I. PURPOSE

To define and describe the accepted indications for Treanda/Bendeka/Belrapzo (bendamustine) usage in the treatment of cancer.

II. DEFINITIONS

Treanda/Bendeka/Belrapzo (bendamustine): is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Its exact mechanism of action is unknown, but it may cause apoptotic and non-apoptotic death of malignant cells by damaging both single- and double-strand DNA, increasing the expression of pro-apoptotic genes, and inhibiting mitotic control. Bendamustine is active against both quiescent and dividing cells.

Treanda/Bendeka/Belrapzo (bendamustine) is FDA approved for the treatment of patients with:

- Chronic lymphoid leukemia/small lymphocytic lymphoma
- Non-Hodgkin's lymphoma: Indolent B-Cell that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

Non-FDA approved indications include:

- Multiple myeloma
- Non-Hodgkin's lymphoma: Mantle Cell, Primary Cutaneous B-Cell, Splenic Marginal Zone Lymphoma
- Waldenstrom's macroglobulinaemia
- Hodgkin Lymphoma

Treanda/Bendeka/Belrapzo (bendamustine) is available as

- Intravenous Powder for Solution: 25 MG, 100 MG.
- Intravenous Solution: 45 MG and 180 MG.
- Intravenous Solution ready to dilute formulation 500 ml solution.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.
Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

**Inclusion Criteria:** Treanda/Bendeka/Belrapzo (bendamustine) may be considered medically necessary when any of the following selection criteria is met:

1. **Chronic lymphoid leukemia/small lymphocytic lymphoma**
   a. As first-line therapy as a single agent or with/without rituximab, ofatumumab, or obinutuzumab for stage II-IV disease or stage I with significant disease related symptoms (i.e. B symptoms, enlarged spleen/lymph nodes, or progressive anemia/thrombocytopenia) without del(17p)/TP53 mutation **OR**
   b. For relapsed or refractory disease without del(17p)/TP53 mutation in combination with rituximab for members age < 65 years without significant comorbidities.

2. **Non-Hodgkin's lymphoma**
   a. Indolent B-Cell/nodal marginal zone/Gastric MALT Lymphoma/Non-Gastric MALT Lymphoma
      i. First line in combination with rituximab/obinutuzumab **OR**
      ii. Second-line or subsequent therapy as a single agent or in combination with rituximab or obinutuzumab.
   b. Diffuse Large B-Cell Lymphoma
      i. Second-line therapy for relapsed or refractory disease in non-candidates for high-dose therapy.
   c. Mantle Cell
      i. Less aggressive induction therapy with rituximab **OR**
      ii. Second-line therapy as a single agent or in combination with rituximab for relapsed, refractory, or progressive disease.
   d. Splenic Marginal Zone Lymphoma
      i. First line therapy in combination with rituximab for disease progression following initial treatment for splenomegaly or second-line or subsequent therapy as a single agent or in combination with rituximab or obinutuzumab for progressive disease in patients with the indications for treatment.

3. **Multiple myeloma**
   a. Salvage therapy for disease relapse or for progressive or refractory disease as a single agent or in combination with lenalidomide/bortezomib and dexamethasone.

4. **Waldenstrom's macroglobulemia**
   a. Used in combination with rituximab or as a single agent as primary therapy **OR**
   b. Salvage therapy for disease that does not respond to primary therapy or for progressive or relapsed disease.
5. **Hodgkin Lymphoma**
   a. Second line or subsequent systemic therapy for relapsed or refractory disease as a component of gemcitabine/bendamustine/vinorelbine ± brentuximab vedotin OR
   b. Subsequent systemic therapy as a single agent for relapsed or refractory disease.

