Diagnosis and Risk Stratification in Chronic Lymphocytic Leukemia (CLL)

BENDEKA® Injection is indicated for treatment of patients with:

- Chronic lymphocytic leukemia (CLL).
- Efficacy relative to first-line therapies other than chlorambucil has not been established.

Important Safety Information

**Contraindication:** BENDEKA is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine HCl, polyethylene glycol 400, propylene glycol, or monothioglycerol.

**Myelosuppression:** Bendamustine HCl caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies. Three patients (2%) died from myelosuppression-related adverse reactions. BENDEKA causes myelosuppression. Monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequently. 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.

Please read additional Important Safety Information throughout and accompanying Full Prescribing Information for BENDEKA starting on page 7.
A 63-YEAR-OLD WOMAN IN OVERALL GOOD HEALTH (FIT) WHO WORKS FULL-TIME, PRESENTS WITH FATIGUE AND PAINLESS SWELLING IN THE RIGHT AXILLA.

Important findings on physical examination:
- Presence of lymphadenopathy (cervical, supraclavicular, axillary, inguinal, femoral)
- Palpable splenomegaly and/or hepatomegaly

Your examination of the patient reveals:
- 2 axillary lymph nodes (2-4 cm) and 1 cervical lymph node (2 cm)
- Palpable spleen tip
- WHO performance status of 1
- Upon careful questioning, the patient reports occasional night sweats and denies early satiety

Laboratory tests, imaging, and procedures included when suspecting CLL:
- CBC
- ß2-microglobulin
- Peripheral B-cell immunophenotype and clonality
- Chest/abdominal/pelvic CT scan
- FISH/cytogenetics for cytogenetic abnormalities
- Other tests or procedures

Features on peripheral blood smear that confirm suspicion of CLL:
The patient’s peripheral blood smear reveals lymphocytosis and a “smudge” cell characteristic of CLL. The immunophenotype of peripheral lymphocytes is: CD5+, CD19+, CD20+(dim), CD23+.

WHO = World Health Organization; CBC = complete blood cell count; CT = computed tomography; FISH = fluorescence in situ hybridization

Important Safety Information (cont)

Infections: Infection, including pneumonia, sepsis, septic shock, hepatitis and death has occurred. Patients with myelosuppression following treatment with BENDEKA are more susceptible to infections. Patients treated with bendamustine HCl are at risk for reactivation of infections including (but not limited to) hepatitis B, cytomegalovirus, Mycobacterium tuberculosis, and herpes zoster. Patients should undergo appropriate monitoring, prophylaxis, and treatment measures prior to administration.

Please read additional Important Safety Information throughout and accompanying Full Prescribing Information for BENDEKA starting on page 7.
Laboratory and FISH test results are as follows:

<table>
<thead>
<tr>
<th>LABORATORY TEST</th>
<th>RESULT</th>
<th>NORMAL RANGE[^4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>9.1 g/dL</td>
<td>12.0–16.0 g/dL (female)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>135 × 10^9/L</td>
<td>150–400 × 10^9/L</td>
</tr>
<tr>
<td>WBC count</td>
<td>43 × 10^9/L</td>
<td>5–10 × 10^9/L</td>
</tr>
<tr>
<td>ALC</td>
<td>36 × 10^9/L</td>
<td>1–4 × 10^9/L</td>
</tr>
<tr>
<td>β_2-microglobulin</td>
<td>3.1 μg/mL</td>
<td>0.70–1.80 μg/mL</td>
</tr>
</tbody>
</table>

[^4]: WBC = white blood cell; ALC = absolute lymphocyte count

<table>
<thead>
<tr>
<th>FISH/CYTOGENETICS[^5,^6]</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>del 11q</td>
<td>✔</td>
</tr>
<tr>
<td>del 13q</td>
<td>—</td>
</tr>
<tr>
<td>del 17p</td>
<td>—</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: Additional mutational testing may be considered

**CLL risk classification and prognosis:**

<table>
<thead>
<tr>
<th>CLASSIFICATION SYSTEM</th>
<th>RISK</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rai[^7]</strong></td>
<td>Stage II (intermediate)</td>
<td>Lymphocytosis, splenomegaly with or without hepatomegaly, enlarged lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Stage III (high)</td>
<td>Lymphocytosis, hemoglobin &lt;11.0 g/dL, with or without splenomegaly, hepatomegaly or enlarged lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Stage IV (high)</td>
<td>Lymphocytosis, platelets &lt;100 × 10^9/L, with or without hemoglobin &lt;11.0 g/dL, splenomegaly, hepatomegaly or enlarged lymph nodes</td>
</tr>
<tr>
<td><strong>Binet[^8]</strong></td>
<td>Stage B</td>
<td>3 or more enlarged areas; hemoglobin ≥10.0 g/dL, and platelets ≥100 × 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Stage C</td>
<td>Any number of enlarged areas; hemoglobin &lt;10.0 g/dL, and/or platelets &lt;100 × 10^9/L</td>
</tr>
</tbody>
</table>

