Understanding my treatment with BENDEKA®

BENDEKA® is indicated for the treatment of patients with

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

- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

Important Safety Information

BENDEKA is not right for everyone: including patients with a known allergic response to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
Getting started

Why did my oncologist prescribe BENDEKA® (bendamustine HCl) for me?

Treating blood cancer is a journey. Depending on where you are in your journey, your oncologist may prescribe BENDEKA—a type of chemotherapy. Chemotherapy is a type of treatment that is designed to kill cancer cells.

BENDEKA is prescribed to treat 2 types of cancer:

- **Chronic lymphocytic leukemia (CLL)**, which starts with certain white blood cells in the bone marrow and then goes into the blood
  - If you have been diagnosed with CLL, you may receive BENDEKA

- **Slow-growing non-Hodgkin lymphoma (NHL)**, which starts with certain white blood cells in the lymph system
  - If you have been previously treated for NHL that has continued to worsen during or after treatment with another medication, your doctor may switch you to BENDEKA

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Important Safety Information

**BENDEKA may cause serious side effects** including: low blood cell counts, infections or recurrence of infections, unexpected responses to BENDEKA when placed in your blood, sudden and severe allergic responses, kidney failure due to fast breakdown of cancer cells, other cancers, and leaking of BENDEKA out of your vein and into your surrounding skin. Some of these side effects, such as low blood counts, infections, liver injury, and severe allergic skin responses (when bendamustine HCl was given alone and in combination with other anticancer medications or allopurinol), have caused death.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
How can this brochure help me?

This brochure was written to help you better understand what you might expect during treatment with BENDEKA. Please contact your health care team with any questions you may have throughout your treatment.

YOU WILL LEARN

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Remember, not every person responds to treatment the same way. This is also true for side effects. People’s emotions may vary too. It may not be easy, but try to stay motivated. Also know that you are not alone on your treatment journey.

Before you start treatment, ask your doctor or nurse any questions you may have. Write down a list of questions before each appointment. Take a family member or friend to your appointment to help you keep track of answers and give support.

This information is not meant to take the place of talking with your health care team about your condition or treatment. If you have questions after reading this brochure, please talk with your health care team.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
Understanding my treatment

How will I get BENDEKA® (bendamustine HCl)?

BENDEKA may be given at your doctor’s office, the hospital, or an infusion center. It is given as an intravenous (IV) infusion that goes directly into your vein through a small needle in your arm.

As part of your treatment process, it takes about **10 minutes** for a BENDEKA infusion.

Important Safety Information

**Tell your doctor if you have any side effects** including: rash, facial swelling, or difficulty breathing during or soon after your infusion with BENDEKA injection. These are signs of an allergic reaction. You also should tell your doctor if you have shortness of breath, significant fatigue, bleeding, bruising, fever, or other signs of infection. Also, tell your doctor if you experience nausea, vomiting, diarrhea, loss of appetite, or a yellow skin tone. In addition, your doctor will perform blood tests to see if you have low blood counts. These are lower-than-normal numbers of red blood cells, white blood cells, or platelets.

**Some serious side effects may require changes in therapy**, such as lowering the amount of BENDEKA given, stopping the use of BENDEKA, or waiting longer than expected between doses of BENDEKA.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
**CLL cycle of treatment**
This calendar shows 1 cycle of treatment for CLL with BENDEKA. Each cycle lasts 28 days. The calendar shows which days you will get your infusion and for how long. This treatment cycle may be repeated up to 6 times.

**NHL cycle of treatment**
This calendar shows 1 cycle of treatment for NHL with BENDEKA. Each cycle lasts 21 days. The calendar shows which days you will get your infusion and for how long. This treatment cycle may be repeated up to 8 times.

**Will my dose ever change?**
As explained earlier, not all patients react to medications the same way, so it may be necessary for your doctor to make changes to the dose of BENDEKA to find out what is right for you or even to stop treatment. Changing the dose or delaying treatment may be necessary if you are experiencing side effects. The most important goal is to find the treatment approach that will help you achieve the best results possible. Your doctor may change, delay, or even stop your treatment.

**TIP**
Talk with your health care team about how often you will get treatment. That way, you can plan for your appointments.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
How will I know if my treatment is working?

TESTS THAT MAY BE DONE

Your health care team will give you a physical exam and ask about your symptoms. Blood samples may be taken or other tests may be done. These tests show how you are responding to treatment with BENDEKA® (bendamustine HCl).

TYPES OF RESPONSES

If the tests do not show any cancer cells, your response is called a complete response. If the number of cancer cells is reduced, your response is called a partial response. Sometimes, a person may not show a response to treatment. If you want to know more about your response to treatment, your doctor can provide more detail.

