metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

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

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

USE IN SPECIAL POPULATION

Pregnancy

Pregnancy Category D

Risk Summary

BENDAWEL™ can cause fetal harm when administered to a pregnant woman. Bendamustine caused malformations in animals, when a single dose was administered to pregnant animals. Advise women to avoid becoming pregnant while receiving BENDAWEL™ and for 3 months after therapy has stopped. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to a fetus. Advise men receiving BENDAWEL™ to use reliable contraception for the same time period.

Animal data

Single intraperitoneal doses of bendamustine from 210 mg/m2 (70 mg/kg) in mice administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (exencephaly, cleft palates, accessory rib, and spinal deformities) and decreased fetal body weights. This dose did not appear to be maternally toxic and lower doses were not evaluated. Repeat intraperitoneal dosing in mice on gestation days 7-11 resulted in an increase in resorptions from 75 mg/m2 (25 mg/kg) and an increase in abnormalities from 112.5 mg/m2 (37.5 mg/kg) similar to those seen after a single intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m2 (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, or 13 caused embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in external [effect on tail, head, and herniation of external organs (exomphalos)] and internal (hydronephrosis and hydrocephalus) malformations were seen in dosed rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

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.

Pediatric Use

The effectiveness of BENDAWEL™ in pediatric patients has not been established. BENDAWEL™ was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The safety profile for BENDAWEL™ in pediatric patients was consistent with that seen in adults, and no new safety signals were identified.

The trial 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). BENDAWEL™ was administered as an intravenous infusion over 60 minutes on Days 1 and 2 of each 21-day cycle. Doses of 90 and 120 mg/m2 were evaluated. The Phase 1 portion of the study determined that the recommended Phase 2 dose of BENDAWEL™ in pediatric patients was 120 mg/m2.

A total of 32 patients entered the Phase 2 portion of the study at the recommended dose and were evaluated for response. There was no treatment response (CR+ CRp) in any patient at this dose. However, there were 2 patients with ALL who achieved a CR at a dose of 90 mg/m2 in the Phase 1 portion of the study.

In the above-mentioned pediatric trial, the pharmacokinetics of BENDAWEL™ at 90 and 120 mg/m2 doses were evaluated in 5 and 38 patients, respectively, aged 1 to 19 years (median age of 10 years).

The geometric mean body surface adjusted clearance of bendamustine was 14.2 L/h/m2. The exposures (AUC0-24 and Cmax) to bendamustine in pediatric patients following a 120 mg/m2 intravenous infusion over 60 minutes were similar to those in adult patients following the same 120 mg/m2 dose.

Geriatric Use

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

Chronic Lymphocytic Leukemia

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

Non-Hodgkin Lymphoma

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

Renal Impairment

No formal studies assessing the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. BENDAWEL™ should be used with caution in patients with mild or moderate renal impairment. BENDAWEL™ should not be used in patients with CrCL < 40 mL/min.

Hepatic Impairment

No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of bendamustine have been conducted. BENDAWEL™ should be used with caution in patients with mild hepatic impairment. BENDAWEL™ should not be used in patients with moderate (AST or ALT 2.5-10 X ULN and total bilirubin 1.5-3 X ULN) or severe (total bilirubin > 3 X ULN) hepatic impairment.

Effect of Gender

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

Chronic Lymphocytic Leukemia

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

Non-Hodgkin Lymphoma

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

OVERDOSE

The intravenous LD50 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 BENDAWEL™ overdose is known. Management of overdosage should include general supportive measures, including monitoring of hematologic parameters and ECGs.

STORAGE

Bendamustin for Injection should be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F). Retain in original package until time of use to protect from light. Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light.

PRESENTATION

Bendamustin Hydrochloride for Injection 25mg & 100mg is presented as a single dose single vial for IV Use only.

HANDLING AND DISPOSAL

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

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by
Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

0700BLDM0415-00

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Bendamustine Lyophilized Hydrochloride Injection

BENDAWEL™

FOR INTRAVENOUS INFUSION ONLY

Rx only

WARNING

Myelosuppression: May warrant treatment delay or dose reduction. Monitor closely and restart treatment based on ANC and platelet count recovery. Complications of myelosuppression may lead to death.

Infections: Monitor for fever and other signs of infection and treat promptly.

