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Gleostine®
(lomustine) Capsules

A Guide for Healthcare Professional

For patients with primary or metastatic brain cancer or Hodgkin's disease

NEXTSOURCE PHARMACEUTICALS

The **Gleostine®® (lomustine)** brand has replaced all versions of lomustine products including **CeeNU®,** a former BMS product.

WARNINGS

Gleostine®® (lomustine) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of Gleostine®® (see WARNINGS and ADVERSE REACTIONS).

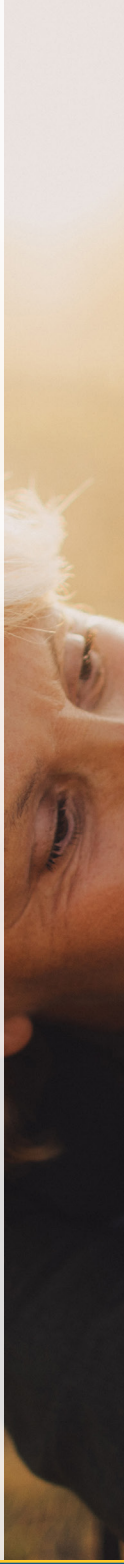
Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of Gleostine®® should not be given more frequently than every 6 weeks.

The bone marrow toxicity of Gleostine®® is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see dosage adjustment table under DOSAGE AND ADMINISTRATION)

INDICATIONS AND USAGE

Brain Tumors
Gleostine® is indicated for the treatment of patients with primary and metastatic brain tumors following appropriate surgical and/or radiotherapeutic procedures.

Hodgkin's Lymphoma
Gleostine® is indicated as a component of combination chemotherapy for the treatment of patients with Hodgkin's lymphoma whose disease has progressed following initial chemotherapy.



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CLINICAL PHARMACOLOGY

Mechanism of Action
Lomustine alkylates DNA and RNA. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins.

Pharmacodynamic
The pharmacodynamics of lomustine are unknown.

Pharmacokinetics
SPECIFIC POPULATIONS
The impact of patient specific (e.g., age, sex, and race) or disease (e.g., renal or hepatic impairment) characteristics on the pharmacokinetics of lomustine is unknown.

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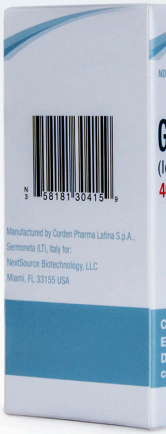
DISTRIBUTION
Lomustine crosses the blood-brain barrier.

ELIMINATION
The serum half-life of lomustine metabolites ranges from 16 hours to 48 hours.

Metabolism: Metabolic pathways involved in the elimination of lomustine have not been characterized.

Excretion: Following oral administration of radioactive lomustine at doses ranging from 30 mg/m^2 to 100 mg/m^2, approximately half of the radioactivity administered was excreted in the urine in the form of degradation products within 24 hours.

10 mg



DOSAGE AND ADMINISTRATION

Important Prescribing and Dispensing Information
PRESCRIBE ONLY ONE DOSE FOR EACH TREATMENT CYCLE. DO NOT DISPENSE ENTIRE CONTAINER. Dispense only a sufficient number of capsules for one dose. Confirm the total dose prescribed by the physician and the appropriate combination of capsule strengths. Dispense only the appropriate number of Gleostine® capsules required for the administration of a single dose. The prescribed dose may consist of two or more different strengths and colors of capsules.

Instruct patients that Gleostine® is taken as a single oral dose and will not be repeated for at least 6 weeks. Taking more than the recommended dose causes toxicities, including fatal outcomes [see Warnings and Precautions (5.2) and Overdosage (10)]. Gleostine® is a cytotoxic drug. Follow applicable special handling and disposal procedures.

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing Gleostine® capsules. Do not break Gleostine® capsules; avoid exposure to broken capsules. If dermal contact occurs, wash areas of skin contact immediately and thoroughly.