This patient has:

- Rai Stage III (lymphocytosis, splenomegaly, enlarged lymph nodes, hemoglobin <11.0 g/dL)
- Binet Stage B (splenomegaly, enlarged lymph nodes, hemoglobin <10.0 g/dL)

Bendamustine (BENDEKA®) is a recommended option within NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)^[^5]

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**Important Safety Information (cont)**

Anaphylaxis and Infusion Reactions: Infusion reactions to bendamustine HCl 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 (Grade 3–4) reactions. Ask patients about symptoms suggestive of infusion reactions after their first cycle of therapy. 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.

Please read additional Important Safety Information throughout and accompanying Full Prescribing Information for BENDEKA starting on page 7.
What options do you consider for front-line CLL?

Is BENDEKA® a good option for this patient?

The patient began treatment with BENDEKA 100 mg/m² administered intravenously over 10 minutes on days 1 and 2 of a 28-day cycle for up to 6 cycles.¹

Dose modifications for hematologic toxicity:
• For Grade 3 or greater hematologic toxicity: Reduce dose to 50 mg/m² on days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m² on days 1 and 2.
• Dose re-escalation may be considered

Dose modifications for non-hematologic toxicity:
• Clinically significant Grade 3 or greater non-hematologic toxicity, reduce the dose to 50 mg/m² on days 1 and 2 of each cycle
• Dose re-escalation may be considered

Additional dosing considerations:
• Delay treatment for Grade 4 hematologic toxicity or clinically significant Grade 2 or greater non-hematologic toxicity
• Store BENDEKA at recommended refrigerated storage conditions (2-8°C or 36-46°F). When refrigerated the contents may partially freeze. Allow the vial to reach room temperature (15-30°C or 59-86°F) prior to use.
• Dilute BENDEKA Injection prior to infusion
• Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine
• Renal impairment: Do not use if creatinine clearance is <30 mL/min
• Hepatic impairment: Do not use in moderate or severe hepatic impairment

What has been your experience with BENDEKA?

Important Safety Information (cont)

Tumor Lysis Syndrome: Tumor lysis syndrome associated with bendamustine HCl has occurred. The onset tends to be within the first treatment cycle with bendamustine HCl 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. There may be an increased risk of severe skin toxicity when bendamustine HCl and allopurinol are administered concomitantly.

Skin Reactions: Fatal and serious skin reactions have been reported with bendamustine HCl and include, 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 bendamustine HCl was given as a single agent and in combination with other anticancer agents or allopurinol. 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 BENDEKA.

Please read additional Important Safety Information throughout and accompanying Full Prescribing Information for BENDEKA starting on page 7.
Important Safety Information (cont)

**Hepatotoxicity:** Fatal and serious cases of liver injury have been reported with bendamustine HCl. Combination therapy, progressive disease or reactivation of hepatitis B were confounding factors in some patients. Most cases were reported within the first three months of starting therapy. Monitor liver chemistry tests prior to and during BENDEKA therapy.

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

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

**Embryo-fetal Toxicity:** Bendamustine HCl can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant while using BENDEKA.

**Most Common Adverse Reactions:**

- Adverse reactions (frequency >5%) during infusion and within 24 hours post-infusion are nausea and fatigue.
- Most common non-hematologic adverse reactions for CLL (frequency ≥15%) are pyrexia, nausea, and vomiting.
- Most common hematologic abnormalities (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia.