TALK WITH YOUR DOCTOR

Don’t worry if you don’t see a response right away. It may take some time before you start seeing positive results. Talk about your progress with your doctor. Together, you can decide on a treatment plan that is right for you.

BENDEKA is indicated for the treatment of patients with

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Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
Important Safety Information

**BENDEKA is not right for everyone:** including patients with a known allergic response to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.

**BENDEKA may cause serious side effects** including: low blood cell counts, infections or recurrence of infections, unexpected responses to BENDEKA when placed in your blood, sudden and severe allergic responses, kidney failure due to fast breakdown of cancer cells, other cancers, and leaking of BENDEKA out of your vein and into your surrounding skin. Some of these side effects, such as low blood counts, infections, liver injury, and severe allergic skin responses (when bendamustine HCl was given alone and in combination with other anticancer medications or allopurinol), have caused death.

**Tell your doctor if you have any side effects** including: rash, facial swelling, or difficulty breathing during or soon after your infusion with BENDEKA injection. These are signs of an allergic reaction. You also should tell your doctor if you have shortness of breath, significant fatigue, bleeding, bruising, fever, or other signs of infection. Also, tell your doctor if you experience nausea, vomiting, diarrhea, loss of appetite, or a yellow skin tone. In addition, your doctor will perform blood tests to see if you have low blood counts. These are lower-than-normal numbers of red blood cells, white blood cells, or platelets.

**Some serious side effects may require changes in therapy,** such as lowering the amount of BENDEKA given, stopping the use of BENDEKA, or waiting longer than expected between doses of BENDEKA.

**BENDEKA may cause fetal harm if taken while pregnant.** Women should avoid becoming pregnant or nursing while receiving BENDEKA.

**Non–blood-related side effects may occur** including: fever, nausea, and vomiting, diarrhea, constipation, loss of appetite, cough, headache, weight loss, difficulty breathing, rash, and mouth irritation.

**Blood-related side effects may occur** including: low red blood cells (oxygen-carrying cells), low platelets (blood-clotting cells), and decreased number of three different types of white blood cells (infection-fighting cells).

These are not all of the possible side effects of BENDEKA. For more information ask your healthcare provider.

You are encouraged to report side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

Please see Full Prescribing Information starting on page 17.

For more information about BENDEKA, ask your doctor, call 1-888-483-8279, or visit BENDEKA.com
Understanding serious side effects

Many people worry about serious side effects from their cancer treatment. The serious side effects listed on this page and the next have been seen in some studies with bendamustine hydrochloride. That is why it is important to talk with your doctor about your treatment and any symptoms you may have.

BENDEKA* (bendamustine HCl) MAY CAUSE BLOOD-RELATED SERIOUS SIDE EFFECTS

Lower than normal blood cell counts

- A low red blood cell count can make you feel tired easily or short of breath
- A low white blood cell count can make you more likely to get an infection
- A low platelet count can make you more likely to have bleeding that is not normal for you

Infections

- Tell your doctor if you have shortness of breath, significant fatigue, bleeding, fever, or other signs of infection

Changes in treatment

Some serious side effects may require changes in your treatment, such as:

- Lowering the amount of BENDEKA given
- Waiting longer between doses of BENDEKA
- Stopping the use of BENDEKA

TIP
Talk with your health care team if you have questions about any side effects.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
Who should not take BENDEKA?
Patients with a known allergic response to bendamustine polyethylene glycol 400, propylene glycol, or monothioglycerol.

Should pregnant women take BENDEKA?
Women should avoid becoming pregnant while receiving BENDEKA because it may cause fetal harm if you take BENDEKA while pregnant.

Can getting an infusion of BENDEKA cause a reaction?
Tell your doctor if you have any side effects including: rash, facial swelling, or difficulty breathing during or soon after your infusion with BENDEKA injection. These are signs of an allergic reaction. You also should tell your doctor if you have shortness of breath, significant fatigue, bleeding, bruising, fever, or other signs of infection. Also, tell your doctor if you experience nausea, vomiting, diarrhea, loss of appetite, or a yellow skin tone. In addition, your doctor will perform blood tests to see if you have low blood counts. These are lower-than-normal numbers of red blood cells, white blood cells, or platelets.

Tell your doctor or nurse right away if you have any of these side effects associated with BENDEKA because some of these effects may become serious and could be fatal if they are not treated in time.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
Understanding common side effects

What side effects might I expect with BENDEKA® (bendamustine HCl)?
Keep track of any side effects you may have between treatments. Be sure to mention them to your doctor and nurse at your next appointment.

