

DRUG NAME: Carmustine**SYNONYM(S):** BCNU¹**COMMON TRADE NAME(S):** BiCNU®, GLIADEL® Wafer**CLASSIFICATION:** alkylating agent*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Carmustine is a highly lipid-soluble **nitrosourea** compound. Carmustine, a bifunctional alkylating agent,² alkylates DNA and RNA, can cross-link DNA, and inhibits several enzymes by carbamoylation.¹ It is cell-cycle phase nonspecific.³ Carmustine is generally not cross-resistant with other alkylating agents,⁴ however, cross-resistance between carmustine and lomustine has occurred.¹

PHARMACOKINETICS:

Table refers to intravenous (IV) dosing. Pharmacokinetic properties of the implantable carmustine-impregnated wafer have not been evaluated.⁵ High-dose⁴ is defined here as >200 mg/m².

Oral Absorption	not known ⁶	
Distribution	highly lipid soluble ⁷ (e.g., enters breast milk, brain)	
	cross blood brain barrier?	passes readily ¹ (15-70% of concurrent plasma concentrations) children ⁸ : >90%
	volume of distribution	3.25 L/kg (5.1 L/kg, high dose) ⁹ children ⁸ : 90 L/m ²
	plasma protein binding	80% children ⁸ : 65-75%
Metabolism	rapid spontaneous decomposition ² ; significant hepatic metabolism ^{2,7}	
	active metabolite(s)	yes ¹
	inactive metabolite(s)	yes ⁶
Excretion	predominately renal; respiratory 6-10% ⁷ as CO ₂	
	urine ⁷	60-70% within 96 h
	feces ¹	<1%
	terminal half life	0.25-0.75 h, non-linear dose-related
	clearance	56 mL/min/kg (78 mL/min/kg, high dose) ⁹ children ⁸ : 1,500-2,000 mL/min/m ²

Adapted from standard reference⁴ unless specified otherwise.

USES:

Table refers to intravenous (IV) dosing except where specified.

Primary uses:

- *Brain tumours
- *Glioma (implantable carmustine-impregnated wafer)
- *Lymphoma, Hodgkin's disease
- *Lymphoma, non-Hodgkin's
- *Multiple myeloma
- *Melanoma
- *Gastrointestinal cancer
- *Health Canada approved indication

Other uses:

- Glioblastoma¹⁰ (implantable carmustine-impregnated wafer)
- Lymphoma, cutaneous T-cell^{1,11} (topical carmustine)

SPECIAL PRECAUTIONS:

Caution: Dose-related pulmonary toxicity may occur with carmustine injection; patients receiving cumulative doses >1,400 mg/m² are at higher risk.⁷ Single doses of >450 mg/m² may be associated with the development of acute lung injury in approximately 20% of patients. For more information, see paragraph following **Side Effects** table.

Special populations: Carmustine injection should be used with extreme caution in **children** due to the high risk of pulmonary toxicity.⁴

Carcinogenicity: Carmustine is carcinogenic in rats and mice, producing a marked increase in tumour incidence with therapeutic doses.⁴

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test.¹² Carmustine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: Carmustine affects fertility in male rats at doses somewhat higher than human doses.⁴

Pregnancy: FDA Pregnancy Category D.⁷ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is contraindicated as carmustine injection is detected in human breast milk.⁷

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse events are included if the incidence is \geq 5% higher in the treatment group.

CARMUSTINE INJECTION:High-dose⁴ is defined here as >200 mg/m².

