VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable) – Bendamustine Products Utilization Management Medical Policy
- Belrapzo™ (bendamustine intravenous infusion – Eagle)
- Bendeka® (bendamustine intravenous infusion – Teva)
- Treanda® (bendamustine intravenous infusion – Cephalon)
- Bendamustine intravenous infusion – various manufacturers

REVIEW DATE: 07/12/2023

OVERVIEW

Bendamustine, an alkylating agent, is indicated for the following uses:[1-3]
- **B-cell non-Hodgkin lymphoma, indolent**, that has progressed during or within 6 months of treatment with rituximab or a rituximab containing regimen.
- **Chronic lymphocytic leukemia**. Efficacy compared to first-line agents other than chlorambucil has not been established.

Guidelines

Bendamustine is addressed in National Comprehensive Cancer Network (NCCN) guidelines:
- **B-Cell Lymphomas:** Guidelines (version 4.2023 – June 2, 2023) recommend bendamustine for the treatment of a variety B-cell lymphomas, including follicular lymphoma (grade 1 and 2), extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites, nodal marginal zone lymphoma, splenic marginal zone lymphoma, histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, DLBCL, high-grade B-cell lymphoma, human immunodeficiency virus (HIV)-related B-cell lymphoma, and post-transplant lymphoproliferative disorders.[4,6] Bendamustine is recommended as monotherapy, or in combination with rituximab (e.g., Rituxan, biosimilars), Polivy™ (polatuzumab vedotin-piiq intravenous [IV] infusion), or Gazyva® (obinutuzumab IV infusion) depending on the lymphoma type and previous treatment history.
- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** Guidelines (version 3.2023 – June 12, 2023) recommend bendamustine, in combination with rituximab or Gazyva, for the first-line treatment of patients without del(17p)/TP53 mutation, who have indications for treatment (not recommended for frail patients).[4,5] Bendamustine in combination with rituximab is recommended for the treatment of relapsed or refractory disease without del(17p)/TP53 mutation in patients ≥ 65 years of age, or in patients < 65 years of age with or without significant comorbidities.
- **Hematopoietic Cell Transplantation:** Guidelines (version 1.2023 – March 31, 2023) recommend bendamustine in combination with etoposide, cytarabine, and melphalan as a conditioning regimen for autologous transplantation for patients with non-Hodgkin lymphoma without central nervous system disease, or Hodgkin lymphoma.[4,30]
- **Hodgkin Lymphoma** and **Pediatric Hodgkin Lymphoma:** Guidelines for Hodgkin lymphoma (version 2.2023 – November 8, 2023) and pediatric Hodgkin lymphoma (version 2.2023 – March 9, 2023) recommend bendamustine for the treatment of recurrent or refractory Hodgkin lymphoma.[4,7,26] In patients ≥ 18 years of age with classic Hodgkin lymphoma, bendamustine in combination with gemcitabine and vinorelbine, or in combination with Adcetris® (brentuximab IV infusion) is recommended for second-line or subsequent therapy (if not previously used), or in combination with carboplatin and etoposide for third-line or subsequent therapy, or as a single agent for subsequent therapy. In patients ≥ 18 years of age with nodular lymphocyte-predominant Hodgkin lymphoma, bendamustine in combination with rituximab is recommended for the

subsequent treatment of progressive, relapsed, or refractory disease. In patients > 60 years of age, bendamustine is recommended as a single agent for palliative therapy of relapsed or refractory disease. For heavily pretreated pediatric patients with Hodgkin lymphoma, bendamustine in combination with Adcetris is recommended for re-induction or subsequent treatment of relapsed or refractory disease.

- **Multiple Myeloma:** Guidelines (version 3.2023 – December 8, 2022) recommend bendamustine as a treatment option for late relapsed or progressive multiple myeloma (patient has received > 3 prior therapies).[4,12] Bendamustine is recommended as a single agent, or in combination with dexamethasone and lenalidomide, with dexamethasone and bortezomib, or with dexamethasone and Kyprolis® (carfilzomib intravenous infusion).
- **Systemic Light Chain Amyloidosis:** Guidelines (version 2.2023 – November 28, 2022) recommend bendamustine in combination with dexamethasone for relapsed/refractory disease.[4,27]
- **T-Cell Lymphomas**: Guidelines (version 1.2023 – January 5, 2023) recommend bendamustine as a single agent for the treatment of relapsed or refractory peripheral T-cell lymphomas, breast implant-associated anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, and refractory hepatosplenic T-cell lymphoma as subsequent therapy.[4,20]
- **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma**: Guidelines (version 1.2023 – July 6, 2022) recommend bendamustine as a single agent or in combination with rituximab for primary treatment, for the treatment of previously treated disease that did not respond, or for progressive or relapsed disease.[4,22]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of bendamustine. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with bendamustine as well as the monitoring required for adverse events and long-term efficacy, approval requires bendamustine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of bendamustine is recommended in those who meet one of the following criteria:

FDA-Approved Indications

---

1. **B-Cell Non-Hodgkin Lymphoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   Note: Examples include follicular lymphoma, extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites, nodal marginal zone lymphoma, splenic marginal zone lymphoma, histologic transformation of indolent lymphomas to diffuse large B-cell lymphoma (DLBCL), DLBCL, and high-grade B-cell lymphoma.
   A) Patient is ≥ 18 years of age; AND
   B) Bendamustine is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 120 mg/m^2 administered by intravenous infusion no more frequently than twice in each 21-day cycle.

---

2. **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Bendamustine is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 100 mg/m^2 administered by intravenous infusion no more frequently than twice in each 28-day cycle.

Other Uses with Supportive Evidence

---

3. **Hematopoietic Cell Transplantation.** Approve for 1 month if the patient meets ALL of the following (A, B, and C):
   A) Bendamustine is used as conditioning prior to autologous hematopoietic cell transplantation; AND
   B) Patient has ONE of the following conditions (i or ii):
      i. Non-Hodgkin lymphoma without central nervous system disease; OR
      ii. Hodgkin lymphoma; AND
   C) Bendamustine is prescribed by or in consultation with an oncologist or a physician who specializes in hematopoietic cell transplantation.

   Dosing. Approve up to 200 mg/m^2 administered by intravenous infusion no more frequently than twice prior to autologous hematopoietic cell transplantation.

---

4. **Hodgkin Lymphoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   A) Bendamustine is used as second-line or subsequent therapy; AND
   B) Bendamustine is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 120 mg/m^2 administered by intravenous infusion no more frequently than twice in each 21-day or 28-day treatment cycle.

---

5. **Multiple Myeloma.** Approve for 6 months if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has been treated with more than 3 prior regimens; AND
   C) Bendamustine is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 150 mg/m^2 administered by intravenous infusion no more frequently than twice in each 28-day cycle.

---

6. **Systemic Light Chain Amyloidosis.** Approve for 6 months if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has relapsed or refractory disease; AND
   C) Bendamustine is used in combination with dexamethasone; AND

D) Bendamustine is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 100 mg/m^2 administered by intravenous infusion no more frequently than twice in each 28-day cycle.

---

7. T-Cell Lymphoma. Approve for 6 months if the patient meets ALL of the following (A, B, and C):
Note: Examples include peripheral T-cell lymphoma, breast implant-associated anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, hepatosplenic T-cell lymphoma.
A) Patient is ≥ 18 years of age; AND
B) Bendamustine is used as a single agent; AND
C) Bendamustine is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 120 mg/m^2 administered by intravenous infusion no more frequently than twice in each 21-day cycle.

---

8. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 6 months if the patient meets BOTH of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Bendamustine is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 90 mg/m^2 administered by intravenous infusion no more frequently than twice in each 28-day cycle.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bendamustine is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Bendeka® intravenous infusion [prescribing information]. North Wales, PA: Teva; October 2021.
2. Treanda® intravenous infusion [prescribing information]. Frazer, PA: Cephalon; June 2021.
3. Belrapzo™ intravenous infusion [prescribing information]. Woodcliff Lake, NJ: Eagle Pharmaceuticals; June 2022.
4. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023. Search term: bendamustine.
5. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2023 – June 12, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
6. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 4.2023 – June 2, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
7. The NCCN Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – November 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
8. Moskowitz AJ, Hamlin PA, Perales MA, et al. Phase II Study of Bendamustine in Relapsed and Refractory Hodgkin Lymphoma. *J Clin Oncol*. 2013;31:456-460.
9. Santoro A, Mazza R, Pulsoni A, et al. Chemotherapy before autologous stem-cell transplantation for relapsed or refractory Hodgkin lymphoma: final results of a multicenter Phase II study. *J Clin Oncol*. 2016;34:3293-3299.
10. LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;132:40-48.
11. Corazzelli G, Angrilli F, D'Arco A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. *Br J Haematol*. 2013;160:207-215.

12. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 3.2023 – December 8, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
13. Michael M, Bruns I, Bolke E, et al. Bendamustine in Patients with Relapsed or Refractory Multiple Myeloma. *Eur J Med Res*. 2010;15:13-19.
14. Lentzsch S, O'Sullivan A, Kennedy RC, et al. Combination of bendamustine, lenalidomide, and dexamethasone (BLD) in patients with relapsed or refractory multiple myeloma is feasible and highly effective: results of phase I/II open-label, dose escalation study. *Blood*. 2012;119:4608-4613.
15. Offidani M, Corvatta L, Maracci L, et al. Efficacy and tolerability of bendamustine, bortezomib and dexamethasone in patients with relapsed-refractory multiple myeloma: a phase II study. *Blood Cancer J.* 2013;3:e162.
16. Mey UJM, Brugger W, Schwarb H, et al. Bendamustine, lenalidomide and dexamethasone (BRd) has high activity as 2nd-line therapy for relapsed and refractory multiple myeloma – a phase II trial. *Br J Haematol*. 2017;176:770-782.
17. Berenson JR, Yellin O, Bessudo A, et al. Phase I/II trial assessing bendamustine plus bortezomib combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. *Br J Haematol*. 2013;160:321-330.
18. Kumar SK, Krishnan A, LaPlant B, et al. Bendamustine, lenalidomide, and dexamethasone (BRD) is highly effective with durable responses in relapsed multiple myeloma. *Am J Hematol*. 2015;90:1106-1110.
19. Ludwiq H, Kasparu H, Leitgeb C, et al. Bendamustine-bortezomib-dexamethasone is an active and well-tolerated regimen in patients with relapsed or refractory multiple myeloma. *Blood*. 2014;123:985-991.
20. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
21. Damaj G, Gressin R, Bouabdallah K, et al. Results from a prospective, open-label, Phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. *J Clin Oncol*. 2013;31:104-110.
22. The NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (version 1.2023 – July 6, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
23. Paludo J, Abeykoon JP, Shreders A, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenstrom macroglobulinemia. *Ann Hematol*. 2018;97:1417-1425.
24. Tedeschi A, Picardi P, Ferrero S, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenstrom macroglobulinemia. *Leuk Lymphoma*. 2015;56:2637-2642.
25. Treon SP, Hanzis C, Tripsas C, et al. Bendamustine therapy in patients with relapsed or refractory Waldenstrom's macroglobulinemia. *Clin Lymphoma Myeloma Leuk.* 2011;11:133-135.
26. The NCCN Pediatric Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
27. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 2.2023 – November 28, 2022). © 2022 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
28. Lentzsch S, Lagos GG, Comenzo RL, et al. Bendamustine with dexamethasone in relapse/refractory systemic light-chain amyloidosis: Results of a Phase II study. *J Clin Oncol*. 2020;38:1455-1462.
29. The NCCN Hematopoietic Cell Transplantation (HCT) Clinical Practice Guidelines in Oncology (version 1.2023 – March 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 26, 2023.
30. Frankiewicz A, Sadus-Wojciechowska M, Najda J, et al. Comparable safety profile of BeEAM (bendamustine, etoposide, cytarabine, melphalan) and BEAM (carmustine, etoposide, cytarabine, melphalan) as conditioning before autologous haematopoietic cell transplantation. *Contemp Oncol (Pozn)*. 2018;22:113-117.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**B-Cell Non-Hodgkin Lymphoma:** Added requirement that the patient is ≥ 18 years of age. Added Note with examples of B-cell lymphomas. **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma:** Added requirement that the patient is ≥ 18 years of age. **Hematopoietic Cell Transplantation:** Added new condition of approval. **Multiple Myeloma:** Added requirement that the patient is ≥ 18 years of age. **Systemic Light Chain Amyloidosis:** Added requirement that the patient is ≥ 18 years of age. **T-Cell Lymphoma:** Added requirement that the patient is ≥ 18 years of age and that bendamustine is used as a single agent. Removed mycosis fungoides/Sezary syndrome and primary cutaneous CD30+ T-cell lymphoproliferative disorders from the Note. **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Added requirement that the patient is ≥ 18 years of age.	07/06/2022
Annual Revision	**B-Cell Non-Hodgkin Lymphoma:** Gastric and nongastric mucosa-associated lymphoid tissue (MALT) lymphoma was removed from the Note. Extranodal marginal zone lymphoma of the stomach and extranodal marginal zone lymphoma of nongastric sites were added to the Note. **Multiple Myeloma:** Relapsed or refractory disease was removed as a requirement. Patient has been treated with more than 3 prior regimens added as a new requirement.	07/12/2023