Please read accompanying Full Prescribing Information for BENDEKA starting on page 7.
For more information about BENDEKA®, please visit BENDEKA.com

Please read accompanying Full Prescribing Information for BENDEKA

References

1. BENDEKA® (bendamustine hydrochloride) Injection [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.5.2018. ©National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 4, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BENDEKA safely and effectively. See full prescribing information for BENDEKA.
BENDEKA® (bendamustine hydrochloride injection), for intravenous use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

BENDEKA (bendamustine hydrochloride) injection is an alkylating drug indicated for the treatment of patients with:
• Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. (1.1)
• Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. (1.2)

DOSAGE AND ADMINISTRATION

For CLL:
• 100 mg/m² infused intravenously over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. (2.1)
• Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce dose to 50 mg/m² on Days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m² on Days 1 and 2. (2.1)
• 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. (2.1)
• Dose re-escalation is considered. (2.1)

For NHL:
• 120 mg/m² infused intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. (2.2)
• 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. (2.2)
• 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. (2.2)

General Dosing Considerations:
• Delay treatment for Grade 4 hematologic toxicity or clinically significant Grade 2 non-hematologic toxicity. (2.1, 2.2)
• Store BENDEKA at recommended refrigerated storage conditions (2-8°C or 36-46°F). When refrigerated, the contents may partially freeze. Allow the vial to reach room temperature (15-30°C or 59-86°F) prior to use. (2.3)
• BENDEKA must be diluted prior to infusion. (2.3)

DOSE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) in a multiple-dose vial. (3)

CONTRAINDICATIONS

BENDEKA is contraindicated in patients with a history of a hypersensitivity reaction to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol. Reactions to bendamustine hydrochloride have included anaphylaxis and anaphylactoid reactions (4, 5, 3).

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Revised: 07/2018
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)

BENDEKA® (bendamustine hydrochloride) injection is indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established.

1.2 Non-Hodgkin Lymphoma (NHL)

BENDEKA (bendamustine hydrochloride) injection 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions for CLL

Recommended Dosage

The recommended dose is 100 mg/m² administered intravenously over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. Dose delays, dose modifications and reinitiation of therapy for NHL:

Recommended Dosage:

The recommended dose is 120 mg/m² administered intravenously over 10 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:

BENDEKA (bendamustine hydrochloride) injection administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant greater than or equal to Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to less than or equal to Grade 1 and/or the blood counts have improved (Absolute Neutrophil Count [ANC] greater than or equal to 1 x 10⁹/L, platelets greater than or equal to 75 x 10⁹/L), BENDEKA (bendamustine hydrochloride) injection can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. [see Warnings and Precautions (5.1)]

Dose modifications for hematologic toxicity: For Grade 3 or greater toxicity, reduce the dose to 50 mg/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.

2.2 Dosing Instructions for NHL

Recommended Dosage

The recommended dose is 120 mg/m² administered intravenously over 10 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:

BENDEKA (bendamustine hydrochloride) injection administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant greater than or equal to Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to less than or equal to Grade 1 and/or the blood counts have improved (Absolute Neutrophil Count [ANC] greater than or equal to 1 x 10⁹/L, platelets greater than or equal to 75 x 10⁹/L), BENDEKA (bendamustine hydrochloride) injection can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. [see Warnings and Precautions (5.1)]

Dose modifications for hematologic toxicity: For Grade 3 or greater toxicity, reduce the dose to 50 mg/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.

2.3 Preparation for Intravenous Administration

BENDEKA (bendamustine hydrochloride) injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.1

BENDEKA is in a multiple-dose vial. At room temperature, BENDEKA is a clear, and colorless to yellow ready-to-dilute solution. Store BENDEKA at recommended refrigerated storage conditions (2-8°C or 36-46°F). When refrigerated, the contents may partially freeze. Allow the vial to reach room temperature (15-30°C or 59-86°F) prior to administration whenever solution and container permit. Any unused contents of the infusion bag. The admixture should be a clear, and colorless to yellow ready-to-dilute solution. Store BENDEKA at recommended refrigerated storage conditions (2-8°C or 36-46°F). When refrigerated, the contents may be stable for up to 28 days when stored in its original carton under refrigeration (2-8°C or 36-46°F). Each vial is not recommended for more than a total of six (6) dose withdrawals. After first use, the partially used vial should be stored in the refrigerator in the original carton at 2°-8°C or 36-46°F and then discarded after 28 days.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) as a clear and colorless to yellow ready-to-dilute solution in a multiple-dose vial.

4 CONTRAINDICATIONS

BENDEKA (bendamustine hydrochloride) injection is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol. [see Warnings and Precautions (5.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Bendamustine hydrochloride caused severe myelosuppression (Grade 3-4) in 98% of patients in the two NHL studies (see Table 4). Three patients (2%) bled from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV).

