/m^2, respectively. Peak plasma concentrations (i.e., C_{max}) ranged from 9942 to 44378 ng/mL for males and 11212 to 58707 ng/mL for females.

Carcinogenesis

The oncologic potential of bendamustine HCl (non-GLP) was evaluated in AB/Jena mice. In this study, mice were given 4 consecutive doses of 12.5 and 25 mg/kg/day via intraperitoneal (i.p.) injection and 62.5 mg/kg/day via oral gavage. In the mice given i.p. injections, fibrosarcoma was

observed as well as an increase in pulmonary adenomas at the highest dose (25 mg/kg), although the incidence of pulmonary adenomas in this high-dose group was comparable with the incidence found in the concurrent controls. In the mice given 62.5 mg/kg orally, reticulosarcoma, subcutaneous sarcoma, mammary carcinoma, and pulmonary adenomas were observed at a higher frequency than in the control mice.

Developmental and Reproductive Toxicity

Studies to assess the embryo/fetal developmental toxicity of bendamustine HCl (non-GLP) were conducted in mice and rats. In these studies, bendamustine was given to groups of mice and rats as single i.p. injections on selected days postmating or as multiple injections over several days postmating. The dosing regimen was not performed over the time from implantation to closure of the hard palate. In both species bendamustine administration produced embryotoxic effects, indicated by an increase in resorptions and reduced fetal weights. An increase in malformations, including exencephaly, dwarfism and cleft palates, was also observed in mice and rats. Based on these findings, bendamustine HCl is embryotoxic and teratogenic.

Local Tolerance

A local tolerance study was conducted to assess the perivenous and intra-arterial tolerance of different concentrations of bendamustine HCl, following a single injection into the ear of New Zealand White rabbits. The injection sites and surround tissue were carefully examined on the day of dosing and daily thereafter until study termination (Day 5). Histologic findings showed a treatment-related effect in the rabbits given the 2 highest concentrations (0.6 and 1.0 mg/mL) by perivenous injection. The effect was characterized by an increase in the incidence and degree of perivascular changes indicative of local irritation, which was also observed in the adjacent subcutaneous tissue. Following intra-arterial injection, an effect of treatment was observed in the arterial wall of rabbits administered 0.2 or 0.6 mg/mL. The lesions located in the arterial wall and perivascular tissue suggested that bendamustine HCl had impeded repair of the arterial wall at the injection site. Based upon the results of this local tolerance study bendamustine HCl at concentrations of 0.2, 0.6, and 1.0 mg/mL was irritating to the vessel and surrounding tissue.

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PART III: CONSUMER INFORMATION

PrTREANDA®
Bendamustine hydrochloride for injection
25 mg and 100 mg per vial

This leaflet is part III of a three-part "Product Monograph" published when TREANDA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TREANDA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TREANDA is a medicine which is used for the treatment of the following types of cancer:

- Relapsed indolent B-cell non-Hodgkin lymphoma (NHL), which has not responded during or following treatment with a rituximab regimen;
- Previously untreated chronic lymphocytic leukemia (CLL) (cancer of the white blood cells).

What it does:
TREANDA has been shown to cause cell death. The exact way in which TREANDA kills cells is not completely understood.

When it should not be used:
Do not use TREANDA if you are allergic to the active substance, bendamustine hydrochloride, or mannitol.

What the medicinal ingredient is:
Bendamustine hydrochloride

What the non-medicinal ingredients are:
Mannitol

What dosage forms it comes in:
TREANDA is available as powder for injection in a vial that contains 25 mg or 100 mg of bendamustine hydrochloride.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

TREANDA should be prescribed and managed by a doctor experienced in the use of cancer drug.

TREANDA should not be used in patients with serious infections.