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i> ¹³	
blood/bone marrow/ febrile neutropenia	anemia (1-10%) ⁷
	<i>myelosuppression</i> (>10%) ⁷ ; onset 7-14 days, nadir 21-35 days, recovery 42-56 days; cumulative, dose related, delayed and often biphasic ¹⁰ ; see paragraph following Side Effects table
cardiovascular (general)	hypotension, due to alcohol content of diluent (high-dose therapy >10%) ⁷
dermatology/skin	<i>extravasation hazard: vesicant</i> ¹⁴
	alopecia ⁶ (1-10%) ⁷
	dermatitis with topical use (50%) ⁹ improves with reduced concentration of compounded product
	flushing, due to alcohol content of diluent (1-10%) ⁷ ; increased with administration times <1-2 h ¹⁵
	hyperpigmentation, transient, ³ with accidental skin contact (>10%) ⁷
	injection site reaction; see paragraph following Side Effects table
gastrointestinal	<i>emetogenic potential</i> ¹⁶ : >250 mg/m ² high; ≤250 mg/m ² high-moderate
	anorexia (1-10%) ⁷
	constipation (1-10%) ⁷
	diarrhea (1-10%) ⁷
	<i>nausea and vomiting</i> (severe (>10%) ⁷ ; begins within 2-4 h of administration and lasts for 4-6 h
	stomatitis (1-10%)
hepatobiliary/pancreas	hepatotoxicity, reversible, delayed up to 60 days after administration (<1%, ¹ high-dose therapy 1-10 % and dose-limiting ¹⁰)
metabolic/laboratory	alkaline phosphatase, reversible increase (>20-25%) ⁷
	bilirubin, reversible increase (>20-25%) ⁷
	SGOT, reversible increase (>20-25%) ⁷
neurology	ataxia (>10%) ⁷
	dizziness (>10%) ⁷
	encephalopathy (<1%, high-dose therapy 1-10% and dose-limiting ¹⁰)
ocular/visual	ocular toxicities, transient conjunctival flushing and blurred vision; retinal hemorrhages (>10%) ⁷
pain	headache ¹
	muscular pain (<1%)
pulmonary	<i>pulmonary toxicity</i> (up to 30%); see paragraph following Side Effects table
	<i>BCNU pneumonitis</i> ¹⁷ (20% for doses >450 mg/m ²) ¹⁷ ; see paragraph following Side Effects table
	<i>interstitial fibrosis</i> (<1%, up to 50% for cumulative doses >1,400 mg/m ²) ⁷
renal/genitourinary	<i>renal toxicity</i> ^{6,10} (<1% for cumulative doses <1,000 mg/m ²)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i> ¹³	
secondary malignancy	acute leukemias, bone marrow dysplasias ⁴ ; following long-term use
sexual/reproductive function	gynecomastia (<1%)
	infertility ⁶
	teratogenesis ⁶
vascular	phlebitis (>10%) ⁷
	veno-occlusive disease ⁶ (high-dose therapy <1%) ¹⁰

Adapted from standard reference⁴ unless specified otherwise.

IMPLANTABLE CARMUSTINE-IMPREGNATED WAFER:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <i>bold, italics</i> ¹⁸	
allergy/immunology	allergic reaction (1%)
cardiovascular (arrhythmia)	tachycardia (2%)
cardiovascular (general)	hypertension (3%)
	hypotension (3%)
constitutional symptoms	accidental injury (1-5%) ¹
	aggravation reaction, defined as progression of tumour or disease or general deterioration (82%) ¹
	asthenia (1%)
	insomnia (1-10%) ⁷
dermatology/skin	alopecia does not occur ¹⁸
	wound healing complications, at site of implantation, ¹⁹ including cerebrospinal fluid leaks, subdural fluid collection and wound healing (12%)
endocrine	Cushing's syndrome (3%) ¹
	Diabetes mellitus (5%) ¹
gastrointestinal	<i>emetogenic potential: rare</i>
	constipation (1%)
	dysphagia (1%)
	vomiting (2%)
hemorrhage	hemorrhage, gastrointestinal (1%)
infection	<i>intracranial infection, meningitis, or abscess</i> ^{5(1-10%)⁷}
	oral moniliasis (3%)
lymphatics	edema, cerebral (1-10%) ⁷
	edema, peripheral (3%)
metabolic/laboratory	hyponatremia (3%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics ¹⁸	
	hypokalemia (1%)
	hyperglycemia (2%)
neurology ⁷	brain swelling: amnesia (1-10%); aphasia (1-10%); ataxia (1-10%); confusion (1-10%); convulsion (1-10%); dizziness (1-10%); hemiplegia (1-10%); hydrocephalus (1-10%); monoplegia (2%); seizures (> 10%); somnolence (1-10%); stupor (1-10%); abnormal thinking (3%)
ocular/visual	diplopia (1-10%) ⁷
pain	chest pain (1%)
	headache (1-10%) ⁷
	pain (4%)
renal/genitourinary	urinary incontinence (2%)
vascular	phlebitis (10%) ¹
	pulmonary embolism (4-8%, at initial surgery) ¹