**Exclusion Criteria:** Treanda/Bendeka/Belrapzo (bendamustine) is not considered medically necessary when any of the following selection criteria is met:

1. Not to be used in members with CrCl < 30 ml/min.
2. Member has disease progression while on Treanda/Bendeka/Belrapzo (bendamustine).
3. Dosing exceeds single dose limit of Treanda/Bendeka/Belrapzo (bendamustine) 120 mg/m².
4. Treatment with Treanda/Bendeka/Belrapzo (bendamustine) exceeds the maximum duration limit of 8 cycles for NHL and 6 cycles for CLL.
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

**IV. Procedure**

Requests for Treanda/Bendeka/Belrapzo (bendamustine) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration**
   a. Chronic lymphoid leukemia/small lymphocytic lymphoma (as a single agent): 100 mg/m² IV over 30 minutes (for Treanda) or 10 minutes (for Bendeka) on days 1 and 2; repeat every 28 days up to a maximum of 6 cycles; allopurinol may be given when initiating treatment in patients at high risk for tumor lysis syndrome.
   b. Non-Hodgkin's lymphoma, previously untreated indolent NHL (including follicular lymphoma): 90 mg/m² IV over 30 minutes (for Treanda) on days 1-2 (or days 1 and 4 in BVR for Gastric MALT lymphoma) repeat every 28 days for 6 cycles
   c. Non-Hodgkin's lymphoma, Indolent B-Cell, refractory to rituximab or rituximab-containing regimens: 120 mg/m² IV over 60 minutes (for Treanda) or 10 minutes (for Bendeka) on days 1 and 2 of a 21-day cycle, up to 8 cycles; allopurinol may be given when initiating treatment in patients at high risk for tumor lysis syndrome.
   d. Multiple myeloma: 80-150 mg/m² IV over 30 minutes (for Treanda) on days 1-2 repeat every 28 days until maximal response, disease progression, or unacceptable toxicity.

2. **Dosage Adjustments**
   a. Renal impairment: CrCl less than 30 mL/min, do not use.
   b. Hepatic impairment: moderate (AST or ALT 2.5 to 10 times the ULN and total bilirubin 1.5 to 3 times the ULN) or severe (total bilirubin greater than 3 times ULN), do not use.
   c. General, hematologic toxicity: grade 4, delay until absolute neutrophil count greater than or equal to 1 x 10⁹/L, and/or platelets greater than or equal to 75 x 10⁹/L.
d. General, nonhematologic toxicity: greater than or equal to grade 2, delay until the nonhematologic toxicity recovers to less than or equal to grade 1.

e. Chronic lymphocytic leukemia, hematologic toxicity: grade 3 or greater, reduce to 50 mg/m² days 1 and 2 per cycle; if grade 3 or greater toxicity recurs, reduce to 25 mg/m² on days 1 and 2 per cycle; dose re-escalation may be considered.

f. Chronic lymphocytic leukemia, nonhematologic toxicity: grade 3 or greater, reduce to 50 mg/m² on days 1 and 2 per cycle; dose re-escalation may be considered.

g. Non-Hodgkin lymphoma, hematologic toxicity: grade 4, reduce to 90 mg/m² days 1 and 2 per cycle; if grade 4 toxicity recurs, reduce to 60 mg/m² on days 1 and 2 per cycle

h. Non-Hodgkin lymphoma, nonhematologic toxicity: grade 3 or greater, reduce to 90 mg/m² on days 1 and 2 per cycle; if grade 3 or greater nonhematologic toxicity recurs, reduce to 60 mg/m² on days 1 and 2 per cycle

3. Monitoring

a. Clinical and radiologic evidence of regression of malignancy

b. Leukocytes, platelets, hemoglobin, neutrophil counts; closely during each cycle

c. Serum creatinine, hepatic function tests

d. Blood chemistries, specifically serum potassium and uric acid levels

e. Signs or symptoms of anaphylactic and anaphylactoid reactions

f. Fever or signs or symptoms of infection, including pneumonia and sepsis; ongoing basis

g. Signs or symptoms of infusion reactions (e.g., fever, chills, pruritus, rash) and tumor lysis syndrome

h. Toxic skin reactions, (e.g., rash, bullous exanthema, toxic epidermal necrolysis)

i. Signs or symptoms of infection.

j. Signs of extravasation at site of infusion (e.g., redness, swelling, pain, infection, necrosis); during and after administration.

V. APPROVAL AUTHORITY

1. Review – UM Department

2. Final Approval – UM Committee

VI. ATTACHMENTS

VII. REFERENCES