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<tr>
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BENDEKA is indicated for the treatment of patients with

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Commonly asked questions about BENDEKA® (bendamustine HCl)

Having a lot of questions about your treatment is normal. We hope you’ll find some answers here. At the treatment center, you’ll meet nurses and support staff who will also be able to answer your questions before you begin treatment.

Can I take other medications while receiving BENDEKA?
Talk with your doctor about any medications you are taking or plan to take. Some types of medication may impact the way BENDEKA works in the body.

Are there any foods I should avoid during treatment?
A healthy diet is important when you’re being treated for cancer. The right diet can help you keep up your strength and energy level. But getting the right nutrition can be hard if you don’t feel well. Some people lose their appetite or have trouble eating because of side effects from chemotherapy.

Try these tips to make sure you are getting the right nutrition:
- Eat several snacks during the day, rather than 3 large meals
- Eat protein-rich foods, such as yogurt, cereal, half a sandwich, a bowl of soup, cheese and crackers
- Avoid foods that make side effects worse. If you have diarrhea, for example, do not eat raw fruits and vegetables. If you have a sore throat, do not eat dry snacks or acidic foods

Tell your health care team about any concerns you have about eating. They can help you make diet changes that will help you cope with the side effects of treatment.

Can I return to work or my normal activities?
That will depend on how you respond to your treatment. Each person responds differently. Ask your doctor what is best for you.

As you return to your daily activities, let your caregiver and friends help you. Allowing friends and family to give moral and emotional support can be very helpful during your treatment.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
What should I do if I am having side effects from treatment?

Get in touch with your doctor or nurse right away if you have any side effects. Don’t wait to share this information at your next office visit.

Tell your doctor if you have any side effects including: rash, facial swelling, or difficulty breathing during or soon after your infusion with BENDEKA injection. These are signs of an allergic reaction. You also should tell your doctor if you have shortness of breath, significant fatigue, bleeding, bruising, fever, or other signs of infection. Also, tell your doctor if you experience nausea, vomiting, diarrhea, loss of appetite, or a yellow skin tone. In addition, your doctor will perform blood tests to see if you have low blood counts. These are lower-than-normal numbers of red blood cells, white blood cells, or platelets.

Will I lose my hair?

In a safety evaluation from a clinical study for CLL, hair loss occurred in 1 of the 153 patients treated with bendamustine hydrochloride compared to 0 (zero) of the 143 patients treated with chlorambucil. In an NHL study, hair loss occurred in 3 of the 100 patients treated with bendamustine hydrochloride.

Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
Answers to questions about treatment costs

How can I find out if my insurance covers BENDEKA® (bendamustine HCI)?

TEVA ONCOLOGY OFFERS A RESOURCE CALLED CORE®

The Comprehensive Oncology Reimbursement Expertise (CORE) Program provides support as well as online tools to help make it easier to understand the reimbursement process.

The CORE hotline (1-888-587-3263) can help:

- Verify benefits and coverage
- Offer precertification and prior authorization support
- Explain coverage guidelines
- Provide support through the claims and appeals process
- Identify programs that may be able to help you pay for treatment

What if I can’t afford my medicine?

The Teva Cares Foundation Patient Assistance Program provides certain Teva medications at no cost to eligible patients in the United States. Eligibility is based on patients’ income and prescription insurance status.

BENDEKA is indicated for the treatment of patients with

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Please read additional Important Safety Information throughout and on page 7 and Full Prescribing Information starting on page 17.
As part of your treatment process, it takes about **10 minutes** for a **BENDEKA** infusion.

**Important Safety Information (cont)**

**BENDEKA is not right for everyone:** including patients with a known allergic response to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.

Please read additional **Important Safety Information** throughout and on page 7 and **Full Prescribing Information** starting on page 17.
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)

DOSE 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 may be 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. (2.2)
• 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 monothioglycol and reactions to bendamustine hydrochloride have included anaphylaxis and anaphylactoid reactions. (4, 5, 3)

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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

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:

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.

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:

If the dose delay is 100 mg/m² administered intravenously over 10 minutes on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m². Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

2.3 Preparation for Intravenous Administration

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

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 be stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA (bendamustine hydrochloride) injection must be completed within this period of time.

In the event that 5% Dextrose 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 36-46°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA (bendamustine hydrochloride) injection must be completed within this period of time.

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

2.4 Admixture Stability

BENDEKA (bendamustine hydrochloride) injection contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

If diluted with 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 36-46°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA (bendamustine hydrochloride) injection must be completed within this period of time.