Possible serious side effects with TREANDA include:

- serious infection
- having other types of cancers
- decreased production of blood cells (myelosuppression)
- serious heart problems
- serious skin reactions

BEFORE you receive TREANDA talk to your doctor or pharmacist if:

- You have a known allergy to bendamustine or mannitol
- You have low blood cell count (white blood cells, platelets, and red blood cells)
- You have any heart problems or high blood pressure
- You have any infection
- You have any skin problem
- You are pregnant or are planning to become pregnant
- You are breast-feeding or plan to breast-feed
- You have kidney or liver problem

TREANDA can harm an unborn baby. Female and male patients should use an effective contraception 2 weeks before receiving TREANDA and until at least 4 weeks after the last dose. If pregnancy is suspected, talk to your doctor immediately.

TREANDA may also affect men who wish to father a child.

TREANDA has not been shown to be effective in patients under 18 years of age.

TREANDA may also cause:

- Extravasation (the leakage of drug from the vein into the surrounding tissue)
- Tumor lysis syndrome (caused by death of cancer cells)
- Infusion reactions and anaphylaxis, symptoms include swelling of the face, lips or tongue, difficulty breathing, rash, or fainting.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without a prescription.

PROPER USE OF THIS MEDICATION

TREANDA is to be given into the vein (intravenous) as an infusion.

Usual dose:

Relapsed indolent non-Hodgkin lymphoma
120 mg/m^2 body surface area given into the vein as an infusion over 60 minutes, on day 1 and 2 of a 21-day cycle, up to 8 cycles.

Chronic lymphocytic leukemia
100 mg/m^2 body surface area given into the vein as an infusion over 30 minutes, on day 1 and 2 of 28-day cycle, up to 6 cycles.

Missed Dose:
TREANDA should be given on a fixed schedule. If you miss an appointment, call your doctor for instructions.

Overdose:

In case of drug overdose, contact your doctor, or your healthcare provider, or a local poison control centre, or go to the emergency room of the nearest hospital.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common blood-related side effects with TREANDA are: low levels of some types of white blood cells (neutrophils, leucocytes), platelets or red blood cells.

The most common non-blood-related side effects with TREANDA are nausea, fatigue, diarrhea, vomiting, fever, constipation.

The most common severe side effects: fatigue, fever associated with low level of neutrophils, pneumonia, potassium deficiency, diarrhea, dehydration, fever, infection, high blood level of uric acid, rash, high blood pressure.

Other important serious side effects: kidney failure, heart failure, myocardial infarction, allergic reaction, skin reactions, lung scarring that can interfere with breathing, decreased production of blood cells by the bone marrow and liver problems.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor		Seek immediate emergency medical attention
		Only if severe	In all cases	
Common	**Nausea and vomiting**	√		
	New fever or temperature higher than 38ºC		√	
	Severe or worsening rash or itching		√	√
	Myelosuppression: Shortness of breath, significant fatigue, bleeding, fever or other signs of infection		√	
Uncommon	**Allergic reaction:** Skin reactions such as rash or itching, facial swelling, or difficulty breathing during or soon after infusion		√	√
	Tumor Lysis Syndrome: Lack of urination, severe muscle weakness, heart rhythm disturbances and seizures		√	√
	Diarrhea	√		
Rare	**Severe Skin Reactions:** Severe or worsening itching, intense redness, formation of hives, blistering or ulceration associated with either fever, joint pain, or a general unwell feeling		√	√
	Heart Failure: Chest pain, dizziness, fatigue, rapid breathing, shortness of breath, swelling of the feet or legs.		√	√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor		Seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	**Heart Attack:** Pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, lightheadedness, clammy skin, sweating, indigestion, anxiety.		√	√
	Liver Injury: Pain in the right abdomen, fever, fatigue, weakness, loss of appetite, jaundice, yellow color in the eyes, dark urine.		√	√

This is not a complete list of serious side effects. For any unexpected effects while taking TREANDA, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For questions or concerns and to find the full product monograph prepared for healthcare professionals, go to http://www.tevacanadainnovation.ca or contact the sponsor, Teva Canada Innovation at 1-855-519-8382.

This leaflet was prepared by Teva Canada Innovation.

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