Adapted from standard reference⁵ unless specified otherwise.

TOPICAL CARMUSTINE:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood and lymphatic system/ febrile neutropenia	leucopenia (4-10%) ²⁰⁻²² ; mild, possibly higher incidence with solution versus ointment and with greater surface area treated
	anemia; mild
skin and subcutaneous tissue	dermatitis (<10%); allergic or irritant
	erythema (>50%); see paragraph following Side Effects table
	telangiectasia

Adapted from standard reference²⁰ unless specified otherwise.

Erythema is experienced by the majority of patients following topical carmustine, particularly with the compounded solution. Erythema is often accompanied by a burning sensation, likened to sunburn, and skin tenderness.^{20,22} The reaction may manifest as hyperpigmentation in individuals with dark hair or dark complexions.^{21,23} Erythema tends to be accentuated in body folds, the groin area, and axillae.²⁰ With total body applications, reactions usually appear within 4-8 weeks.^{21,22} Reactions may require treatment with intensive topical corticosteroids, cool compresses or baths, and emollients. In severe, and sometimes even moderate erythematous reactions, the reaction may be followed by a benign telangiectasia. Telangiectasia usually involutes within a few months, but in severe cases may persist for years before gradually resolving. Secondary skin cancers were not reported.^{20,22,24}

Injection reaction: Burning and hyperemia at the injection site, or along the course of the vein, are common during carmustine injection.⁴ Vasospasm is also common, but thrombosis and thrombophlebitis are rare.¹ Rapid IV infusion may result in flushing of the skin and conjunctiva, likely due to the alcohol diluent. These effects can occur within 2 hours and may continue for 4 hours after administration of carmustine. Infusions should run over 1-2 hours; for high-dose carmustine, the maximum rate is 3 mg/m²/minute to avoid excessive flushing, agitation, and hypotension.⁷

Myelosuppression: Delayed myelosuppression occurs frequently with carmustine injection, and may be severe.⁴ This is cumulative and usually occurs 4-6 weeks after administration of the drug.¹ Thrombocytopenia is generally greater than leukopenia; however, both may be dose-limiting toxicities. Anemia also occurs but is generally less severe. Due to the delayed and cumulative myelosuppressive effects, carmustine is usually given at intervals of at least 6 weeks. However, repeat courses of carmustine should not be administered until leukocyte and platelet counts have returned to acceptable levels.

Pulmonary toxicity: Pulmonary fibrosis and **pulmonary infiltrates** can occur with carmustine injection. Pulmonary toxicities²⁵ are more common with prolonged therapy and with cumulative doses >1,400 mg/m²; however, pulmonary toxicity has occurred with lower doses.¹ Early-onset pulmonary toxicity appears within 3 years of therapy (9 days to 43 months)⁴; however, late-onset pulmonary fibrosis has been reported up to 17 years after treatment. Risk factors include smoking, pre-existing respiratory condition(s), sequential or concomitant thoracic irradiation, and the use of other drugs that cause lung damage. Pulmonary function tests should be performed at baseline and throughout treatment. Patients should be advised to immediately report any signs of respiratory complications, and this should result in discontinuation of therapy. Note that carmustine therapy during childhood may result in asymptomatic lung fibrosis that may become symptomatic in adulthood.

