



**TREANDA®: Discover the benefits of effective dose management**

**Dosing guidance and safety considerations for patients receiving TREANDA**

*Please see accompanying full Prescribing Information.*

 **TREANDA®**  
(bendamustine HCl)  
for Injection

**Built for Action™**

## DOSING FOR CLL

### DOSE MODIFICATIONS MAY HELP PATIENTS CONTINUE THERAPY AND ACHIEVE TREATMENT RESULTS

#### Labeled dosing for CLL

CLL Dose: 100 mg/m <sup>2</sup> *						
<b>Day 1</b> 30-minute IV infusion	<b>Day 2</b> 30-minute IV infusion	Day 3	Day 4	Day 5	Day 6	Day 7
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28

up to  
**6**  
cycles

IV=intravenous.

\*In the pivotal trial, patients randomized to chlorambucil were administered 0.8 mg/kg PO on Days 1 and 15 of a 28-day cycle, up to 6 cycles.<sup>1</sup>

- 100 mg/m<sup>2</sup> infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles

**Adverse reactions may require interventions such as decreasing the dose of TREANDA, or withholding or delaying treatment**

#### Indication

TREANDA 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.

#### Important Safety Information

- Serious adverse reactions, including myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions including SJS/TEN, other malignancies, and extravasation, have been associated with TREANDA. Some reactions, such as myelosuppression, infections, and SJS/TEN (when TREANDA was administered concomitantly with allopurinol and other medications known to cause SJS/TEN), have been fatal. Patients should be monitored closely for these reactions and treated promptly if any occur
- TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol. Women should be advised to avoid becoming pregnant while using TREANDA
- The most common non-hematologic adverse reactions (frequency  $\geq 15\%$ ) were pyrexia, nausea, and vomiting. The most common hematologic abnormalities (frequency  $\geq 15\%$ ) were anemia, thrombocytopenia, neutropenia, lymphopenia, and leukopenia

## DOSE REDUCTIONS/DELAYS FOR CLL

### Dose reductions

DOSE REDUCTIONS FOR CLL			
Description		Toxicity grade*	On Days 1 and 2, reduce dose to <sup>†</sup>
Hematologic toxicity	Initial	≥3	50 mg/m <sup>2</sup>
	Recurrence	≥3	25 mg/m <sup>2</sup>
Non-hematologic toxicity	Initial	≥3 <sup>‡</sup>	50 mg/m <sup>2</sup>
	Recurrence	N/A	N/A

\*To download the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0, go to <http://ctep.cancer.gov/reporting/ctc.html><sup>2</sup>

<sup>†</sup>Dose re-escalation in the treatment of CLL in subsequent cycles may be considered at the discretion of the treating physician.

<sup>‡</sup>Clinically significant Grade 3 or greater toxicity.

### Dose delays

DOSE DELAYS FOR CLL		
Description	Delay dose	Reinitiate dose <sup>§</sup>
Hematologic toxicity	Grade 4	Recovery to ANC ≥1 x 10 <sup>9</sup> /L and platelets ≥75 x 10 <sup>9</sup> /L
Non-hematologic toxicity	Clinically significant ≥Grade 2	Recovery to ≤Grade 1

ANC=absolute neutrophil count.

<sup>§</sup>Treatment may be reinitiated at the discretion of the treating physician.

- Continued toxicity despite dose modifications or certain severe reactions (see Warnings and Precautions on pages 8-9) may warrant discontinuation

*Please see accompanying full Prescribing Information.*

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## DOSing FOR INDOLENT B-CELL NHL THAT HAS PROGRESSED

**DOSE MODIFICATIONS MAY HELP PATIENTS CONTINUE THERAPY AND ACHIEVE TREATMENT RESULTS**

### Labeled dosing for indolent B-cell NHL that has progressed

Indolent B-cell NHL that has progressed Dose: 120 mg/m <sup>2</sup>						
<b>Day 1</b> 60-minute IV infusion	<b>Day 2</b> 60-minute IV infusion	Day 3	Day 4	Day 5	Day 6	Day 7
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21

up to  
**8**  
cycles

- 120 mg/m<sup>2</sup> infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles

**Adverse reactions may require interventions such as decreasing the dose of TREANDA, or withholding or delaying treatment**

#### Indication

TREANDA is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

#### Important Safety Information

- Serious adverse reactions, including myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions including SJS/TEN, other malignancies, and extravasation, have been associated with TREANDA. Some reactions, such as myelosuppression, infections, and SJS/TEN (when TREANDA was administered concomitantly with allopurinol and other medications known to cause SJS/TEN), have been fatal. Patients should be monitored closely for these reactions and treated promptly if any occur
- TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol. Women should be advised to avoid becoming pregnant while using TREANDA
- The most common non-hematologic adverse reactions (frequency ≥30%) were nausea, fatigue, vomiting, diarrhea, and pyrexia. The most common hematologic abnormalities (frequency ≥15%) were lymphopenia, leukopenia, anemia, neutropenia, and thrombocytopenia

