DRUG NAME: Carmustine

SYNONYM(S): BCNU[1]

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-dose[4] is defined here as >200 mg/m^2.

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 reference[4] unless specified otherwise.

Developed: September 1994
Revised: 1 December 2023

USES:

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

Primary uses:	***Other uses:***
*Brain tumours	Glioblastoma[10] (implantable carmustine-impregnated wafer)
*Glioma (implantable carmustine-impregnated wafer)	Lymphoma, cutaneous T-cell[1,11] (topical carmustine)
*Lymphoma, Hodgkin's disease	
*Lymphoma, non-Hodgkin's	
*Multiple myeloma	
*Melanoma	
*Gastrointestinal cancer	

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- Dose-related ***pulmonary toxicity*** is reported with carmustine injection; patients receiving cumulative doses more than 1,400 mg/m^2 are at higher risk. Single doses of >450 mg/m^2 may be associated with the development of acute lung injury in approximately 20% of patients.[7]
- The amount of alcohol in the intravenous formulation may affect the ability to drive or operate machinery.[12]

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.[13] 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: In animal studies, carmustine is embryotoxic and teratogenic at doses equivalent to human doses.[14]

Breastfeeding is contraindicated as carmustine 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 ≥ 5% higher in the treatment group.

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CARMUSTINE INJECTION:

High-dose[4] is defined here as >200 mg/m^2.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***[15]	
blood/bone marrow/ febrile neutropenia	anemia (1-10%)[7]
	myelosuppression (>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	*extravasation hazard:* vesicant[16]
	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]; incidence increased with administration times <1-2 h[17]
	hyperpigmentation (>10%)[7] with accidental skin contact; transient[3]
	injection site reaction; see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential*[18]: >250 mg/m^2 high; ≤250 mg/m^2 high-moderate
	anorexia (1-10%)[7]
	constipation (1-10%)[7]
	diarrhea (1-10%)[7]
	nausea and vomiting (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 (>10%)[7]; including transient conjunctival flushing and blurred vision, retinal hemorrhages
pain	headache[1]
	muscular pain (<1%)
pulmonary	***pulmonary toxicity*** (≤30%); see paragraph following **Side Effects** table
	pneumonitis[19] (20% for doses >450 mg/m^2)[19]; see paragraph following **Side Effects** table
	interstitial fibrosis (<1%, ≤50% for cumulative doses >1,400 mg/m^2)[7]
renal/genitourinary	***renal toxicity***[6,10](<1% for cumulative doses <1,000 mg/m^2)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***[15]	
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 reference[4] unless specified otherwise.

IMPLANTABLE CARMUSTINE-IMPREGNATED WAFER:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***[20]	
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 [20]
	wound healing complications at site of implantation[21] (12%); including cerebrospinal fluid leaks, subdural fluid collection and impaired wound healing
endocrine	Cushing's syndrome (3%)[1]
	diabetes mellitus (5%)[1]
gastrointestinal	*emetogenic potential:* rare
	constipation (1%)
	dysphagia (1%)
	vomiting (2%)
hemorrhage	hemorrhage, gastrointestinal (1%)
infection	***intracranial infection, meningitis, or abscess***[5] (1-10%)[7]
	oral moniliasis (3%)
lymphatics	edema, cerebral (1-10%)[7]

Developed: September 1994
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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***[20]	
	edema, peripheral (3%)
metabolic/laboratory	hyponatremia (3%)
	hypokalemia (1%)
	hyperglycemia (2%)
neurology[7]	amnesia (1-10%)
	abnormal thinking (3%)
	aphasia (1-10%)
	ataxia (1-10%)
	confusion (1-10%)
	convulsion (1-10%)
	dizziness (1-10%)
	hemiplegia (1-10%)
	hydrocephalus (1-10%)
	monoplegia (2%)
	peritumoural edema after wafer placement[22]
	seizures (>10%)
	somnolence (1-10%)
	stupor (1-10%)
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 reference[5] unless specified otherwise.

Developed: September 1994
Revised: 1 December 2023

TOPICAL CARMUSTINE:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	leucopenia (4-10%)[23-25]; 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 reference[23] 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.[23,25] The reaction may manifest as hyperpigmentation in individuals with dark hair or dark complexions.[24,26] Erythema tends to be accentuated in body folds, the groin area, and axillae.[23] With total body applications, reactions usually appear within 4-8 weeks.[24,25] 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.[23,25,27]

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/m^2/min to avoid excessive flushing, agitation, and hypotension.[7]

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]

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 fibrosis and ***pulmonary infiltrates*** can occur with carmustine injection. Pulmonary toxicities[28] are more common with prolonged therapy and with cumulative doses >1,400 mg/m^2; 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. Monitor pulmonary function tests 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 pulmonary fibrosis, BCNU ***pneumonitis***[19] (also known as BCNU lung or idiopathic pneumonia syndrome[29-31]) may occur following a single dose or course of therapy. BCNU pneumonitis requires emergency treatment as it is potentially fatal.[15] Patients typically present 30-100 days after autologous BMT with fever, cough, dyspnea and pulmonary infiltrates on x-ray.[19] Risk factors include those identified for pulmonary fibrosis, as well as female sex.[29,32] It has been suggested that doses less than 475 mg/m^2 may reduce the risk,[33] particularly in females.[29]