Recommended Dose
The recommended dose of Gleostine® in adult and pediatric patients is 130 mg/m^2 taken as a single oral dose every 6 weeks. Round doses to the nearest 5 mg. Give

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40 mg

100 mg

as a single oral dose and do not repeat for at least 6 weeks. Reduce dose to 100 mg/m^2 every 6 weeks in patients with compromised bone marrow function. Also reduce dose accordingly when using with other myelosuppressive drugs.

Dose Modifications
Perform weekly complete blood counts and withhold each subsequent dose for more than 6 weeks if needed until platelet counts recover to 100,000/mm^3 or greater and leukocytes recover to 4000/mm3 or greater [see Warnings and Precautions (5.1)].

Modify each dose of Gleostine® according to the hematologic response of the preceding dose as described in table below:

Nadir After Prior Dose		Dose Adjustment
Leukocytes (/mm^3)	Platelets (/mm^3)	
≥ 4000	≥ 100,000	None
3000 – 3999	75,000 – 99,999	None
2000 – 2999	25,000 – 74,999	Reduce dose by 30%
< 2000	< 25,000	Reduce dose by 50%

DOSAGE FORMS AND STRENGTHS

Gleostine® capsules are available in four strengths, distinguishable by the color of the capsules, in individual bottles of 5 capsules each. [see Table below].

Overdosage

Overdosage with Gleostine® has occurred, including fatal cases [see Dosage and Administration (2.1), Warnings and Precautions (5.2)]. Overdosage causes severe myelosuppression, as well as abdominal pain, diarrhea, vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath. No antidotes exist for Gleostine® overdosage.

HOW IS GLEOSTINE® SUPPLIED?

Gleostine® capsules are available in four strengths, distinguishable by the color of the capsules, in individual bottles of 5 capsules each. [see Table below].

100 mg capsules (green/green)

40 mg capsules (white/green)

10 mg capsules (white/white)

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STORAGE AND HANDLING

Gleostine® should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Avoid temperatures over 40°C (104°F).

Gleostine® is a cytotoxic drug. Follow applicable special handling and disposal procedures.

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing Gleostine® capsules. Do not break Gleostine® capsules; avoid exposure to broken capsules. If dermal contact occurs, wash areas of skin contact immediately and thoroughly.

CONTRAINDICATIONS

None

CAPSULE DESCRIPTION

Moss green cap and body, imprinted in black ink, with "CPL" over "3042" on the cap and "100 mg" on the body of the capsule.

White cap and a moss green body, imprinted in black ink, with "CPL" over "3041" on the cap and "40 mg" on the body of the capsule.

White cap and body, imprinted in black ink, with "CPL" over "3040" on the cap and "10 mg" on the body of the capsule.

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PATIENT COUNSELING

Myelosuppression
Advise patients that periodic assessment of their blood counts are required. Advise patients to contact their healthcare provider for new onset of bleeding or fever or symptoms of infection [see Warnings and Precautions (5.1)].

Overdosage
Advise patients that toxicity including fatal toxicity occurs with Gleostine® overdosage [see Warnings and Precautions (5.2), Overdosage (10), Dosage and Administration (2.1)].

Advise patients to take Gleostine® as directed:

- Gleostine® is taken as a single oral dose that will not be repeated for at least 6 weeks.
- Use of the recommended dose at less than 6 week intervals leads to toxicities including fatal toxicities.
- Each dose may consist of 2 or more different strengths and colors of capsules.

Pulmonary Fibrosis
Advise patients to contact their healthcare provider for new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.3)].

Hepatotoxicity
Inform patients that Gleostine® can cause hepatotoxicity and that liver function monitoring during treatment is necessary [see Warnings and Precautions (5.5)].

Nephrotoxicity
Inform patients that Gleostine® can cause nephrotoxicity and that renal function and electrolyte monitoring during treatment is necessary [see Warnings and Precautions (5.6)].

Embryo-Fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.7), Use in Specific Populations (8.1)].

