Bicnu (carmustine)

Effective Date: 10/22/13

Date Developed: 9/3/13 by Albert Reeves MD

Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19, 2/18/20, 8/3/21, 2/1/22, 1/31/23, 2/13/24, 2/18/25

Pharmacologic Category: Antineoplastic Agent; Alkylating Agent (Nitrosourea)

Preauthorization Criteria:

Injection: Palliative treatment: brain tumors (glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors), multiple myeloma, Hodgkin's lymphoma (relapsed or refractory), non-Hodgkin's lymphomas (relapsed or refractory)

Wafer (implant): Adjunct to surgery in patients with recurrent glioblastoma multiforme; adjunct to surgery and radiation in patients with newly diagnosed high-grade malignant glioma

Off-Label: Hematopoietic cell or bone marrow transplant, autologous, conditioning regimen; Mycosis fungoides, early stage (topical)

Dosing:

NOTE: Carmustine (IV) is associated with a high emetic potential; antiemetics are recommended to prevent nausea and vomiting

NOTE: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

NOTE: Consult current product information for potential updates.

NOTE: Utilize patient's actual body weight (full weight) for calculation of body surface area or weight-based dosing in obese patients (refer to ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer)

Adult: Brain tumors, Hodgkin's lymphoma, multiple myeloma, non-Hodgkin's lymphoma (per manufacturer labeling): I.V.: 150-200 mg/m^2 every 6 weeks or 75-100 mg/m^2/day for 2 days every 6 weeks

Glioblastoma multiforme (recurrent), newly diagnosed high-grade malignant glioma: Implantation (wafer): 8 wafers placed in the resection cavity (total dose 61.6 mg); should the size and shape not accommodate 8 wafers, the maximum number of wafers allowed (up to 8) should be placed

Indication-specific dosing:

Brain tumor, primary (unlabeled doses): I.V.:

80 mg/m^2/day for 3 days every 8 weeks for 6 cycles (Brandes, 2004)

200 mg/m^2 every 8 weeks [maximum cumulative dose: 1500 mg/m^2] (Selker, 2002)

Hodgkin's lymphoma, relapsed or refractory (unlabeled dose): I.V.: Mini-BEAM regimen: 60 mg/m^2 day 1 every 4-6 weeks (in combination with etoposide, cytarabine, and melphalan) (Colwill, 1995; Martin, 2001)

Multiple myeloma, relapsed, refractory (unlabeled dose): I.V.: VBMCP regimen: 20 mg/m^2 day 1 every 35 days (in combination with vincristine, melphalan, cyclophosphamide, and prednisone) (Kyle, 2006; Oken, 1997)

Mycosis fungoides, early stage (unlabeled use; Zackheim, 2003): Topical:

Ointment (10 mg/100 grams petrolatum): Apply (with gloves) once daily to affected areas

Solution (0.2% solution in alcohol; dilute 5 mL in 60 mL water): Apply (with gloves) once daily to affected areas

Stem cell or bone marrow transplant, autologous (unlabeled use): I.V.:

BEAM regimen: 300 mg/m^2 6 days prior to transplant (in combination with etoposide, cytarabine, and melphalan) (Chopra, 1993; Linch, 2010)

CBV regimen: 600 mg/m^2 3 days prior to transplant (in combination with cyclophosphamide and etoposide) (Reece, 1991)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

I.V.: The FDA-approved labeling does not contain renal dosing adjustment guidelines. The following dosage adjustments have been used by some clinicians (Kintzel, 1995):

Cl_{cr} 46-60 mL/minute: Administer 80% of dose

Cl_{cr} 31-45 mL/minute: Administer 75% of dose

Cl_{cr} ≤30 mL/minute: Consider use of alternative drug.

Dosing: Hepatic Impairment

Dosage adjustment may be necessary; however, no specific guidelines are available.

resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs, 2012).