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However, BCNU pneumonitis is also reported at lower doses (e.g., 300 mg/m^2). Treatment includes high-dose prednisone, as well as antibiotics if pneumonia is suspected.[15]

INTERACTIONS:

Table refers to IV administration only. Interactions with the implantable carmustine-impregnated wafer and compounded topical formulation have not been evaluated.[5]

AGENT	EFFECT	MECHANISM	MANAGEMENT
cimetidine[34]	delayed, major, suspected; increased carmustine toxic effect	possible inhibition of carmustine metabolism	avoid concomitant use
digoxin tablets[34,35]	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[28,36,37]	increased risk of pulmonary toxicity	melphalan may reduce the threshold for carmustine-induced pulmonary toxicity	caution; monitor for pulmonary toxicity
phenytoin[34]	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:

Injection: SteriMax Inc. supplies carmustine as 100 mg single use (preservative free) vials of lyophilized powder. Store in fridge. Supplied diluent is dehydrated alcohol injection.[12]

Additional information:

- Carmustine powder should appear as dry flakes or a dry, rigid mass. Carmustine has a low melting point and is subject to liquefaction at temperatures greater than 27 ºC. Discard if oily film is present as this is a sign of disintegration.[12]

Wafer: Arbor Pharmaceuticals LLC supplies ***c***armustine in a polifeprosan wafer. It is 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. The product must be stored at or below -20ºC. Unopened foil pouches may be kept at ambient room temperature for a maximum of six hours.[5]

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:

- accidental contact of carmustine with the skin has caused burns and excessive pigmentation in affected areas[12]

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- to facilitate mixing, allow powder and supplied diluent (dehydrated alcohol) to come to room temperature prior to mixing[12]
- precipitation may occur following refrigeration of the reconstituted solution; precipitates may be dissolved by warming the vial to room temperature and gently shaking[12]
- diluted carmustine is unstable in PVC containers; use glass or polypropylene containers for preparation[12]
- alternative reconstitution directions have been suggested to minimize the volume of ethanol used; however, there is limited evidence to support their clinical use[38-41]
- protect diluted carmustine from light during storage and administration[12]
- prior to administration, final product should be gently shaken for approximately 10 sec to remix bag contents[12]
- administer carmustine using non-PVC administration sets[12]

Additional information for topical carmustine ointment:
To yield a 0.4% ointment in white petrolatum:
- Reconstitute each 100 mg carmustine vial with 3 mL absolute alcohol (supplied diluent) to give 33.3 mg/mL. Shake to dissolve.
- Withdraw vial contents and mix with 25 g of white petrolatum per vial.[26]

The final product is stable for 6 months in the refrigerator[25] or 3 months at room temperature.[26] A change in colour to brown indicates occurrence of oxidation, and the ointment should be discarded.[25]

PARENTERAL ADMINISTRATION:

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

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Intratumoural	implantable carmustine-impregnated wafer
Direct intravenous	no information found
Intermittent infusion	***over 1-2 h***; administer using non-PVC administration set[12]
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:	
Intravenous:	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])

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

	Cycle Length: 6 weeks[42]:	***100 mg/m² IV for one dose on day 1*** (total dose per cycle 100 mg/m²)
	6-8 weeks[7]:	150-200 mg/m² 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/m²)
	6-8 weeks[7]:	75-120 mg/m² IV once daily for 2 consecutive days starting on day 1 (total dose per cycle 150-240 mg/m²)
	6-8 weeks[7]:	40-80 mg/m² IV once daily for three consecutive days starting on day 1 (total dose per cycle 120-240 mg/m²)
	Bone marrow transplant[43,44]:	combination therapy***: 500 mg/m² IV for one dose*** (on day -2) (total dose 500 mg/m²) **Note: these doses are fatal without bone marrow/stem cell transplant.**
	Bone marrow transplant[45]*:*	combination therapy: ***300 mg/m² IV for one dose*** (on day -6) (total dose 300 mg mg/m²) **Note: these doses are fatal without bone marrow/stem cell transplant.**
Intratumoural[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 surgery and for 2 weeks after surgery.[1,5]
Topical:	n/a:	***0.4% ointment in white petrolatum applied once daily*** to individual lesions or regional areas[23-25,46] Rub into skin surface to apply and wash off after 6-8 hours with soap and water.[25]
	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]

Developed: September 1994
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BC Cancer usual dose noted in ***bold, italics***

Concurrent radiation:

Cycle Length:

- carmustine injection[15]: consolidation irradiation may be required to residual masses post-transplant after count recovery and overall improvement
- implantable carmustine-impregnated wafer[5]: 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 modification[42] (NOT to be used for BMT dosing)

ANC (x 10^9/L)	**Platelets** (x 10^9/L)	**Dose** (as percentage of prior dose)
>1.5	>125	100%
1-1.5	100-125	75%
<1	<100	omit

Dosage in renal failure[47]:

GFR <10 mL/min: discontinue

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

no information found; dosage adjustment may be necessary based on liver function test results[3]

Dosage in dialysis[47]:

no information found

Children:

Cycle Length:

Intravenous[48]:

4-6 week: 200-250 mg/m^2 IV for one dose on day 1 (total dose per cycle 200-250 mg/m^2)

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Developed: September 1994
Revised: 1 December 2023