## DOSE REDUCTIONS/DELAYS FOR INDOLENT B-CELL NHL THAT HAS PROGRESSED

INDOLENT B-CELL NHL  
THAT HAS PROGRESSED

### Dose reductions

DOSE REDUCTIONS FOR INDOLENT B-CELL NHL THAT HAS PROGRESSED			
Description		Toxicity grade*	On Days 1 and 2, reduce dose to
Hematologic toxicity	Initial	4	90 mg/m <sup>2</sup>
	Recurrence	4	60 mg/m <sup>2</sup>
Non-hematologic toxicity	Initial	≥3	90 mg/m <sup>2</sup>
	Recurrence	≥3	60 mg/m <sup>2</sup>

\*To download the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0, go to <http://ctep.cancer.gov/reporting/ctc.html>

### Dose delays

DOSE DELAYS FOR INDOLENT B-CELL NHL THAT HAS PROGRESSED		
Description	Delay dose	Reinitiate dose†
Hematologic toxicity	Grade 4	Recovery to ANC ≥1 x 10 <sup>9</sup> /L and platelets ≥75 x 10 <sup>9</sup> /L
Non-hematologic toxicity	Clinically significant ≥Grade 2	Recovery to ≤Grade 1

ANC=absolute neutrophil count.

†Treatment may be reinitiated at the discretion of the treating physician.

- Continued toxicity despite dose modifications or certain severe reactions (see Warnings and Precautions on pages 8-9) may warrant discontinuation

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## SPECIAL POPULATIONS

### TREATMENT CONSIDERATIONS FOR SPECIAL POPULATIONS

#### Use of TREANDA in patients with renal impairment

Mild to moderate	
CrCL 40-80 mL/min	Use with caution
Severe	
CrCL <40 mL/min	Should not be used

- In a population pharmacokinetic analysis of TREANDA in patients receiving 120 mg/m<sup>2</sup>, there was no meaningful effect of renal impairment (CrCL 40-80 mL/min, N=31) on the pharmacokinetics of TREANDA
- TREANDA has not been studied in patients with CrCL <40 mL/min
- No formal studies assessing the impact of renal impairment on the pharmacokinetics of TREANDA have been conducted
- In preclinical studies, approximately 90% of TREANDA administered was recovered primarily in the feces

#### Use of TREANDA in patients with hepatic impairment





Mild	
<ul style="list-style-type: none"><li>• Total bilirubin ≤ULN</li><li>• AST ≥ULN to 2.5 x ULN and/or ALP ≥ULN to 5.0 x ULN</li></ul>	Use with caution
Moderate	
<ul style="list-style-type: none"><li>• AST or ALT 2.5-10 x ULN and total bilirubin 1.5-3.0 x ULN</li></ul>	Should not be used
Severe	
<ul style="list-style-type: none"><li>• Total bilirubin &gt;3.0 x ULN</li></ul>	Should not be used

- In a population pharmacokinetic analysis of TREANDA in patients receiving 120 mg/m<sup>2</sup>, there was no meaningful effect of mild (total bilirubin ≤ULN, AST ≥ULN to 2.5 x ULN, and/or ALP ≥ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of TREANDA
- TREANDA has not been studied in patients with moderate or severe hepatic impairment
- No formal studies assessing the impact of hepatic impairment on the pharmacokinetics of TREANDA have been conducted

ULN=upper limit of normal; AST=aspartate aminotransferase; ALP=alkaline phosphatase; ALT=alanine aminotransferase.

## DRUG INTERACTIONS

**Concomitant CYP1A2 inhibitors or inducers have the potential to affect the exposure of TREANDA**

	CYP1A2 Inhibitors	CYP1A2 Inducers
Plasma concentration of TREANDA		
Plasma concentration of active metabolite		

- TREANDA is primarily metabolized via hydrolysis
  - Active metabolites of TREANDA, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 CYP1A2
- Use caution or consider alternative treatments when used with concomitant CYP1A2 inhibitors/inducers
  - Inhibitors of CYP1A2 include fluvoxamine and ciprofloxacin
  - Inducers of CYP1A2 include omeprazole and smoking
- No formal clinical assessments of pharmacokinetic drug-drug interactions between TREANDA and other drugs have been conducted