Infusion Reactions and Anaphylaxis: Severe anaphylactic reactions have occurred. Monitor clinically and discontinue drug for severe reactions. Ask patients about reactions after the first cycle. Consider pre-treatment for cycles subsequent to milder reactions.

Tumor Lysis Syndrome: May lead to acute renal failure and death. Take precautions in patients at high risk.

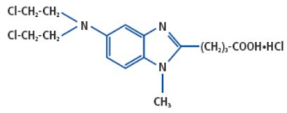
Skin Reactions: Discontinue for severe skin reactions.

Other Malignancies: Pre-malignant and malignant diseases have been reported.

Use in Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving bendamustine hydrochloride

DESCRIPTION

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



BENDAWEL™ (bendamustine hydrochloride) for Injection is intended for intravenous infusion only after reconstitution with Sterile Water for Injection, IP, and after further dilution with either 0.9% Sodium Chloride Injection, IP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, IP.

COMPOSITION

BENDAWEL™ is supplied in sterile non-pyrogenic white to off-white lyophilized powder in a single-use vial in 2 strengths, 25mg/vial and 100mg/vial

Each vial of BENDAWEL™ 100mg Contains

Bendamustin Hydrochloride	100mg
Mannitol IP	170mg

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.

PHARMCOKINETICS & PHARMACODYNAMICS

Pharmacodynamics

Based on the pharmacokinetics/pharmacodynamics analyses of data from adult NHL patients, nausea increased with increasing bendamustine Cmax.

Cardiac Electrophysiology

The effect of bendamustine on the QTc interval was evaluated in 53 patients with indolent NHL and mantle cell lymphoma on Day 1 of Cycle 1 after administration of rituximab at 375 mg/m2 intravenous infusion followed by a 30-minute intravenous infusion of bendamustine at 90 mg/m2/day. No mean changes greater than 20 milliseconds were detected up to one hour post-infusion. The potential for delayed effects on the QT interval after one hour was not evaluated.

Pharmacokinetics

Absorption

Following a single IV dose of bendamustine hydrochloride Cmax 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 a mass balance study, plasma radioactivity levels were sustained for a greater period of time than plasma concentrations of bendamustine, γ hydroxy bendamustine (M3), and N desmethyl bendamustine (M4). This suggests that there are bendamustine derived materials (detected via the radiolabel), that are rapidly cleared and have a longer half-life than bendamustine and its active metabolites.
The mean steady-state volume of distribution (Vss) of bendamustine was approximately 20-25 L. Steady-state volume of distribution for total radioactivity was approximately 50 L, indicating that neither bendamustine nor total radioactivity are extensively distributed into the tissues.
Metabolism
In vitro data indicate that bendamustine is primarily metabolized via hydrolysis to monohydroxy (HP1) and dihydroxy-bendamustine (HP2) metabolites with low cytotoxic activity. Two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, 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 confirm that bendamustine is extensively metabolized via hydrolytic, oxidative, and conjugative pathways.
In vitro studies using human liver microsomes indicate that bendamustine does not inhibit CYP1A2, 2C9/10, 2D6, 2E1, or 3A4/5. Bendamustine did not induce metabolism of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A4/5 enzymes in primary cultures of human hepatocytes.
Elimination
Mean recovery of total radioactivity in cancer patients following IV infusion of [14C] bendamustine hydrochloride was approximately 76% of the dose. Approximately 50% the dose was recovered in the urine and approximately a 25% of the dose was recovered in the feces. Urinary excretion was confirmed as a relatively minor pathway of elimination of bendamustine, with approximately 3.3% of the dose recovered in the urine as parent. 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/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.
Renal Impairment
In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m2 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 mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 mL/min. [See Use in Specific Populations]
Hepatic Impairment
In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m2 there was no meaningful effect of mild (total bilirubin ≤ULN, AST ≥ULN to 2.5 x ULN, and/or ALP ≥ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment.
These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5 - 10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment. [See Use in Specific Populations]
Effect of Age
Bendamustine exposure (as measured by AUC and Cmax) has been studied in adult patients ages 31 through 84 years. The pharmacokinetics of bendamustine (AUC and Cmax) were not significantly different between patients less than or greater than/equal to 65 years of age. [See Use in Specific Populations]
Effect of Gender
The pharmacokinetics of bendamustine were similar in male and female patients.

NON CLINICAL 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.