Dosing: Adjustment for Toxicity

Hematologic toxicity: Based on nadir counts with previous dose (manufacturer's labeling). I.V.:

If leukocytes >3000/mm^3 and platelets >75,000/mm^3: Administer 100% of dose

If leukocytes 2000-2999/mm^3 or platelets 25,000-74,999/mm^3: Administer 70% of dose

If leukocytes <2000/mm^3 or platelets <25,000/mm^3: Administer 50% of dose

Major Adverse Reactions and Black Box Warnings: **I.V.:** Frequency not defined:

Cardiovascular: Arrhythmia (with high doses), chest pain, flushing (with rapid infusion), hypotension, tachycardia

Central nervous system: Ataxia, dizziness

Central nervous system: Ethanol intoxication (with high doses), headache

Dermatologic: Hyperpigmentation/skin burning (after skin contact)

Gastrointestinal: Nausea (common; dose related), vomiting (common; dose related), mucositis (with high doses), toxic enterocolitis (with high doses)

Hematologic: Leukopenia (common; onset: 5-6 weeks; recovery: after 1-2 weeks), thrombocytopenia (common: onset: ~4 weeks; recovery: after 1-2 weeks), anemia, neutropenic fever, secondary malignancies (acute leukemia, bone marrow dysplasia)

Hepatic: Alkaline phosphatase increased, bilirubin increased, hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease; with high doses), transaminases increased

Local: Injection site reactions (burning, erythema, necrosis, pain, swelling)

Ocular: Conjunctival suffusion (with rapid infusion), neuroretinitis

Renal: Kidney size decreased, progressive azotemia, renal failure

Respiratory: Interstitial pneumonitis (with high doses), pulmonary fibrosis, pulmonary hypoplasia, pulmonary infiltrates

Miscellaneous: Allergic reaction, infection (with high doses)

Wafer:

≥4% (percentages reported only where incidence was greater compared to placebo):

Cardiovascular: Deep thrombophlebitis (10%), facial edema (6%), chest pain (5%)

Central nervous system: Brain edema (4% to 23%), confusion (10% to 23%), depression (16%), headache (15%), somnolence (14%), fever (12%), speech disorder (11%),

intracranial hypertension (9%), anxiety (7%), facial paralysis (7%), pain (7%), ataxia (6%), hypesthesia (6%), hallucination (5%), seizure (grand mal 5%), meningitis (4%)

Dermatologic: Abnormal wound healing (14% to 16%), rash (5% to 12%)

Endocrine: Diabetes (5%)

Gastrointestinal: Nausea (8% to 22%), vomiting (8% to 21%), constipation (19%), abdominal pain (8%), diarrhea (5%)

Genitourinary: Urinary tract infection (21%)

Hematologic: Hemorrhage (7%)

Local: Abscess (4% to 8%)

Neuromuscular & skeletal: Weakness (22%), back pain (7%)

Contraindications

Hypersensitivity to carmustine or any component of the formulation

BOXED WARNINGS:

Bone marrow suppression (primarily thrombocytopenia and leukopenia) is the major carmustine toxicity; generally, is delayed. Monitor blood counts weekly for at least 6 weeks after administration. Myelosuppression is cumulative. When given at the FDA-approved doses, treatment should not be administered less than 6 weeks apart. Consider nadir blood counts from prior dose for dosage adjustment. May cause bleeding (due to thrombocytopenia) or infections (due to neutropenia), monitor closely. Patients must have platelet counts >100,000/mm^3 and leukocytes >4000/mm^3 for a repeat dose. Anemia may occur (less common and less severe than leukopenia or thrombocytopenia).

- Hepatic: Reversible increases in transaminases, bilirubin, and alkaline phosphatase have been reported (rare). Monitor liver function tests periodically during treatment.
- Infusion site reactions: Injection site burning and local tissue reactions, including swelling, pain, erythema, and necrosis have been reported. Monitor infusion site closely for infiltration or injection site reactions.