BENDeka (bendamustine hydrochloride) injection causes myelosuppression. Monitor complete blood counts, including leukocytes, platelets, hemoglobin (Hgb), and neutrophils frequency. In the clinical trials, blood counts were monitored every week initially. Hematologic nadirs occurred 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. [see Dosage and Administration (2.1)]
5.2 Infections
Infection, including pneumonia, sepsis, septic shock, hepatitis and death has occurred in adult and pediatric patients in clinical trials and in postmarketing reports for bendamustine hydrochloride. Patients with myelosuppression following treatment with bendamustine hydrochloride are more susceptible to infections. Advise patients with myelosuppression following BENDEKA (bendamustine hydrochloride) injection treatment to consult a physician immediately if they have symptoms or signs of infection. Patients treated with bendamustine hydrochloride are at risk 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 treatment) for infection and infection reactivation prior to administration.

5.3 Anaphylaxis and Infusion Reactions
Infusion reactions to bendamustine hydrochloride 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 experienced Grade 3 or worse allergic-type reactions were not typically 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 BENDEKA (bendamustine hydrochloride) injection for patients with Grade 4 infusion reactions. Consider discontinuation for Grade 3 infusion reactions as clinically appropriate considering individual benefits, risks, and supportive care.

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

5.5 Skin Reactions
Fatal and serious skin reactions have been reported with bendamustine hydrochloride injection treatment in clinical trials and postmarketing 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 was observed when bendamustine hydrochloride injection was given as a single agent and in combination with other antacancer agents or allopurinol. 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 BENDEKA (bendamustine hydrochloride) injection.

5.6 Hepatotoxicity
Fatal and serious cases of liver injury have been reported with bendamustine hydrochloride injection. Combination therapy, progressive disease or reactivation of hepatitis B were confounding factors in some patients [see Warnings and Precautions (5.2)]. Most cases were reported within the first three months of starting therapy. Monitor liver chemistry tests prior to and during bendamustine therapy.

5.7 Other Malignancies
There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with bendamustine hydrochloride, including myelodysplasia syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with BENDEKA (bendamustine hydrochloride) injection therapy has not been determined.

5.8 Extravasation Injury
Bendamustine hydrochloride extravasations have been reported in postmarketing resulting in hospitalizations from erythema, marked swelling, and pain. Assure good venous access prior to starting drug infusion and monitor the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of BENDEKA (bendamustine hydrochloride) injection.

5.9 Embryo-fetal Toxicity
Bendamustine hydrochloride can cause fetal harm when administered to a pregnant woman. Single intrauterine doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights. [See Use in Specific Populations (8.1)]

6 ADVERSE REACTIONS
The following serious adverse reactions have been associated with bendamustine hydrochloride in clinical trials and are discussed in greater detail in other sections of the prescribing information.

- Myelosuppression [see Warnings and Precautions (5.1)]
- Infections [see Warnings and Precautions (5.2)]
- Anaphylaxis and Infusion Reactions [see Warnings and Precautions (5.3)]
- Tumor Lysis Syndrome [see Warnings and Precautions (5.4)]
- Skin Reactions [see Warnings and Precautions (5.5)]
- Hepatotoxicity [see Warnings and Precautions (5.6)]
- Other Malignancies [see Warnings and Precautions (5.7)]
- Extravasation Injury [see Warnings and Precautions (5.8)]

6.1 Adverse Events in Clinical Trials
The data described below reflect exposure to bendamustine hydrochloride in 329 patients who participated in an actively controlled trial (N=153) for the treatment of CLL and two single arm studies (N=176) for the treatment of indolent B cell NHL. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of BENDEKA (bendamustine hydrochloride) injection administered IV as a 50 mL admixture over a 10-minute infusion is supported by clinical trials using bendamustine hydrochloride administered IV as a 500 mL admixture over standard infusion time (30-60 minutes) and BENDEKA administered as a 50 mL admixture in a ‘short-time’ infusion over 10 minutes. The safety and tolerability of BENDEKA was evaluated in an 8-week clinical study of BENDEKA in 81 ‘end-of-life’ cancer patients, diagnosed with solid tumors and hematologic malignancies (excluding CLL). The population was 40-82 years of age, 58% females, 84% white, 12.3% Black, 1.2% Asian and 2.5% were classified as ‘other’. BENDEKA was administered IV at a 120 mg/m² dose as a 50 mL admixture over 10 minutes. Patients in the study received BENDEKA (50 mL IV, over 10 minutes) or bendamustine hydrochloride (500 mL IV, over 60 minutes) on Days 1 and 2 every 28 days for two consecutive 2-day cycles.