INDICATION
Chronic Lymphocytic Leukemia (CLL)
BENDAWEL™ 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 Lymphoma (NHL)
BENDAWEL™ is indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

DOSAGE AND ADMINISTRATION
Dosing Instructions for CLL
Recommended Dosage
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.
Dose Delays, Dose Modifications and Reinitiation of Therapy for CLL:
BENDAWEL™ administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant = Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to = Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) = 1 x 109/L, platelets = 75 x 109/L], BENDAWEL™ can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted.
Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m2 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/m2 on Days 1 and 2 of each cycle.
Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

Dosing Instructions for NHL
Recommended Dosage:
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 for NHL:
BENDAWEL™ 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 109/L, platelets = 75 x 109/L], BENDAWEL™ can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted.
Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m2 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/m2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60 mg/m2 on Days 1 and 2 of each cycle.

Reconstitution/Preparation for Intravenous Administration
Aseptically reconstitute each BENDAWEL™ vial as follows:
· 25 mg BENDAWEL™ vial: Add 5 mL of only Sterile Water for Injection, USP.
· 100 mg BENDAWEL™ vial: Add 20 mL of only Sterile Water for Injection, USP.
Shake well to yield a clear, colorless 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 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
BENDAWEL™ contains no antimicrobial preservative. 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 is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of BENDAWEL™ must be completed within this period.

CONTRAINDICATIONS
BENDAWEL™ is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine.

ADVERSE EVENTS
The following serious adverse reactions have been associated with BENDAWEL™ in clinical trials and are discussed in greater detail in other sections of the label.
· Myelosuppression
· Infections
· Anaphylaxis and Infusion Reactions and Anaphylaxis
· Tumor Lysis Syndrome
· Skin Reactions
· Other Malignancies
· Extravasation injury

The data described below reflect exposure to BENDAWEL™ in 329 patients who participated in an actively-controlled trial (N=153) for the treatment of CLL and two single-arm trials (N=176) for the treatment of indolent B-cell NHL. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

WARNING AND PRECAUTIONS
Myelosuppression
BENDAWEL™ caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies (see Table 4). Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).
In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs were observed predominantly in the third week of therapy. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the ANC should be = 1 x 109/L and the platelet count should be = 75 x 109/L.

Infections
Infection, including pneumonia, sepsis, septic shock, and death have occurred in adult and pediatric patients in clinical trials and in postmarketing reports. Patients with myelosuppression following treatment with BENDAWEL™ are more susceptible to infections. Advise patients with myelosuppression following BENDAWEL™ treatment to contact a physician if they have symptoms or signs of infection.

Anaphylaxis and Infusion Reactions
Infusion reactions to BENDAWEL™ 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. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experience Grade 3 or worse allergic-type reactions should not be rechallenged. Consider measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids in subsequent cycles in patients who have experienced Grade 1 or 2 infusion reactions. Discontinue BENDAWEL™ for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusions reactions as clinically appropriate considering individual benefits, risks, and supportive care.

Tumor Lysis Syndrome
Tumor lysis syndrome associated with BENDAWEL™ treatment has occurred in patients in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of BENDAWEL™ and, without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of BENDAWEL™ therapy. However, there may be an increased risk of severe skin toxicity when BENDAWEL™ and allopurinol are administered concomitantly.

Skin Reactions
Skin reactions have been reported with BENDAWEL™ treatment in clinical trials and postmarketing safety reports, including rash, toxic skin reactions and bullous exanthema. Some events occurred when BENDAWEL™ was given in combination with other anticancer agents.
In a study of BENDAWEL™ (90 mg/m2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert). Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when BENDAWEL™ was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to BENDAWEL™ cannot be determined.
Where skin reactions occur, they may be progressive and increase in severity with further treatment. Monitor patients with skin reactions closely. If skin reactions are severe or progressive, withhold or discontinue BENDAWEL™.

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

Extravasation Injury
BENDAWEL™ extravasations have been reported in post marketing resulting in hospitalizations from erythema, marked swelling, and pain. Assure good venous access prior to starting BENDAWEL™ infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of BENDAWEL™.

Embryo-fetal Toxicity
BENDAWEL™ 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.

DRUG INTERACTION
No formal clinical assessments of pharmacokinetic drug-drug interactions between BENDAWEL™ and other drugs have been conducted. Bendamustine's active