Advise females of reproductive potential to use effective contraception during treatment with Gleostine® and for at least 2 weeks after the final dose [see Use in Specific Populations (8.3)].

Advise male patients with female partners of reproductive potential to use condoms during treatment with Gleostine® and for 4 months after the final dose [see Use in Specific Populations (8.3)].

Lactation
Advise women not to breastfeed during treatment with Gleostine® and for 2 weeks after the final dose [see Use in Specific Populations (8.2)].

Infertility
Advise females and males of reproductive potential of the potential for reduced fertility from Gleostine® [see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary: Based on animal data and its mechanism of action, Gleostine® can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no available data on Gleostine® exposure in pregnant women. Lomustine was teratogenic in rats and embryotoxic in rabbits at total dose levels approximately two to four times the total human dose of 130 mg/m^2 over 6 weeks (0.18 to 0.27 times the single human dose of 130 mg/m^2) based on BSA [see Data]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data (Animal): Lomustine was administered by intraperitoneal injection daily to pregnant rats during the period of organogenesis at dose levels of 0, 2, 4, 6, and 8 mg/kg. Resorption rates and post-implantation loss occurred at doses greater than or equal to 4 mg/kg (approximately 0.18 times the clinical dose

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of 130 mg/m^2 based on BSA or approximately twice the total clinical dose of lomustine over 6 weeks). Malformations (omphalocele, ectepia cordis, scoliosis, syndactyly, hydrocephalus, microphthalmia, anophthalmia, anomalies of aortic arch, dextrocardia, malpositioning of the ovaries and testes, sternoschisis, and shortened/misshapen bone of the fore or hind limbs) and decreased fetal body weight occurred at all dose levels. In pregnant rabbits treated with lomustine at 3 mg/kg (approximately 0.27 times the 130 mg/m^2 clinical dose based on BSA or approximately four times the total clinical dose of lomustine over 6 weeks) during organogenesis, there were increases in abortions and decreases in surviving pup weight that persisted postnatally.

Lactation

Risk Summary: There is no information on the presence of lomustine or its metabolites in human milk, its effects on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from Gleostine®, advise women not to breastfeed during treatment with Gleostine® and for 2 weeks after the final dose.

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential
Contraception
Females: Based on animal data and its mechanism of action, Gleostine® can cause fetal harm [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment and for 2 weeks after the final dose.

Males: Based on Gleostine®'s mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment with Gleostine® and for 3.5 months after the final dose [see Clinical Pharmacology (12.1)].

Infertility: Based on animal findings and its mechanism of action, Gleostine® may result in reduced fertility in males and females of reproductive potential [see Nonclinical Toxicology (13.1)].

Pediatric Use
Pediatric use, including dose, is not based on adequate and well-controlled clinical studies.

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Geriatric Use
No data in the clinical studies of Gleostine® are available for patients 65 years of age and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Lomustine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.

WARNINGS AND PRECAUTIONS

Delayed Myelosuppression
Gleostine® causes myelosuppression that can result in fatal infections and bleeding. Myelosuppression from Gleostine® is delayed, dose-related, and cumulative. It usually occurs 4 to 6 weeks after drug administration and persists for 1 to 2 weeks. Thrombocytopenia is generally more severe than leukopenia. Cumulative myelosuppression from Gleostine® is manifested by greater severity and longer duration of cytopenias.

Monitor blood counts for at least 6 weeks after each dose. Do not give Gleostine® more frequently than every 6 weeks. Adjust dose based on nadir blood counts from prior dose [see Dosage and Administration (2.3)].

Risk of Overdosage
Fatal toxicity occurs with overdosage of Gleostine®. Dispensing or administering more than one dose can lead to fatal toxicity.

Prescribe only one dose at a time. Dispense only enough capsules for one dose. Both physician and pharmacist should emphasize to the patient that only one dose of Gleostine® is taken every 6 weeks [see Dosage and Administration (2.1) and Overdosage (10)].

