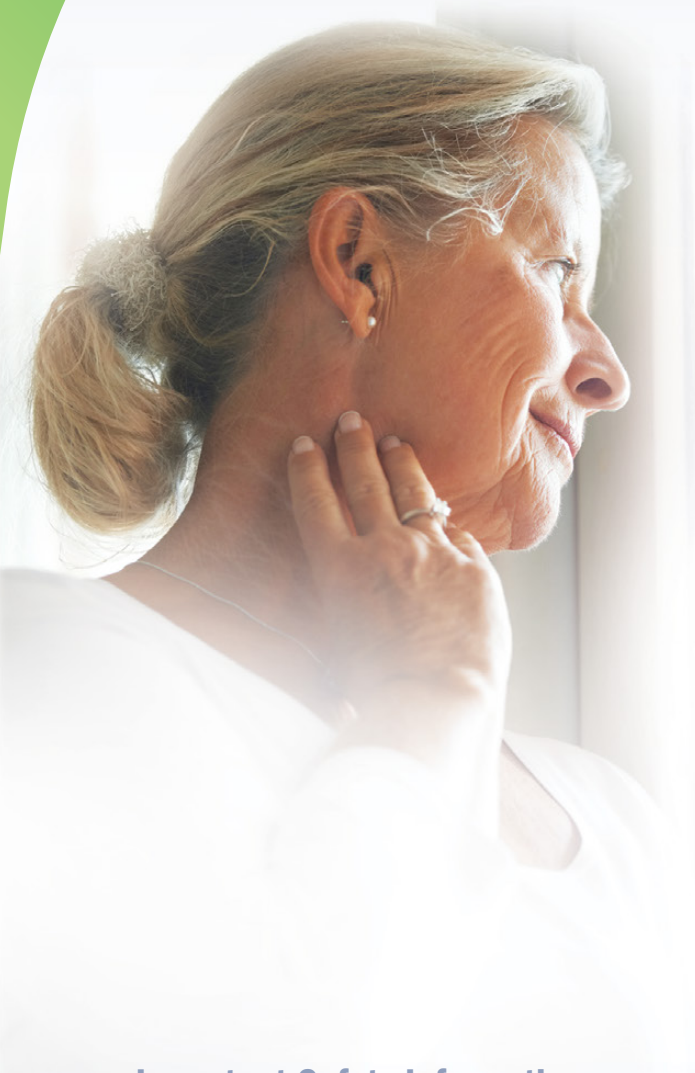
BENDEKA®
(bendamustine HCl)
injection



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, 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)[2]
- Palpable splenomegaly and/or hepatomegaly[2]

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
- $ß_2$-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.[3] The immunophenotype of peripheral lymphocytes is: CD5+, CD19+, CD20+(dim), CD23+.[3]

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

Important Safety Information (continued)

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 BENDEKA 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.

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CLL CASE STUDY

Laboratory and FISH test results are as follows:

LABORATORY TEST	RESULT	NORMAL RANGE[4]
Hemoglobin	9.1 g/dL	12.0–16.0 g/dL (female)
Platelet count	135 × 10^9/L	150–400 × 10^9/L
WBC count	43 × 10^9/L	5–10 × 10^9/L
ALC	36 × 10^9/L	1–4 × 10^9/L
$ß_2$-microglobulin	3.1 µg/mL	0.70–1.80 µg/mL

WBC = white blood cell; ALC = absolute lymphocyte count

FISH/CYTOGENETICS[5,6]	
del 11q	✔
del 13q	—
del 17p	—
Trisomy 12	—

Note: Additional mutational testing may be considered

CLL risk classification and prognosis:

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

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 (continued)

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.

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BENDEKA® (bendamustine HCl) injection

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/m^2 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/m^2 on days 1 and 2; if Grade 3 or greater toxicity recurs, reduce dose to 25 mg/m^2 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/m^2 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 non-hematologic toxicity
- **Concomitant CYP1A2:** Consider alternative therapies that are not CYP1A2 inducers or inhibitors during treatment with BENDEKA
- **Renal impairment:** Do not use in patients with creatinine clearance <30 mL/min.
- **Hepatic impairment:** Do not use in patients with total bilirubin 1.5-3 × ULN and AST or ALT 2.5-10 × ULN, or total bilirubin > 3 × ULN

What has been your experience with BENDEKA?

Important Safety Information (continued)

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.

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BENDEKA®
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Important Safety Information (continued)

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 bendamustine hydrochloride 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: BENDEKA can cause fetal harm when administered to a pregnant woman. Conduct pregnancy testing prior to initiating treatment and advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with BENDEKA and for at least 6 months after the final dose and males with female partners of reproductive potential to use effective contraception for at least 3 months after the final dose. BENDEKA may also impair fertility in males.

Lactation: Advise patients that breastfeeding is not recommended during treatment with BENDEKA, and for at least 1 week after the last dose.

Most Common Adverse Reactions:

- Adverse reactions (frequency >5%) during infusion and within 24 hours post-infusion are nausea and fatigue.
- Most common adverse reactions for CLL (frequency ≥15%) are anemia, thrombocytopenia, neutropenia, lymphopenia, leukopenia, hyperbilirubinemia, pyrexia, nausea, and vomiting
- Most common adverse reactions for NHL (frequency ≥15%) are lymphopenia, leukopenia, anemia neutropenia, thrombocytopenia, nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis

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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.
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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.
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BEN-40846 December 2019

with female partners of reproductive potential to use effective contraception during treatment with BENDEKA and for 3 months after the nal dose *[see Use in Specific Populations (8.3), and Nonclinical Toxicology (13.1)]*.

Lactation

Advise females not to breastfeed during treatment with BENDEKA and for at least 1 week after the nal dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that BENDEKA may impair fertility *[see Use in Specific Populations (8.3)]*.

BEN-009

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