Adverse reactions (any grade) that occurred with a frequency greater than 5% during BENDEKA infusion and within one hour post-infusion were nausea (8.2%) and fatigue (5.5%).

Adverse reactions (any grade) that occurred with a frequency greater than 5% within 24 hours of BENDEKA were nausea (10.9%) and fatigue (8.2%).

Adverse reactions leading to study withdrawal in 4 patients receiving BENDEKA were pyrexia (1.2%), nausea (1.2%), vomiting (1.2%), pneumonia (1.2%) and fatigue (1.2%).

6.2 Clinical Trials Experience in CLL
The data described below reflect exposure to bendamustine hydrochloride in 153 patients. Bendamustine hydrochloride was studied in an active-controlled randomized trial. The population was 45-77 years of age, 63% male, 100% white, and had treatment naive CLL. All patients started the study at a dose of 100 mg/m² intravenously over 30 minutes on Days 1 and 2 every 28 days. Adverse reactions were reported according to NCI CTG v2.0. In the randomized CLL clinical study, non-hematologic adverse reactions (any grade) in the bendamustine hydrochloride group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%).

Other adverse reactions seen frequently in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis. Worsening hypertension was reported in 4 patients treated with bendamustine hydrochloride in the randomized CLL clinical study and in none treated with chlorambucil. Three of these 4 adverse reactions were described as a hypertensive crisis and were managed with oral medications and resolved. The most frequent adverse reactions leading to study withdrawal for patients receiving bendamustine hydrochloride were hypersensitivity (2%) and pyrexia (1%). Table 1 contains the treatment emergent adverse reactions, regardless of attribution, that occurred in ≥ 5% of patients in either treatment group in the randomized CLL clinical study.

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

<table>
<thead>
<tr>
<th>Number (%) of patients</th>
<th>Bendamustine Hydrochloride (N=153)</th>
<th>Chlorambucil (N=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>System organ class</td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Preferred term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (20)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (16)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36 (24)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Continued
Table 2: Incidence of Hematology Laboratory Abnormalities in Patients Who Received bendamustine hydrochloride or Chlorambucil in the Randomized CLL Clinical Study

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin Decreased</td>
<td>Bendamustine Hydrochloride (N=153)</td>
<td>134 (89)</td>
<td>20 (13)</td>
<td>115 (82)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>Bendamustine Hydrochloride (N=153)</td>
<td>116 (77)</td>
<td>16 (11)</td>
<td>110 (78)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Leukocytes Decreased</td>
<td>Bendamustine Hydrochloride (N=153)</td>
<td>92 (61)</td>
<td>42 (28)</td>
<td>26 (18)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Lymphocytes Decreased</td>
<td>Bendamustine Hydrochloride (N=153)</td>
<td>102 (68)</td>
<td>70 (47)</td>
<td>27 (19)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>Bendamustine Hydrochloride (N=153)</td>
<td>113 (75)</td>
<td>65 (43)</td>
<td>86 (61)</td>
<td>30 (21)</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil (N=143)</td>
<td>115 (83)</td>
<td>14 (10)</td>
<td>110 (80)</td>
<td>15 (11)</td>
</tr>
</tbody>
</table>

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

6.3 Clinical Trials Experience in NHL

The data described below reflect exposure to bendamustine hydrochloride in 176 patients with indolent B-cell NHL treated in two single-arm studies. The population was 31-84 years of age, 60% male, and 40% female. The race distribution was 89% White, 7% Black, 3% Hispanic, 1% other, and <1% Asian. These patients received bendamustine hydrochloride at a dose of 120 mg/m² intravenously on Days 1 and 2 for up to eight 21-day cycles.

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

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

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Preferred term</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number of patients with at least 1 adverse reaction</td>
<td>176 (100)</td>
<td>94 (53)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Tachycardia</td>
<td>13 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>132 (75)</td>
<td>7 (4)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>71 (40)</td>
<td>5 (3)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>65 (37)</td>
<td>6 (3)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>51 (29)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>27 (15)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>22 (13)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>20 (11)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux disease</td>
<td>18 (10)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>15 (9)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>8 (5)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abdominal distension</td>
<td>8 (5)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>101 (57)</td>
<td>19 (11)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>59 (34)</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>24 (14)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>23 (13)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>19 (11)</td>
<td>4 (2)</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>11 (6)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Infusion site pain</td>
<td>11 (6)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>10 (6)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Catheter site pain</td>
<td>8 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Herpes zoster</td>
<td>18 (10)</td>
<td>5 (3)</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>18 (10)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>17 (10)</td>
<td>4 (2)</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>15 (9)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>14 (8)</td>
<td>9 (5)</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia</td>
<td>11 (6)</td>
<td>11 (6)</td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis</td>
<td>11 (6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>11 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>31 (18)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td>40 (23)</td>
<td>3 (2)</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>24 (14)</td>
<td>8 (5)</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>22 (13)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>15 (9)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>25 (14)</td>
<td>5 (3)</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>11 (6)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pain in extremity</td>
<td>8 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
<td>8 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>36 (21)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>25 (14)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
<td>13 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>Insomnia</td>
<td>23 (13)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>14 (8)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>10 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