SPECIAL POPULATIONS

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## WARNINGS AND PRECAUTIONS

### MYELOSUPPRESSION

#### Observations

- Patients treated with TREANDA are likely to experience myelosuppression
- In the two NHL studies, 98% of patients had Grade 3-4 myelosuppression. Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection (CMV)

#### Considerations

- In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb), and neutrophils closely
- In the clinical trials, blood counts were monitored every week initially
- Hematologic nadirs were observed predominantly in the third week of therapy
- Hematologic nadirs may require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle
- Prior to the initiation of the next cycle of therapy, the ANC should be  $\geq 1 \times 10^9/L$  and the platelet count should be  $\geq 75 \times 10^9/L$

### INFECTIONS

#### Observations

- Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports
- Infection has been associated with hospitalization, septic shock, and death
- Patients with myelosuppression following treatment with TREANDA are more susceptible to infections

#### Considerations

- Patients with myelosuppression following treatment with TREANDA should be advised to contact a physician if they have symptoms or signs of infection

### INFUSION REACTIONS AND ANAPHYLAXIS

#### Observations

- Infusion reactions to TREANDA have occurred commonly in clinical trials
- Symptoms include fever, chills, pruritus, and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy
- Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged

#### Considerations

- Monitor clinically and discontinue drug for severe reactions
- Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy
- Measures to prevent severe reactions, including antihistamines, antipyretics, and corticosteroids, should be considered in subsequent cycles in patients who have previously experienced Grade 1 or Grade 2 infusion reactions
- Discontinuation should be considered in patients with Grade 3 or Grade 4 infusion reactions

### TUMOR LYSIS SYNDROME

#### Observations

- Tumor lysis syndrome associated with TREANDA treatment has been reported in patients in clinical trials and in post-marketing reports
- The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death
- Allopurinol has been used during the beginning of TREANDA therapy. However, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly

## WARNINGS AND PRECAUTIONS

### Considerations

- Preventive measures include:
  - Maintaining adequate volume status
  - Close monitoring of blood chemistry (particularly potassium and uric acid levels)

## SKIN REACTIONS

### Observations

- A number of skin reactions have been reported in clinical trials and post-marketing safety reports, including rash, toxic skin reactions, and bullous exanthema
- Some events occurred when TREANDA was given in combination with other anti-cancer agents, so the precise relationship to TREANDA is unknown
- In a study of TREANDA (90 mg/m<sup>2</sup>) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert)
- Cases of Stevens-Johnson syndrome (SJS) and TEN, some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to TREANDA cannot be determined
- Where skin reactions occur, they may be progressive and increase in severity with further treatment

### Considerations

- Patients with skin reactions should be monitored closely
- If skin reactions are severe or progressive, TREANDA should be withheld or discontinued

## OTHER MALIGNANCIES

### Observation

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

## EXTRAVASATION

### Observation

- There are postmarketing reports of bendamustine extravasations resulting in hospitalization from erythema, marked swelling, and pain

### Considerations

- Precautions should be taken to avoid extravasation, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA

## USE IN PREGNANCY

- TREANDA can cause fetal harm when administered to a pregnant woman
- Women should be advised to avoid becoming pregnant throughout treatment and for 3 months after TREANDA therapy has stopped
- Men receiving TREANDA should use reliable contraception throughout treatment and for 3 months after TREANDA therapy has stopped
- 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
- Advise patients to report pregnancy immediately
- Advise patients to avoid nursing

*Please see accompanying full Prescribing Information.*



# RECONSTITUTION AND PREPARATION

## RECONSTITUTION AND PREPARATION

### STEP 1

#### Reconstitution

Aseptically reconstitute each TREANDA vial as follows:

- 25 mg TREANDA vial: Add 5 mL of only **Sterile Water for Injection, USP**
- 100 mg TREANDA vial: Add 20 mL of only **Sterile Water for Injection, USP**

### STEP 2

#### Preparation

Shake well to yield a clear, colorless to a pale yellow solution with a bendamustine HCl concentration of 5 mg/mL.

- The lyophilized powder should completely dissolve in 5 minutes. If particulate matter is observed, the reconstituted product should not be used
- The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution

### STEP 3

#### Preparation for IV administration

Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline).

- As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), a 500 mL infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered
- The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2-0.6 mg/mL

### STEP 4

#### Mixture

After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless to slightly yellow solution.