Pulmonary toxicity: Injection: **Dose-related pulmonary toxicity (**characterized by pulmonary infiltrates and/or fibrosis) **may occur; patients receiving cumulative doses >1400 mg/m^2 are at higher risk. Delayed onset of pulmonary fibrosis (may be fatal) has occurred in children up to 17 years after treatment**

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Dosage Forms:

Solution Reconstituted, Intravenous:

Bicnu: 100 mg (1 ea) [contains alcohol, usp]

Generic: 100 mg (1 ea)

Wafer, Implant:

Gliadel Wafer: 7.7 mg (8 ea) [contains polifeprosan 20]

Topical: requires compounding (10mg/100gm petrolatum)

References:

1. Benekli M, Smiley SL, Younis T, et al, “Intensive Conditioning Regimen of Etoposide (VP-16), Cyclophosphamide and Carmustine (VCB) Followed by Autologous Hematopoietic Stem Cell Transplantation for Relapsed and Refractory Hodgkin's Lymphoma,” *Bone Marrow Transplant*, 2008, 41(7):613-9. [PubMed 18071290]
2. Brandes AA, Tosoni A, Amistà P, et al, “How Effective is BCNU in Recurrent Glioblastoma in the Modern Era? A Phase II Trial,” *Neurology*, 2004, 63(7):1281-4. [PubMed 15477552]
3. Chopra R, McMillan AK, Linch DC, et al, “The Place of High-Dose BEAM Therapy and Autologous Bone Marrow Transplantation in Poor-Risk Hodgkin's Disease. A Single-Center Eight-Year Study of 155 Patients,” *Blood*, 1993, 81(5):1137-45. [PubMed 8443375]
4. Colwill R, Crump M, Couture F, et al,, “Mini-BEAM as Salvage Therapy for Relapsed or Refractory Hodgkin's Disease Before Intensive Therapy and Autologous Bone Marrow Transplantation,” *J Clin Oncol*, 1995, 13(2):396-402. [PubMed 7844600]
5. Durando X, Lemaire JJ, Tortochaux J, et al, “High-Dose BCNU Followed by Autologous Hematopoietic Stem Cell Transplantation in Supratentorial High-Grade Malignant Gliomas: A Retrospective Analysis of 114 Patients,” *Bone Marrow Transplant*, 2003, 31(7):559-64. [PubMed 12692621]
6. Fleming AB and Saltzman WM, “Pharmacokinetics of the Carmustine Implant,” *Clin Pharmacokinet*, 2002, 41(6):403-19. [PubMed 12074689]
7. Griggs JJ, Mangu PB, Anderson H, et al, “Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline,” *J Clin Oncol*, 2012, 30(13):1553-61. [PubMed 22473167]
8. Kim JE, Lee DH, Yoo C, et al, “BEAM or BuCyE High-Dose Chemotherapy Followed by Autologous Stem Cell Transplantation in Non-Hodgkin's Lymphoma Patients: A Single Center Comparative Analysis of Efficacy and Toxicity,” *Leuk Res*, 2011, 35(2):183-7. [PubMed 20684990]
9. Kintzel PE and Dorr RT, "Anticancer Drug Renal Toxicity and Elimination: Dosing Guidelines for Altered Renal Function," *Cancer Treat Rev*, 1995, 21(1):33-64. [PubMed 7859226]
10. Kyle RA, Leong T, Li S, et al, “Complete Response in Multiple Myeloma: Clinical Trial E9486, an Eastern Cooperative Oncology Group Study Not Involving Stem Cell Transplantation,” *Cancer*, 2006, 106(9):1958-66. [PubMed 16565956]
11. Linch DC, Yung L, Smith P, et al, “Final Analysis of the UKLG LY02 Trial Comparing 6-8 Cycles of CHOP With 3 Cycles of CHOP Followed by a BEAM Autograft in Patients <65 Years With Poor Prognosis Histologically Aggressive NHL,” *Br J Haematol*, 2010, 149(2):237-43. [PubMed 20201949]
12. Mahendra P, Johnson D, Scott MA, et al, “Peripheral Blood Progenitor Cell Transplantation: A Single Centre Experience Comparing Two Mobilisation Regimens in 67 Patients,” *Bone Marrow Transplant*, 1996, 17(4):503-7. [PubMed 8722346]
13. Martín A, Fernández-Jiménez MC, Caballero MD, et al, “Long-Term Follow-Up in Patients Treated