continued
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, CYP2C9, and/or CYP3A4, or to induce metabolism of substrates of cytochrome P450 enzymes.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

- **Pregnancy Category D** [see Warnings and Precautions (5.9)]

**Risk Summary**

Bendamustine hydrochloride 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 BENDEKA (bendamustine hydrochloride) injection 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 the fetus. Advise men receiving BENDEKA (bendamustine hydrochloride) injection 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 (encephaly, 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 anomalies from 112.5 mg/m² (37.5 mg/kg) similar to those seen after intraperitoneal administration. Single intraperitoneal doses of bendamustine from 120 mg/m² (20 mg/kg) in rats administered on gestation days 4, 7, 9, 11, 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 (hydrenephrosis and hydrocoeleus) malformations were seen in dosed rats. There was no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

#### 8.3 Nursing Mothers

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

#### 8.4 Pediatric Use

The effectiveness of bendamustine hydrochloride in pediatric patients has not been established. Bendamustine hydrochloride was evaluated in a single Phase 1/2 trial in pediatric patients with leukemia. The safety profile for bendamustine hydrochloride 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 lymphoblastic leukemia (ALL) and 16 patients with acute myeloid leukemia (AML). Bendamustine hydrochloride 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 bendamustine hydrochloride in pediatric patients was 120 mg/m².

A total of 32 patients entered the Phase 2 portion of the study at the recommended dose evaluated for response. There was no treatment response (CR or 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 bendamustine hydrochloride 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.

#### 8.5 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 DOLL clinical study, 153 patients received bendamustine hydrochloride. The overall response rate for patients younger than 65 years of age was 70% (n = 82) for bendamustine hydrochloride and 30% (n = 49) for chlorambucil. The overall response rate for patients 65 years or older was 47% (n = 71) for bendamustine hydrochloride and 22% (n = 79) for chlorambucil. In patients younger than 65 years of age, the median progression-free survival was 19 months in the bendamustine hydrochloride group and 8 months in the chlorambucil group. In patients 65 years or older, the median progression-free survival was 12 months in the bendamustine hydrochloride 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.
BENDEKA® (bendamustine hydrochloride) injection

8.6 Renal Impairment
No formal studies assessing the impact of renal impairment on the pharmacokinetics of bendamustine have been conducted. BENDEKA (bendamustine hydrochloride) injection should not be used in patients with CrCL < 30 mL/min. [see Clinical Pharmacology (12.3)]

8.7 Hepatic Impairment
No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of bendamustine have been conducted. BENDEKA (bendamustine hydrochloride) injection should not be used in patients with moderate (AST or ALT 2.5-10 X ULN and total bilirubin 1.5-3 X ULN) or severe (total bilirubin > 3 X ULN) hepatic impairment. [see Clinical Pharmacology (12.3)]

8.8 Effect of Gender
No clinically significant differences between genders were seen in the overall incidences of adverse reactions in CLL or NHL studies. Chronic Lymphocytic Leukemia

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

10 OVERDOSAGE
The intravenous LD₅₀ of bendamustine hydrochloride is 240 mg/m² in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress. Across all clinical experience, the reported maximum single dose received was 280 mg/m². Three of four patients treated at this dose showed ECG changes considered dose-limiting at 7 and 21 days post-dosing. These changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave deviations (two patients) and left anterior fascicular block (one patient). Cardiac enzymes and ejection fractions remained normal in all patients.