In the event that 5% Dextrose Injection, USP is utilized, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for only 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA (bendamustine hydrochloride) injection must be completed within this period of time.

Retain the partially used vial in original package to protect from light and store refrigerated (2-8°C or 36-46°F) if additional dose withdrawal from the same vial is intended.

2.5 Stability of Partially Used Vials (Needle Punctured Vials)

BENDEKA is supplied in a multiple-dose vial. Although it does not contain any antimicrobial preservatives, BENDEKA is bacteriostatic. The partially used vials are 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/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 frequently. 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 Dose 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 contact 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 as, and without intervention, may lead to acute renal failure and death. Preventive measures include vigorous hydration, control of 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. [see Warnings and Precautions (5.5)]

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, and toxic epidermal necrolysis. Toxic skin reactions occurred 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 myelodysplastic 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 reporting 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 intraarterial 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 naïve CLL. All patients started the study at a dose of 100 mg/m² intravenously over 30 minutes on Days 1 and 2 every 28 days for two consecutive 2-day cycles.

Adverse reactions were reported according to NCI CTC v.2.0. In the randomized CLL clinical study, non-hematologic adverse reactions (any grade) in the bendamustine hydrochloride group that occurred with a frequency greater than 15% were pyrexia (24%), nausea (20%), and vomiting (16%).

Other adverse reactions seen in > 10% of patients in one or more studies included asthenia, fatigue, malaise, and weakness; dry mouth; somnolence; cough; constipation; headache; mucosal inflammation and stomatitis. Worsening hypotension 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 were reported 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>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>Number (%) of patients with at least 1 adverse reaction</td>
<td>121 (79)</td>
<td>52 (34)</td>
<td>96 (67)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>System organ class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (20)</td>
<td>1 (&lt;1)</td>
<td>21 (15)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (16)</td>
<td>1 (&lt;1)</td>
<td>9 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (9)</td>
<td>2 (&lt;1)</td>
<td>5 (3)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36 (24)</td>
<td>6 (4)</td>
<td>8 (6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (9)</td>
<td>2 (1)</td>
<td>8 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>13 (8)</td>
<td>0</td>
<td>6 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (6)</td>
<td>0</td>
<td>1 (&lt;1)</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>Laboratory Abnormality</th>
<th>Bendamustine Hydrochloride N=153</th>
<th>Chlorambucil N=143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin Decreased</td>
<td>All Grades n (%)</td>
<td>Grade 3/4 n (%)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>116 (77)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Leukocytes Decreased</td>
<td>92 (61)</td>
<td>42 (28)</td>
</tr>
<tr>
<td>Lymphocytes Decreased</td>
<td>102 (68)</td>
<td>67 (47)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>113 (75)</td>
<td>65 (43)</td>
</tr>
</tbody>
</table>

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

### 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 n (%)</th>
<th>Grade 3/4 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>12 (8)</td>
<td>4 (3)</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>5 (3)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

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 fatigue (75%), nausea (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.

6.3 **Clinical Trials Experience in NHL**

The data described above 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 fatigue (75%), nausea (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.
BENDEKA® (bendamustine hydrochloride) injection

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 isozymes CYP1A2, CYP2C9, 2D6, 2E1, or 3A4/5, or to induce metabolism of substrates of cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category 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 men 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 a 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 palate, 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 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 doses rates. There was inadequate 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 tumorogenicity 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 lymphocytic 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. These were 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 (AU(C0-2) 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 Seizure Disorders

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 DLL 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=69) 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.

In both studies, serious adverse reactions, regardless of causality, were reported in 37% of patients receiving bendamustine hydrochloride. The most common serious adverse reactions occurring in ≥5% of patients were febrile neutropenia and pneumonia. Other important serious adverse reactions reported in clinical trials and/or postmarketing experience were acute renal failure, cardiac failure, hypersensitivity, skin reactions, pulmonary fibrosis, and myelodysplastic syndrome. Serious drug-related adverse reactions reported in clinical trials included myelo-suppression, infection, pneumonia, tumor lysis syndrome and infusion reactions. [see Warnings and Precautions (5.5)] Adverse reactions occurring less frequently but possibly related to bendamustine hydrochloride treatment were hemorrhosis, dysgeusia/taste disorder, atypical pneumonia, sepsis, herpes zoster, erythema, dermatitis, and rash.