With Mini-BEAM as Salvage Therapy for Relapsed or Refractory Hodgkin's Disease," *Br J Haematol*, 2001, 113(1):161-71. [PubMed 11328296]
14. National Institute for Occupational Safety and Health (NIOSH), "NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2012." Available at http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf. Accessed January 21, 2013.
15. Oken MM, Harrington DP, Abramson N, et al, "Comparison of Melphalan and Prednisone With Vincristine, Carmustine, Melphalan, Cyclophosphamide, and Prednisone in the Treatment of Multiple Myeloma: Results of Eastern Cooperative Oncology Group Study E2479," *Cancer*, 1997, 79(8):1561-7. [PubMed 9118039]
16. Reece DE, Barnett MJ, Connors JM, et al, "Intensive Chemotherapy With Cyclophosphamide, Carmustine, and Etoposide Followed by Autologous Bone Marrow Transplantation for Relapsed Hodgkin's Disease," *J Clin Oncol*, 1991, 9(10):1871-9. [PubMed 1919637]
17. Selker RG, Shapiro WR, Burger P, et al, "The Brain Tumor Cooperative Group NIH Trial 87-01: A Randomized Comparison of Surgery, External Radiotherapy, and Carmustine Versus Surgery, Interstitial Radiotherapy Boost, External Radiation Therapy, and Carmustine," *Neurosurgery*, 2002, 51(2):343-55. [PubMed 12182772]
18. Trissel LA, Xu QA, and Baker M, "Drug Compatibility With New Polyolefin Infusion Solution Containers," *Am J Health-Syst Pharm*, 2006, 63(23):2379-82. [PubMed 17106012]
19. Weingart JD and Brem H, "Carmustine Implants: Potential in the Treatment of Brain Tumors," *CNS Drugs*, 1996, 4:263-9.
20. Zackheim HS, "Topical Carmustine (BCNU) in the Treatment of Mycosis Fungoides," *Dermatol Ther*, 2003,16(4):299-302. [PubMed 14686972].
21. BiCNU (carmustine) [prescribing information]. East Brunswick, NJ: Avet Pharmaceuticals Inc; November 2021
22. Griggs JJ, Bohlke K, Balaban EP, et al. Appropriate systemic therapy dosing for obese adult patients with cancer: ASCO guideline update. J Clin Oncol. 2021;39(18):2037-2048.
23. Herrstedt J, Clark-Snow R, Ruhlmann CH, et al; participants of the MASCC/ESMO Consensus Conference 2022. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open. 2024;9(2):102195. doi:10.1016/j.esmoop.2023.

Revision History:

Date Approved by P&T Committee: 10/22/13
Date Reviewed/No Updates: 1/28/14 by C. Sanders MD
Date Approved by P&T Committee: 1/28/14
Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD
Date Approved by P&T Committee: 1/27/15
Date Approved by P&T Committee: 1/26/16
Date Reviewed/No Updates: 1/24/17 by C. Sanders, MD
Date Approved by P&T Committee: 1/24/17
Date Reviewed/No Updates: 1/23/18 by C. Sanders, MD
Date Approved by P&T Committee: 1/23/18
Date Reviewed/No Updates: 1/22/19 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/22/19
Date Reviewed/No Updates: 2/18/20 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/18/20
Date Reviewed/ Updated: 8/3/21 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 8/3/21
Date Reviewed/No Updates: 2/1/22 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/1/22
Date Reviewed/No Updates: 1/31/23 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/31/23
Date Reviewed/Updated: 2/18/25 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/18/25

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Revision Date	Content Revised (Yes/No)	Contributors	Review/Revision Notes
1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/23/18	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/22/19	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
2/18/20	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
8/3/21	Yes	Howard Taekman, MD; Robert Sterling, MD	Updated preauthorization criteria and Boxed Warnings section
2/1/22	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
1/31/23	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
2/13/24	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
2/18/25	Yes	Howard Taekman, MD; Robert Sterling, MD	Added Off Label Use. Updated dosing information. Removed administration section and modified major adverse reactions and black box warning sections