Unlike the toxicity described above, a condition called BCNU **pneumonitis**,¹⁷ BCNU lung, or idiopathic pneumonia syndrome,²⁶⁻²⁸ may occur following a single dose or course of therapy. BCNU pneumonitis requires emergency treatment as it is potentially fatal.¹³ Patients typically present 30-100 days after autologous BMT with fever, cough, dyspnea and pulmonary infiltrates on x-ray.¹⁷ Risk factors include the ones identified previously, as well as female sex.^{26,29} It has been suggested that doses <475 mg/m² may reduce the risk,³⁰ particularly in females.²⁶ However, BCNU pneumonitis can occur with lower doses; e.g., 300 mg/m². Treatment includes high-dose prednisone, as well as antibiotics if pneumonia is suspected. If this complication is suspected, please contact one of the physicians affiliated with the Leukemia / Bone Marrow Transplant Program of BC.¹³

INTERACTIONS:

Table refers to IV dosing. Interactions with the implantable carmustine-impregnated wafer have not been evaluated.⁵

AGENT	EFFECT	MECHANISM	MANAGEMENT
cimetidine ³¹	delayed, major, suspected; increased carmustine toxic effect	possible inhibition of carmustine metabolism	avoid concomitant use
digoxin tablets ^{31,32}	delayed, moderate, suspected; decreased effect of digoxin	changes to intestinal mucosa may decrease digoxin absorption	consider monitoring digoxin levels; adjust digoxin dose as needed
melphalan ^{25,33,34}	increased risk of pulmonary toxicity	melphalan may reduce the threshold for carmustine-induced pulmonary toxicity	caution; monitor for pulmonary toxicity
phenytoin ³¹	delayed, moderate, suspected; decreased phenytoin levels	decreased absorption or increased metabolism of phenytoin	monitor serum phenytoin levels during and after carmustine therapy; adjust phenytoin dose as needed

SUPPLY AND STORAGE:

Carmustine in polifeprosan wafer⁵: available in a single-dose treatment box containing eight individually pouched wafers. Each wafer contains 7.7 mg (3.85%) of carmustine. Each wafer is packaged in two aluminum foil laminate pouches. The inner pouch is sterile and maintains the sterility of the wafer. The second pouch is a peelable overwrap. The aluminum foil pouches containing GLIADEL® should be delivered to the operating room and remain unopened until ready to implant the wafers.⁴ The product must be stored at or below -20°C. Unopened foil pouches may be kept at ambient room temperature for a maximum of six hours.

Injection: Bristol-Myers Squibb Canada supplies carmustine as 100 mg vials of sterile lyophilized powder. Store in fridge.³⁵

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see [Chemotherapy Preparation and Stability Chart in Appendix](#).

Additional information for carmustine injection:

- The powder in the unopened vial should have a physical appearance ranging from lacy flakes to a congealed mass.⁴ If the vial has been exposed to temperatures higher than 30.5-32.0 °C, the powder will liquefy and appear as an oily film in the bottom of the vial. This is a sign of decomposition and the vial should be discarded.
- Allow supplied diluent (absolute alcohol) to come to room temperature before mixing.⁴
- Use glass or polyolefin containers when preparing carmustine.¹⁵ The rate of loss of carmustine in D5W in PVC containers due to sorption is substantially greater than in glass or polyolefin containers.¹⁵ For infusion times longer than 1-2 hours use a polyethylene-lined administration set to avoid sorption.¹⁵
- Reconstituted vials stored under refrigeration should be examined for crystal formation prior to use. Crystals can be redissolved by warming the vial to room temperature and shaking the vial.
- Although alternative reconstitution directions have been suggested to minimize the volume of ethanol used, there is limited evidence to support their clinical use.³⁶⁻³⁹

Additional information for topical carmustine ointment:

To yield a 0.4% ointment in white petrolatum:

- Reconstitute each 100mg carmustine vial with 3mL absolute alcohol to give 33.3mg/mL. Shake to dissolve.
 - Withdraw vial contents and mix with 25g of white petrolatum per vial.²³
- The final product is stable for 6 months in the refrigerator²² or 3 months at room temperature.²³ A change in colour to brown indicates occurrence of oxidation, and the ointment should be discarded.²²