#### Additional dilution recommendations

- Use Sterile Water for Injection, USP, for reconstitution and then either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, for dilution, as outlined in the steps for reconstitution and preparation
- No other diluents have been shown to be compatible
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit
- Any unused solution should be discarded according to institutional procedures for antineoplastics

#### Admixture stability

- TREANDA contains no antimicrobial preservative
- The admixture should be prepared as close as possible to the time of patient administration
- Once diluted with either 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of TREANDA must be completed within this period. (See full Prescribing Information for specific direction on preparation of admixture)

## STORAGE, HANDLING, AND DELIVERY

### STORAGE AND HANDLING

#### Storage

- TREANDA may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) (see USP Controlled Room Temperature). Retain in original package until time of use to protect from light

#### Safe handling and disposal

- As with other potentially toxic anti-cancer agents, care should be exercised in the handling and preparation of solutions prepared from TREANDA. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of TREANDA contacts the skin, wash the skin immediately and thoroughly with soap and water. If TREANDA contacts the mucous membranes, flush thoroughly with water
- Procedures for the proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on the subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

### HOW SUPPLIED

TREANDA is available in 100-mg and 25-mg vials



- TREANDA for Injection single-use vial containing either 25 mg or 100 mg of bendamustine HCl as white to off-white lyophilized powder

PREPARATION AND HANDLING

*Please see accompanying full Prescribing Information.*

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**CEPHALON ONCOLOGY REIMBURSEMENT EXPERTISE:  
COMMITTED TO PROVIDING SUPPORT FOR YOUR PATIENTS**

**CORE information resources can be accessed online or with personalized support via a toll-free hotline**

- **1-888-587-3263**
- **www.CephalonOncologyCORE.com**

**CORE offers assistance related to**

- Benefit verification and coverage determination
- Precertification/prior authorization support
- Coverage guidelines and claim requirements of payers
- Personalized support through the claims and appeals process
- Templates for letters of medical necessity
- Referrals to CephalonCares® Foundation



**CEPHALONCARES® FOUNDATION OFFERS A PATIENT ASSISTANCE PROGRAM**

- The program provides Cephalon, Inc. products free of charge for patients who qualify

**Key patient advocacy organizations have programs designed to help patients access the treatments they need**

Organization	Phone number	Web site
The Leukemia & Lymphoma Society (LLS)	(877) 557-2672	www.lls.org www.lls.org/copay
National Organization for Rare Disorders (NORD)	(800) 999-6673	www.rarediseases.org
Partnership for Prescription Assistance	(888) 477-2669	www.pparx.org
American Cancer Society	(800) 277-2345	www.cancer.org
CancerCare	(800) 813-4673	www.cancercare.org
Patient Access Network Foundation	(866) 316-7263	www.panfoundation.org
Patient Advocate Foundation	(800) 532-5274	www.patientadvocate.org
Patient Services Incorporated	(800) 366-7741	www.uneedpsi.org
HealthWell Foundation	(800) 675-8416	www.healthwellfoundation.org
NeedyMeds.org	No phone help line	www.needymeds.org

RESOURCES

- Each of these independent, nonprofit organizations has its own eligibility criteria
- Cephalon Oncology neither influences nor controls the operations and decisions of these organizations



# TREANDA®: Discover how effective dose management can help patients continue therapy

## Dosing for patients with CLL

CLL Dose: 100 mg/m <sup>2</sup> *						
Day 1 30-minute IV infusion	Day 2 30-minute IV infusion	Day 3	Day 4	Day 5	Day 6	Day 7
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28

up to  
**6**  
cycles

IV=intravenous.

\*In the pivotal trial, patients randomized to chlorambucil were administered 0.8 mg/kg PO on Days 1 and 15 of a 28-day cycle, up to 6 cycles.

## Dosing for patients with indolent B-cell NHL that has progressed

Indolent B-cell NHL that has progressed Dose: 120 mg/m <sup>2</sup>						
Day 1 60-minute IV infusion	Day 2 60-minute IV infusion	Day 3	Day 4	Day 5	Day 6	Day 7
Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21

up to  
**8**  
cycles

**Adverse reactions may require interventions such as decreasing the dose of TREANDA, or withholding or delaying treatment**

### Important Safety Information

- Serious adverse reactions, including myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions including SJS/TEN, other malignancies, and extravasation, have been associated with TREANDA. Some reactions, such as myelosuppression, infections, and SJS/TEN (when TREANDA was administered concomitantly with allopurinol and other medications known to cause SJS/TEN), have been fatal. Patients should be monitored closely for these reactions and treated promptly if any occur
- TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol. Women should be advised to avoid becoming pregnant while using TREANDA
- The most common non-hematologic adverse reactions associated with TREANDA (frequency ≥15%) are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash, and stomatitis. The most common hematologic abnormalities associated with TREANDA (frequency ≥15%) are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia

**References:** 1. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol.* 2009;27:4378-4384. 2. National Cancer Institute. Cancer Therapy Evaluation Program. <http://ctep.cancer.gov/reporting/ctc.html>. Accessed January 4, 2011.

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