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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-butanoic acid, S-[6-(2-chloroethyl)aminol]-1 methyl-, monohydrochloride. Its empirical molecular formula is C₁₅H₁₆ClN₂O₃.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:

\[
\begin{align*}
\text{ClCH₂CH₂} & \quad \text{N} \\
\text{ClCH₂CH₂} & \quad \text{N} \\
\end{align*}
\]

BENDEKA (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 mg of Monothioglycerol, 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 mechloethamine derivative containing a purine-like benzimidazole ring. Mechloethamine and its derivatives form electrophilic alkylating 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.

12.2 Pharmacodynamics
Based on the pharmacokinetics/pharmacodynamics analyses of data from adult NHL patients, nausea increased with increasing bendamustine Cₘ₉₀. [see Cardio Electrophysiology]

Cardio 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.

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 (Cₘ₉₀) and equivalent systemic exposure (AUC), compared to a single dose of Treanda (bendamustine hydrochloride) (120 mg/m²) infused over 60 minutes. The mean Cₘ₉₀ 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 desmethylobendamustine (M4). This suggests that there are bendamustine-derived materials (detected via the radiolabel), that are rapidly cleared and have a t1/2 of 6-9 minutes. In this study, 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 dihydroxybendamustine (HP2) metabolites with low cytotoxic activity. In vivo, studies indicate that two active minor metabolites, M3 and M4, are primarily formed via CYP1A2. However, concentrations of these metabolites in plasma are 1/100th 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, CYP1B1, CYP2B6, CYP3A4, or CYP3A5. Bendamustine did not induce metabolism of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, or CYP3A7 enzymes, and bendamustine is metabolized via hydrolytic, oxidative, and conjugative pathways.

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, and less than 5% of the dose was recovered in the urine as HP1.

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 and ALT ≤ 2.5 x ULN, and/or ALP ≤ ULN to 5 x ULN) hepatic impairment. [see Use in Specific Populations (8.4, 8.5)]

Effect of Age
Bendamustine exposure (as measured by AUC and Cₘ₉₀) has 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.
BENDEKA® (bendamustine hydrochloride) injection

13 NONCLINICAL TOXICITY

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/ena 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 micro-nucleated 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 may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacities.

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. 68% Binet B), lymphadenopathy (78% vs. 82%), enlarged spleen (76% vs. 80%), enlarged liver (48% vs. 46%), hypercellular bone marrow (79% vs. 73%), B symptoms (51% vs. 53%), lymphocyte count (mean 65.7 x 10⁹/L vs. 65.1 x 10⁹/L), and serum lactate dehydrogenase concentration (mean 370.2 vs. 388.4 U/L). Ninety percent of patients in both treatment groups had immuno-phenotrophic confirmation of CLL (CLL, CO23 and either CO19 or CO20 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 (Brock'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=146)</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, 66)</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 (nP) **</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>
<tr>
<td>Duration of Response (DR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>18 (11.7, 23.5)</td>
<td>6 (5.6, 8.6)</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.27 (0.17, 0.43)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*CR was defined as peripheral lymphocyte count < 4 x 10⁹/L, neutrophils ≥ 1.5 x 10¹⁰/L, platelets >100 x 10⁹/L, hemoglobin >110 g/L or 6.5 mg/dL, 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.

**nP 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, neutrophils ≥ 50% reduction in lymphadenopathy, platelet count ≥ 50% reduction in the size of spleen or liver, as well as one of the following hemato logical improvements: neutrophils ≥ 1.5 x 10¹⁰/L or 50% improvement over baseline, platelets >100 x 10⁹/L or 50% improvement over baseline, hemoglobin >110 g/L or 50% improvement over baseline without transfusions, for a period of at least 56 days.

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

BENDEKA (bendamustine hydrochloride) injection is a cytotoxic drug. Follow applicable special handling and disposal procedures. Care should be exercised in the handling and preparation of solutions prepared from BENDEKA (bendamustine hydrochloride) injection. 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 BENDEKA (bendamustine hydrochloride) injection contacts the skin, wash the skin immediately and thoroughly with soap and water. If BENDEKA (bendamustine hydrochloride) injection contacts the mucous membranes, flush thoroughly with water.

16.2 How Supplied

BENDEKA (bendamustine hydrochloride) injection is supplied in individual cartons of 5 mL, clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, and colorless to yellow ready-to-dilute solution.

16.3 Storage

Store BENDEKA (bendamustine hydrochloride) injection in refrigerator, 2°-8°C (36°-46°F). Retain in original carton until time of use to protect from light.
17 PATIENT COUNSELING INFORMATION

Allergic (Hypersensitivity) Reactions
Inform patients of the possibility of serious or mild allergic reactions and to immediately 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) injection 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 serious 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 symptomatic 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 treatment 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)].