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in **bold, italics**

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Intratumoral	implantable carmustine-impregnated wafer
Direct intravenous	no information found
<i>Intermittent infusion</i>	<i>over 1-2 h¹⁵</i>
Continuous infusion	not used due to corrosive nature
Intraperitoneal	no information found
Intrapleural	not used due to corrosive nature
Intrathecal	not used due to corrosive nature
Intra-arterial	has been used ⁴
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
<i>Intravenous:</i>	4-6 weeks ⁷ :	20-65 mg/m ² (0.5-1 mg/kg) IV for one dose on day 1 (total dose per cycle 20-65 mg/m ² [0.5-1 mg/kg])
	6 weeks ⁴⁰ :	<i>100 mg/m² IV for one dose on day 1 for 3-6 cycles (total dose per cycle 100 mg/m²)</i>
	6-8 weeks ⁷ :	150-200 mg/m ² IV once daily as a single dose on day 1, or divided into daily injections on 2 consecutive days starting on day 1 (total dose per cycle 150-200 mg/m ²)
	6-8 weeks ⁷ :	75-120 mg/m ² IV once daily for 2 consecutive days starting on day 1 (total dose per cycle 150-240 mg/m ²)
	6-8 weeks ⁷ :	40-80 mg/m ² IV once daily for three consecutive days starting on day 1 (total dose per cycle 120-240 mg/m ²)
	<i>Bone marrow transplant</i> ^{41,42} :	combination therapy: <i>500 mg/m² IV for one dose (on day -2) (total dose 500 mg/m²)</i> Note: these doses are fatal without bone marrow/stem cell transplant.
<i>Bone marrow transplant</i> ⁴³ :	combination therapy: <i>300 mg/m² IV for one dose (on day -6) (total dose 300 mg/m²)</i> Note: these doses are fatal without bone marrow/stem cell transplant.	
<i>Intratumoral</i> ⁵ :	n/a:	implantation: up to 8 wafers placed in the resection cavity (total dose 61.6 mg); if the size and shape does not accommodate 8 wafers, the maximum number of wafers allowed should be placed In patients undergoing surgery and intracranial implantation of carmustine wafers for recurrent malignant glioma, chemotherapy is held for at least 4 weeks (6 weeks for nitrosoureas) prior to and 2 weeks after surgery. ^{1,5}

BC Cancer usual dose noted in ***bold, italics***

Topical: Cycle Length:
n/a: ***0.4% ointment in white petrolatum applied once daily to individual lesions or regional areas.***^{20-22,44}
Rub into skin surface to apply and wash off after 6-8 hours with soap and water²².

OR
n/a: 10 mg daily (as an alcoholic solution or ointment) usually applied once daily for 7-14 weeks (maximum 17 weeks). If inadequate response, a second course of topical therapy is administered after a rest interval of 6 weeks, using 20 mg daily for 4-8 weeks, as tolerated.^{1,11}

Concurrent radiation:

- carmustine injection¹³: consolidation irradiation may be required to residual masses post transplant after count recovery and overall improvement
- implantable carmustine-impregnated wafer⁵: external beam radiation initiated no sooner than 3 weeks after implantation

Dosage in myelosuppression: modify according to protocol by which patient is being treated; suggested dose modification⁴⁰; not to be used for BMT dosing

ANC x 10 ⁹ /L	Platelets x 10 ⁹ /L	Percent of prior dose to be given
>1.5	>125	100%
1-1.5	100-125	75%
<1	<100	omit

Dosage in renal failure⁴⁵: GFR <10 mL/min: discontinue

Dosage in hepatic failure³: dosage adjustment may be necessary based on liver function test results, no specific guidelines available

Dosage in dialysis⁴⁵: no information found

Children:

Intravenous⁴⁶: Cycle Length:
4-6 week: 200-250 mg/m² IV for one dose on day 1
(total dose per cycle 200-250 mg/m²)

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