

DRUG NAME: Lomustine**SYNONYM(S):** CCNU¹**COMMON TRADE NAME(S):** CeeNU®**CLASSIFICATION:** alkylating agent,² cytotoxic³*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Lomustine is a highly lipid-soluble nitrosurea compound.⁴ Unlike carmustine, it is administered orally. Lomustine, a monofunctional alkylating agent, alkylates DNA and RNA, can cross-link DNA, and inhibits several enzymes by carbamoylation.^{5,6} It is cell cycle phase-nonspecific. Cross-resistance between carmustine and lomustine has occurred.¹

PHARMACOKINETICS:

Oral Absorption	rapidly absorbed ¹	
Distribution	widely distributed ¹	
	cross blood brain barrier?	passes readily; $\geq 50\%$ of concurrent plasma concentrations
	volume of distribution	no information found
	plasma protein binding	50% ⁷
Metabolism	hepatic ⁸	
	active metabolite(s)	yes ¹
	inactive metabolite(s)	yes ¹
Excretion	renal ⁷ ; respiratory <10% as CO ₂	
	urine	metabolites
	feces	<5% ⁷
	terminal half life	16-72 h ⁷ active metabolite ⁷ : 31.2-48 h
	clearance	no information found

Adapted from standard reference² unless specified otherwise.**USES:****Primary uses:**

- *Brain tumours
- *Breast cancer
- *Lung cancer
- *Lymphoma, Hodgkin's
- *Melanoma

*Health Canada approved indication

Other uses:Colon cancer⁷**SPECIAL PRECAUTIONS:**

Caution: Dose-related pulmonary toxicity may occur; patients receiving cumulative doses >1,100 mg/m² are at higher risk.² For more information, see paragraph following **Side Effects** table.

Carcinogenicity: Lomustine is carcinogenic in rats and mice, producing significant increase in tumour production at doses approximating human doses.²

Mutagenicity: Not reported to be Mutagenic in Ames test and mammalian *in vitro* mutation test.⁹ Lomustine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.¹⁰

Fertility: Lomustine affects fertility in male rats at doses somewhat higher than human doses.² Prolonged azoospermia in humans likely.¹¹

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). No congenital anomalies were observed in three children of women who had been treated in childhood or adolescence with lomustine for cancer.¹²

Breastfeeding is not recommended due to the potential secretion into breast milk.¹

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.¹³ When placebo-controlled trials are available, adverse events are included if the incidence is $\geq 5\%$ higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood/bone marrow/ febrile neutropenia	anemia (1-10%) ⁷
	<i>leukopenia (>10%)⁷: onset 14 days, nadir 28-35 days, recovery 42 days; cumulative, dose-related, delayed;</i> see paragraph following Side Effects table
	<i>thrombocytopenia (> 10%)⁷: onset 14 days, nadir 28-35 days, recovery 42 days; cumulative, dose-related, delayed;</i> see paragraph following Side Effects table
constitutional symptoms	lethargy
dermatology/skin	alopecia (1-10%) ^{1,7}
	rash (1-10%) ⁷
gastrointestinal	<i>emetogenic potential: low-moderate¹⁴</i>
	<i>anorexia; begins 2-3 days after oral dose, and may last for several days¹</i>
	diarrhea (1-10%) ⁷
	<i>nausea and vomiting (45-100%)¹; typically begins within 45 min-6 h after oral dose and lasts for less than 24 h; frequency and duration can be reduced by the administration of lomustine to fasting patients</i>
	stomatitis (1-10%) ⁷
hepatobiliary/pancreas	hepatotoxicity (<1%) ⁷
metabolic/laboratory	alkaline phosphatase; reversible increase ⁸
	bilirubin; reversible increase ⁸
	transaminase; reversible increase ⁸ (1-10%) ¹³
neurology	ataxia

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	disorientation
	dysarthria
ocular/visual	visual disturbances ¹ (<1%)
pulmonary	pulmonary toxicity (<1%); see paragraph following Side Effects table
renal/genitourinary	renal toxicity (1-10%) ⁷ ; decreased kidney size, ² progressive azotemia and renal failure; dose-related
secondary malignancy	acute leukemia after long-term use
	bone marrow dysplasias after long-term use
sexual/reproductive function	prolonged azoospermia likely, ¹¹ conclusive data not available

Adapted from standard reference² unless specified otherwise.