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Pulmonary Toxicity
Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis occurs with Gleostine®. Patients with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLCO) are at increased risk. The onset of pulmonary toxicity occurs after an interval of 6 months or longer from the start of therapy, with cumulative doses of Gleostine® usually greater than 1100 mg/m^2.

Obtain baseline pulmonary function tests prior to initiating treatment and repeat frequently during treatment. Permanently discontinue Gleostine® in patients diagnosed with pulmonary fibrosis.

Secondary Malignancies
Secondary malignancies, including acute leukemia and myelodysplasia, occur with long term use.

Hepatotoxicity
Hepatic toxicity, manifested by increased levels of transaminases, alkaline phosphatase, and bilirubin occurs with Gleostine®. Monitor liver function.

WARNINGS AND PRECAUTIONS

Nephrotoxicity
Progressive renal failure with a decrease in kidney size occurs with Gleostine®. Monitor renal function.

Embryo-Fetal Toxicity
Based on animal data and its mechanism of action, Gleostine® can cause fetal harm when administered to a pregnant woman. Embryo-fetal toxicity and teratogenicity occurred in rats and rabbits receiving lomustine daily during organogenesis at doses approximately two to four times the total human dose of 130 mg/m^2 over 6 weeks (0.18 to 0.27 times the single human dose of 130 mg/m^2) based on body surface area (BSA). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Gleostine® and for 2 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Gleostine® and for 3.5 months after the final dose [see Use in Specific Populations (8.1, 8.3)].

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Delayed myelosuppression [see Warnings and Precautions (5.1)]
- Risks of overdosage [see Warnings and Precautions (5.2)]
- Pulmonary toxicity [see Warnings and Precautions (5.3)]
- Secondary malignancies [see Warnings and Precautions (5.4)]
- Hepatotoxicity [see Warnings and Precautions (5.5)]
- Nephrotoxicity [see Warnings and Precautions (5.6)]

The following adverse reactions associated with the use of Gleostine® were identified in clinical trials or postmarketing reports.

Because these reactions were reported from a population of uncertain size, it is not possible to estimate their frequency, reliability, or establishment a causal relationship to drug exposure.

- Gastrointestinal disorders: nausea, vomiting, and stomatitis
- Ocular disorders: optic atrophy, visual disturbances, and blindness
- Neurologic disorders: disorientation, lethargy, ataxia, and dysarthria
- Other: alopecia

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NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
Gleostine® is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses lower than those employed clinically.

In female rats, daily intraperitoneal treatment with lomustine for 2 weeks prior to mating with untreated males resulted in dose dependent decreases in number of corpora lutea and resorption rates with no live births at a dose of 3 mg/kg (approximately 0.14 times the recommended clinical dose of 130 mg/m^2 based on body surfacearea (BSA), or approximately twice the total clinical dose of lomustine over 6 weeks) and decreased pup survival during the first 4 postnatal days at doses greater than or equal to 1.5 mg/kg (a daily dose of approximately 0.06 times the recommended clinical dose of 130 mg/m^2 based on BSA or approximately equal to the total clinical dose of lomustine over 6 weeks).

Gleostine® may also result in decreased male fertility. Intraperitoneal injection of lomustine resulted in decreased fertility in male rats mated to untreated females based on decreased implantations and decreased fetal body weight at weekly doses greater than or equal to 5 mg/kg (approximately 0.23 times the single clinical dose of 130 mg/m^2 based on BSA, or approximately equal to the total clinical dose of lomustine over 6 weeks), and increased resorptions at doses greater than or equal to 2.5 mg/kg/week.

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REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J Health-Syst Pharm. 2006;63:1172–1193. 10

4. Polovich M, White JM, Kelleher LO, eds. 2005. Chemotherapy and biotherapy guidelines and recommendations for practice. 2nd ed. Pittsburgh, PA: Oncology Nursing Society.

Gleostine™

(lomustine) Capsules