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

11 DESCRIPTION
BENDEKA (bendamustine hydrochloride) injection is an alkylating agent. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanolic acid, S-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is C₁₆H₂₁Cl₂N₃O₂ ∙ HCl, and the molecular weight is 394.7. Bendamustine hydrochloride contains a methylethanesulfonic acid and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:

\[
\text{Cl-CH₂-CH₂-CH₂-CH₂-N} \quad \text{(CH₃)₂-COOH+HCl}
\]

\[
\text{CH₃}
\]

BENDA (bendamustine hydrochloride) injection is supplied as a sterile, clear, and colorless to yellow ready-to-dilute solution in a multiple-dose clear glass vial. Each milliliter contains 25 mg of bendamustine hydrochloride, 0.1 mL of Propylene Glycol, USP, 5 mL of Monoethylglycol, NF, in Polyethylene Glycol 400, NF. Sodium hydroxide may have been used to adjust the acidity of polyethylene glycol 400.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bendamustine is a bifunctional methylethanesulfonate derivative containing a purine-like benzimidazole ring. Methylethanesulfonic and its derivatives form electrophilic alkylating agents which covalently bind to DNA. 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.

12.2 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 QT 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.

12.3 Pharmacokinetics

Absorption
In a pharmacokinetic study conducted in patients with cancer (N=60), a single IV dose of BENDEKA (bendamustine hydrochloride) injection (120 mg/m²; administered as a 10 minutes infusion), resulted in a higher maximum plasma concentration (Cₘₐₓ) and equivalent systemic exposure (AUC), compared to a single dose of Treanda (bendamustine hydrochloride) (120 mg/m²) infused over 60 minutes. The mean Cₘₐₓ achieved was 35 μg/mL (range 6 to 49 μg/mL), occurring typically at the end of infusion.

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 hydroxybendamustine (M₃), and N desmethylbendamustine (M₄). This suggests that there are bendamustine derived materials (detected via the radiolabel), that are rapidly cleared and have a shorter plasma half-life than bendamustine.

In vitro, the 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 dihydroxybendamustine (HP2) metabolites with low cytotoxic activity. In vitro, studies indicate that two active minor metabolites, M₃ and M₄, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are 1/10th and 1/100th of 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, CYP1B1, 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% of the dose was recovered in the urine and approximately 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. Less than 5% of the dose was recovered in the urine as HP1 and HP2.

After a single dose of 120 mg/m² bendamustine IV over 1-hour the intermediate t₁/₂ of the parent compound is approximately 40 minutes. The mean apparent terminal elimination t₁/₂ of M₃ and M₄ are approximately 3 hours and 30 minutes respectively. Little or no accumulation in plasma is expected for bendamustine administered on Days 1 and 2 of a 28-day cycle. Bendamustine clearance in humans is approximately 700 mL/minute.

Renal Impairment
In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m², there was no meaningful effect of renal impairment (CrCL 30 - 80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL < 30 mL/min and should not be used in these patients.

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 X ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment.

Bendamustine should not be used in patients with moderate (AST or ALT 2.5 - 10 X ULN and total bilirubin 1.5 - 3 X ULN) or severe (total bilirubin > 3 X ULN) hepatic impairment. [see Use in Specific Populations (8.7)]

Effect of Age
Bendamustine exposure (as measured by AUC and Cₘₐₓ) has been studied in 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 50 years of age. [see Use in Specific Populations (8.4, 8.5)]

Effect of Gender
The pharmacokinetics of bendamustine were similar in male and female patients. [see Use in Specific Populations (8.8)]

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

13.1 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/etha 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 the in vivo Ames assay, bendamustine was shown to increase revertant frequency in the Ames assay, and bendamustine was clastogenic in the in vivo Ames assay. Bendamustine was shown to increase revertant frequency in the Ames assay, and bendamustine was clastogenic in the in vivo Ames assay. Bendamustine was shown to increase revertant frequency in the Ames assay, and bendamustine was clastogenic in the in vivo Ames assay.

14 CLINICAL STUDIES

14.1 Chronic Lymphocytic Leukemia (CLL)

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

The patient populations in the bendamustine hydrochloride and chlorambucil treatment groups were balanced with regard to the following baseline characteristics: age (median 63 vs. 66 years), gender (63% vs. 61% male), Binet stage (71% vs. 69% Binet B), lymphadenopathy (78% vs. 82%), enlarged spleen (78% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), B symptoms (51% vs. 53%), lymphocyte count (mean 65.7 x10⁹/L vs. 65.1 x10⁹/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immunopheno-typic confirmation of CLL (CD19 and CD23 or both). Patients were randomly assigned to receive either bendamustine hydrochloride at 100 mg/m², administered intravenously over a period of 30 minutes on Days 1 and 2 or chlorambucil at 0.8 mg/kg (Broca's normal weight) administered orally on Days 1 and 15 of each 28-day cycle. Efficacy endpoints of objective response rate and progression-free survival were calculated using a pre-specified algorithm based on NCI working group criteria for CLL.

