Drug Monograph

A - Drug Name

lomustine

SYNONYM(S): CCNU

COMMON TRADE NAME(S): CeeNU®

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B - Mechanism of Action and Pharmacokinetics

Lomustine is a highly lipophilic nitrosourea compound, which undergoes hydrolysis *in vivo* to form reactive metabolites. These metabolites cause alkylation and cross-linking of DNA. Other biologic effects include inhibition of DNA and RNA synthesis. Nitrosoureas generally lack cross-resistance with other alkylating agents; however, cross-resistance between lomustine and carmustine has been described.

Absorption	Bioavailability	Rapidly and completely absorbed (in 30-60 minutes)
Distribution	Highly lipid soluble, rapid and extensive tissue distribution.	
	Cross blood brain barrier?	Yes (CSF achieves ≥ 50% of plasma levels)
	PPB	No information found
Metabolism	Actively metabolized by hepatic microsomal enzyme oxidation system (P450)	
	Active metabolites	Yes

	Inactive metabolites	Yes
Elimination	Predominantly renal; < 5% in feces.	
	Urine	~50% within 24 hours (metabolites)
	Half-life	16-48 hours (metabolites)

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C - Indications and Status

Health Canada Approvals:

- Brain tumours
- Hodgkin's lymphoma

Refer to the product monograph for a full list and details of approved indications

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

Extravasation Potential: Not applicable

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Alopecia (rare)	E
Gastrointestinal	Mucositis (rare)	E
	Nausea (or vomiting - 45-100%)	I
	Vomiting	I
General	Fatigue	E
Hematological	Myelosuppression (65%)	D
Hepatobiliary	↑ LFTs (transient, unusual)	E
Neoplastic	Leukemia (secondary)	L

	MDS	L
Nervous System	Ataxia (rare)	E
	Confusion (disorientation - rare)	E
	Dysarthria (rare)	E
Ophthalmic	Blurred vision (blindness - rare)	E
	Optic nerve disorder (optic atrophy - rare)	E
Renal	Nephrotoxicity	L
Reproductive and breast disorders	Infertility	L
Respiratory	Lung infiltrate (rare, dose-related)	D
	Pulmonary fibrosis (rare, dose-related)	D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

Myelosuppression is the principal dose limiting toxicity, may be delayed in onset (4-6 weeks) and is cumulative.

Nausea and vomiting is very common. Nausea may be minimized by giving the dose on an empty stomach; antiemetics should be used prophylactically.

Pulmonary toxicity with infiltrates and pulmonary fibrosis have been reported at cumulative doses usually greater than 1,100 mg/m2. The onset of toxicity has varied from 6 months after initiation of therapy, to as late as 15 years after.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Dose should be calculated to the nearest 10 mg to accommodate capsule sizes.

Adults:

Normal marrow function:
Oral: 130 mg/m² Every 6 weeks

Compromised marrow function:
Oral: 100 mg/m² Every 6 weeks

In combination: Reduced dosing has been used. Refer to specific protocol.

Dosage with Toxicity:

Dosage with myelosuppression:

- Do not retreat until leukocytes > 4 x 10^9/L and platelets > 100 x 10^9/L.
- Reduce next dose according to nadir counts as follows:

Nadir after prior dose		
Leukocytes (x 10^9/L)	Platelets (x 10^9/L)	Lomustine (% previous dose)
≥ 4	≥ 100	100 %
3 – <4	75 – <100	100 %
2 – <3	25 – <75	70 %
<2	< 25	50 %

Dosage with Hepatic Impairment:

No specific recommendations found. Although the metabolites are mainly excreted by the kidney, the liver is involved in lomustine metabolism. Monitor closely in patients with hepatic impairment and adjust dose based on hematologic toxicity.

Dosage with Renal Impairment:

The following dose is suggested for renal impairment (Aronoff et al):

Creatinine clearance (mL/min)	Lomustine (% previous dose)
> 50	100 %
10 – 50	75 %
< 10	50 %

Other references suggested to discontinue lomustine for creatinine clearance < 30mL/min (Krens et al 2019, Kintzel et al 1995).

Dosage in the elderly:

No specific recommendations found.

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F - Administration Guidelines

- Lomustine capsules should be swallowed whole with a glass of water, and not crushed, dissolved, or opened.
- Administer lomustine on an empty stomach to prevent nausea and vomiting.
- If the patient vomits after 30-45 minutes, do not repeat the dose. Studies indicated that the nausea and vomiting occur after drug absorption has taken place.
- Store at room temperature. Protect from light. Avoid excessive heat (over 40°C).

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or any of its components
- Patients with severe leukopenia and/or thrombocytopenia

Other Warnings/Precautions:

- Use extreme caution in patients with FVC or DL_{CO} < 70% of normal due to increased risk for pulmonary toxicity; monitor patients closely.
- Use of live vaccines is not recommended in immunosuppressed patients, including patients treated with lomustine, due to increased risk of fatal systemic vaccine disease.

Other Drug Properties:

- Carcinogenicity: Yes
  Secondary malignancies, including acute leukemia and bone marrow dysplasias, have been reported following nitrosoureas therapy.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Mutagenicity: Yes
- Teratogenicity: Yes
- Pregnancy:
  Lomustine is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose.
- Excretion into breast milk: Likely
  Breastfeeding is not recommended during treatment.
- Fertility effects: Probable
  Documented in animal studies with male animals. Consider sperm preservation prior to treatment.

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H - Interactions

No drug interaction studies have been performed. Animal studies suggest that CYP2C19, CYP2D6 and CYP3A4 are involved in lomustine metabolism.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cimetidine	Potentiates marrow toxicity of lomustine	Possibly by ↓ metabolism of lomustine	Do not use cimetidine; choose a different H2 blocker
Enzyme-inducing antiepileptic drugs (e.g. carbamazepine, phenytoin)	May affect antiepileptic and lomustine efficacy	Possible ↑ in drug metabolism due to enzyme induction	Avoid concurrent use. If unavoidable, monitor both drugs for reduced efficacy.
Enzyme inhibitors drugs (e.g., valproic acid)	May ↑ lomustine toxicity	Possible ↓ in drug metabolism due to enzyme inhibition	Caution.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, before each cycle, and as clinically indicated (more frequently after initiation)
Liver and renal function tests	Baseline and before each cycle
Pulmonary function test and pulmonary exam	Baseline and as clinically indicated
Clinical toxicity assessment for infection, bleeding, lung and GI effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- lomustine ()

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K - References

Aronoff, G. R (2007). Drug prescribing in renal failure : dosing guidelines for adults (5th ed.). American College of Physicians

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Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. Cancer Treat Rev 1995;21(1):33-64.

Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08..

Lomustine: Cancer Drug Manual , British Columbia Cancer Agency (BCCA) Drug Manual, Jun 5, 2018.

Lomustine: Chemotherapy Drug Manual, Clin-eguide.

Prescribing Information: Gleostine® (lomustine). NextSource Biotechnology, LLC. September 2018.

Product Information: CeeNU® (lomustine). Bristol-Myers Squibb Australia Pty Ltd. 22 May 2024.

Product Monograph: CeeNU® (lomustine). Bristol-Myers Squibb Canada, February 20, 2009 and February 17, 2016.

Summary of Product Characteristics: Lomustine “medac” 40 mg. medac, 04/2024.

August 2024 Updated Pharmacokinetics, Indications, Dosing, Administration Guidelines, Special Precautions, Interactions and Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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