Myelosuppression: The most frequent and serious toxicity of lomustine is delayed myelosuppression.² It is cumulative and usually occurs 28-42 days after drug administration and is dose-related. Thrombocytopenia is usually more severe than leukopenia, but both may be dose-limiting. Anemia also occurs, but is less frequent and less severe. Due to the delayed and cumulative myelosuppressive effects, lomustine is usually given at intervals of at least 6 weeks. However, repeat courses of lomustine should not be administered until leukocyte and platelet counts have returned to acceptable levels. For more information, see **Dosage Guidelines**.

Pulmonary toxicity: Pulmonary fibrosis and pulmonary infiltrates can occur rarely with lomustine use.¹⁰ Pulmonary toxicity is more common with cumulative doses exceeding 1100 mg/m²; however, it has occurred with lower doses. Early onset pulmonary toxicity can occur as early as 6 months from the start of therapy; however, late onset pulmonary fibrosis has been reported up to 15 years after treatment. Patients with baseline Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DL_{co}) below 70% of predicted levels are particularly at risk. Pulmonary function tests should be performed at baseline and throughout treatment. Patients should be advised to immediately report any signs of respiratory complications, and therapy should be discontinued.

INTERACTIONS: No documented drug interactions.

Lomustine is a major CYP2D6 substrate.⁷ Lomustine is a weak CYP2D6 and CYP3A4 inhibitor.⁷

SUPPLY AND STORAGE:

Capsules: Bristol Laboratories of Canada supplies lomustine as a 10 mg, 40 mg and 100 mg capsule.² Protect from light. Avoid excessive heat (over 40 °C).

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:

BCCA usual dose noted in ***bold, italics***

Oral:	Cycle Length: 4-6 weeks ¹⁵ :	<i>110 mg/m² PO for one dose on day 1 (total dose per cycle 110 mg/m²)</i> <ul style="list-style-type: none"> • <i>Round dose to the nearest 10 mg.</i> • <i>Administering on an empty stomach^{1,2} (one hour before or two hours after eating)⁷ may help reduce nausea.</i>
	6 weeks ¹⁶⁻¹⁸ :	<i>75-130 mg/m² PO for one dose on day 1 (total dose per cycle 75-130 mg/m²)</i> <ul style="list-style-type: none"> • <i>Round dose to the nearest 10 mg.</i> • <i>Administering on an empty stomach^{1,2} (one hour before or two hours after eating)⁷ may help reduce nausea.</i>
	6-8 weeks ¹⁹ :	<i>130 mg/m² (range 80-160 mg/m²) PO for one dose on day 1 (total dose per cycle 130 mg/m² [range 80-160 mg/m²])</i> <ul style="list-style-type: none"> • <i>Round dose to the nearest 10 mg.</i> • <i>Administering on an empty stomach^{1,2} (one hour before or two hours after eating)⁷ may help reduce nausea.</i>

Concurrent radiation: currently not used in neuro-oncology¹³

Dosage in myelosuppression: modify according to protocol by which patient is being treated; suggested dose modification¹⁷:

ANC x 10 ⁹ /L		Platelets x 10 ⁹ /L	Dose
>1.5	or	>100	give 100%
1.0-1.5	and/or	80-100	give 80%
<1.0	and/or	<80	delay 1 week and resume at 60% of the original dose <ul style="list-style-type: none"> • Note: this will be the new 100% dose thereafter.

Dosage in renal failure:

Suggested dose modification ⁷ :	
Creatinine clearance (mL/min)	Dose
10-50	75%
<10	50%

Dosage in hepatic failure: hold lomustine if AST/SGT >5 x ULN or bilirubin >25 µmol/L until liver function returns to normal^{17,18}

Dosage in dialysis: hemodialysis⁷: supplemental dose for dialysis is not required

Children:Oral⁶:

Cycle Length:

4-6 weeks:

100-150 mg/m² for one dose on day 1
(total dose per cycle 100-150 mg/m²)For more information on oral administration, see **Dosage Guidelines: Adults.****REFERENCES:**

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