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

Table 5: Efficacy Data for CLL

<table>
<thead>
<tr>
<th>Response Rate n (%)</th>
<th>Bendamustine Hydrochloride (N=153)</th>
<th>Chlorambucil (N=148)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>90 (59)</td>
<td>38 (26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(51, 66.6)</td>
<td>(18.6, 32.7)</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)*</td>
<td>13 (8)</td>
<td>1 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Nodular partial response (nPR) **</td>
<td>4 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)†</td>
<td>73 (48)</td>
<td>37 (25)</td>
<td></td>
</tr>
</tbody>
</table>

** Progression-Free Survival††

<table>
<thead>
<tr>
<th>Median, months (95% CI)</th>
<th>18 (11.7, 23.5)</th>
<th>6 (5.6, 8.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.27 (0.17, 0.43)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI = confidence interval

*Bleeding was defined as peripheral lymphocyte count < 4 x 10⁹/L, neutrophils > 1.5 x 10⁹/L, platelets > 100 x 10⁹/L, hemoglobin > 110 g/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 laboratory criteria were required to be maintained for a period of at least 56 days.

*PR was defined as ≥50% decrease in peripheral lymphocyte count from the pretreatment baseline value, complete remission (CR), or partial remission (PR). Complete remission includes ≥50% reduction in lymphadenopathy, ≥50% reduction in the size of spleen or liver, as well as one of the following hematologic improvements: neutrophils ≥ 1.5 x 10⁹/L, lymphocytes ≥ 1 x 10⁹/L, platelets ≥ 100 x 10⁹/L, hemoglobin > 110 g/L without transfusions, absence of palpable lymphadenopathy and cytosis, or absence of symptoms of lymphomatous disease. Kaplan-Meier estimates of progression-free survival comparing bendamustine hydrochloride with chlorambucil are shown in Figure 1.
17 PATIENT COUNSELING INFORMATION

Allergic (Hypersensitivity) Reactions
Inform patients of the possibility of serious or mild allergic reactions and to immedi-
ately report rash, facial swelling, or difficulty breathing during or soon after infusion 
[see Warnings and Precautions (5.5)].

Myelosuppression
Inform patients of the likelihood that BENDEKA (bendamustine hydrochloride) injec-
tion will cause a decrease in white blood cells, platelets, and red blood cells. They will 
need frequent monitoring of these parameters. They should be instructed to report 
shortness of breath, significant fatigue, bleeding, fever, or other signs of infection 
[see Warnings and Precautions (5.1)].

Hepatotoxicity
Inform patients of the possibility of developing liver function abnormalities and seri-
ous hepatic toxicity. Advise patients to immediately contact their healthcare provider 
if signs of liver failure occur, including jaundice, anorexia, bleeding or bruising [see 
Warnings and Precautions (5.6)].

Fatigue
Advise patients that BENDEKA (bendamustine hydrochloride) injection may cause 
tiredness and to avoid driving any vehicle or operating any dangerous tools or 
machinery if they experience this side effect [see Adverse Reactions (6.1)].

Nausea and Vomiting
Advise patients that BENDEKA (bendamustine hydrochloride) injection may cause 
nausea and/or vomiting. Patients should report nausea and vomiting so that symp-
tomatic treatment may be provided [see Adverse Reactions (6.1)].

Diarrhea
Advise patients that BENDEKA (bendamustine hydrochloride) injection may cause 
diarrhea. Patients should report diarrhea to the physician so that symptomatic treat-
ment may be provided [see Adverse Reactions (6.1)].

Rash
Advise patients that a mild rash or itching may occur during treatment with BENDEKA 
(bendamustine hydrochloride) injection. Advise patients to immediately report severe 
or worsening rash or itching [see Warnings and Precautions (5.5)].

Pregnancy and Nursing
BENDEKA (bendamustine hydrochloride) injection can cause fetal harm. Women 
should be advised to avoid becoming pregnant throughout treatment and for 
3 months after bendamustine hydrochloride therapy has stopped. Men receiving 
BENDEKA (bendamustine hydrochloride) injection should use reliable contraception 
for the same time period. Advise patients to report pregnancy immediately. Advise 
patients to avoid nursing while receiving BENDEKA (bendamustine hydrochloride) 
[see Use in Specific Populations (8.1) and (8.3)].

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