Prior Authorization DRUG Guidelines

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

Pharmacologic Category: Antineoplastic Agent; Alkylating Agent

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

**Dosing: Adult**: Brain tumors, Hodgkin’s lymphoma, multiple myeloma, non-Hodgkin’s lymphoma (per manufacturer labeling): I.V.: 150-200 mg/m² every 6 weeks or 75-100 mg/m²/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/m²/day for 3 days every 8 weeks for 6 cycles (Brandes, 2004)
- 200 mg/m² every 8 weeks [maximum cumulative dose: 1500 mg/m²] (Selker, 2002)

Hodgkin’s lymphoma, relapsed or refractory (unlabeled dose): I.V.: Mini-BEAM regimen: 60 mg/m² 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/m² 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/m² 6 days prior to transplant (in combination with etoposide, cytarabine, and melphalan) (Chopra, 1993; Linch, 2010)

CBV regimen: 600 mg/m² 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):

\[Cl_{cr} 46-60 \text{ mL/minute}: \text{Administer 80\% of dose}\]
\[Cl_{cr} 31-45 \text{ mL/minute}: \text{Administer 75\% of dose}\]
\[Cl_{cr} \leq 30 \text{ mL/minute}: \text{Consider use of alternative drug.}\]

**Dosing: Hepatic Impairment**

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

**Dosing: Obesity**

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer *(Note: Excludes HSCT dosing)*: Utilize patient’s actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider 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/mm³ and platelets >75,000/mm³: Administer 100\% of dose
- If leukocytes 2000-2999/mm³ or platelets 25,000-74,999/mm³: Administer 70\% of dose
- If leukocytes <2000/mm³ or platelets <25,000/mm³: Administer 50\% of dose
Administration: Injection: Irritant (alcohol-based diluent). Significant absorption to PVC containers; should be prepared in either glass or polyolefin containers. Infuse over 2 hours (infusions <2 hours may lead to injection site pain or burning); infuse through a free-flowing saline or dextrose infusion, or administer through a central catheter to alleviate venous pain/irritation.

High-dose carmustine (transplant dose; unlabeled use): Infuse over at least 2 hours to avoid excessive flushing, agitation, and hypotension; was infused over 1 hour in some trials (Chopra, 1993). **High-dose carmustine may be fatal if not followed by stem cell rescue.** Monitor vital signs frequently during infusion; patients should be supine during infusion and may require the Trendelenburg position, fluid support, and vasopressor support.

Implant: Double glove before handling; outer gloves should be discarded as chemotherapy waste after handling wafers. Any wafer or remnant that is removed upon repeat surgery should be discarded as chemotherapy waste. The outer surface of the external foil pouch is not sterile. Open pouch gently; avoid pressure on the wafers to prevent breakage. Wafer that are broken in half may be used, however, wafers broken into more than 2 pieces should be discarded in a biohazard container. Oxidized regenerated cellulose (Surgicel®) may be placed over the wafer to secure; irrigate cavity prior to closure.

**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%)

<4% (Limited to important or life-threatening): Abnormal thinking, allergic reaction, amnesia, aspiration pneumonia, cerebral hemorrhage, cerebral infarction, coma, cyst formation, diplopia, dizziness, dysphagia, eye pain, fecal incontinence, gastrointestinal hemorrhage, hydrocephalus, hyperglycemia, hyper-/hypotension, hypokalemia, hyponatremia, insomnia, leukocytosis, monoplegia, neck pain, paranoia, peripheral edema, sepsis, thrombocytopenia, urinary incontinence, visual field defect

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/mm³ and leukocytes >4000/mm³ 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 may occur; patients receiving cumulative doses >1400 mg/m² are at higher risk.** Delayed onset of pulmonary fibrosis (may be fatal) has occurred in children up to 17 years after treatment; this occurred in ages 1-16 for the treatment of intracranial tumors; cumulative doses ranged from 770-1800 mg/m² (in combination with cranial radiotherapy). Pulmonary toxicity is characterized by pulmonary infiltrates and/or fibrosis and has been reported from 9 days to 43 months after nitrosourea treatment (including carmustine). Although pulmonary toxicity generally occurs in patients who have received prolonged treatment, pulmonary fibrosis has been reported with cumulative doses <1400 mg/m². In addition to high cumulative doses, other risk factors for pulmonary toxicity include history of lung disease and baseline predicted forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) <70%. Baseline and periodic pulmonary function tests are recommended. For high-dose treatment (transplant; unlabeled dose), acute lung injury may occur ~1-3 months post-transplant; advise patients to contact their transplant physician for dyspnea, cough, or fever; interstitial pneumonia may be managed with a course of corticosteroids.

**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:


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- Date Approved by P&T Committee: 10/22/13
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