

PRODUCT MONOGRAPH

PrCeeNU*

(Lomustine-CCNU)

Capsules; 10, 40 and 100 mg

Antineoplastic Agent

Bristol-Myers Squibb Canada
Montreal, Canada

Date of Preparation:
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CeeNU

(Lomustine - CCNU)

Capsules; 10, 40 and 100 mg

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: CeeNU (LOMUSTINE-CCNU) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW IS SEEN.

ACTION AND CLINICAL PHARMACOLOGY

It is generally agreed that CeeNU (lomustine-CCNU) acts as an alkylating agent but, as with other nitrosoureas, it may also inhibit several key enzymatic processes.

CeeNU may be given orally. Following oral administration of radioactive CeeNU at doses ranging from 30 mg/m² to 100 mg/m², about half of the radioactivity given was excreted within 24 hours. The serum half-life of the drug and/or metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at a physiological pH, CeeNU crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50 percent or greater than those measured concurrently in plasma.

INDICATIONS AND CLINICAL USES

CeeNU (lomustine-CCNU) is indicated as adjuvant therapy to surgery and radiotherapy or in combination therapy with other chemotherapeutic agents in the following:

1. Brain tumors - both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.
2. Lung Cancer - squamous cell, anaplastic large cell, and adenocarcinoma. CeeNU has been used alone and in combination with other appropriate antineoplastic drugs, such as cyclophosphamide.
3. Malignant melanoma - alone or in combination with other active drugs, such as vincristine.
4. Hodgkin's Disease - alone or in combination with other active drugs.
5. Breast carcinoma - in advanced disease after conventional therapy has failed.

CeeNU has been used in renal cell carcinoma although the response rate is low in this resistant cancer. Responses have also been observed with non-Hodgkin's lymphoma, ovarian and pancreatic carcinoma but data is insufficient to make a definite recommendation.

CONTRAINDICATIONS

CeeNU (lomustine-CCNU) should not be given to individuals who have demonstrated a previous hypersensitivity to it. Also it is contraindicated in patients having severe leukopenia and/or thrombocytopenia.

WARNINGS

CeeNU (lomustine-CCNU) should be administered by individuals experienced in the use of antineoplastic therapy.

Delayed 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 CeeNU.

Blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of CeeNU should not be given more frequently than every 6 weeks.

The bone marrow toxicity of CeeNU 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).

Caution should be used in administering CeeNU to patients with decreased circulating platelets, leukocytes or erythrocytes (see DOSAGE AND ADMINISTRATION).

Pulmonary toxicity from CeeNU appears to be dose related (see ADVERSE REACTIONS).

Long term use of nitrosoureas has been reported to be possibly associated with the development of secondary malignancies.

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

Pregnancy

Safe use in pregnancy has not been established. CeeNU is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patients should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Carcinogenesis, Mutagenesis, Impairment of Fertility

CeeNu is carcinogenic in rats and mice, producing a marked increase in tumour incidence in doses approximating those employed clinically.

Nitrosourea therapy does have carcinogenic potential. The occurrence of acute leukemia and bone

marrow dysplasias has been reported in patients following nitrosourea therapy.

CeeNU also affects fertility in male rats at doses somewhat higher than the human dose.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CeeNU, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PRECAUTIONS

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least six weeks after a dose.

Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DL_{co}) are particularly at risk.

Since CeeNU (lomustine-CCNU) may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

ADVERSE REACTIONS

1. **Gastrointestinal**: Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. The frequency and duration may be reduced by the use of antiemetics prior to dosing and by the administration of CeeNU (lomustine-CCNU) to fasting patients.
2. **Hematologic Toxicity**: The most frequent and most serious toxicity of CeeNU is delayed myelosuppression. It usually occurs four to six weeks after drug administration and is dose related. Thrombocytopenia occurs at about four weeks post-administration and persists for one to two weeks.

Leukopenia occurs at five to six weeks after a dose of CeeNU and persists for one to two weeks.

Approximately 65% of patients receiving 130 mg/m² develop white blood counts below 5000 /mm³. Thirty-six percent developed white blood cell counts below 3000 /mm³. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

CeeNU may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.

The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long term nitrosourea therapy. Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

3. Pulmonary Toxicity: Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely with CeeNU. Onset of toxicity has occurred after an interval of six months or longer from the start of therapy with cumulative doses of CeeNU usually greater than 1100 mg/m². There is one report of pulmonary toxicity at a cumulative dose of only 600 mg.

Delayed onset pulmonary fibrosis occurring up to 15 years after treatment has been reported in patients with intracranial tumors who received related nitrosoureas during their childhood and early adolescence.

4. Other Toxicities: Stomatitis, alopecia, anemia have been reported infrequently.

Neurological reactions such as disorientation, lethargy, ataxia and dysarthria have been noted in some patients receiving CeeNU. However, the relationship to medication in these patients is unclear.

5. Nephrotoxicity: Renal abnormalities consisting of decrease in kidney size, progressive azotemia and renal failure have been reported in patients who receive large cumulative doses after prolonged therapy with CeeNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.
6. Hepatotoxicity: A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase and bilirubin levels, has been reported in a small percentage of patients receiving CeeNU.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the case of overdosage, the patient should be treated symptomatically.

DOSAGE AND ADMINISTRATION

The recommended dose of CeeNU (Iomustine-CCNU) is 130 mg/m² as a single dose by mouth every 6 weeks.

In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m² every 6 weeks.

A repeat course of CeeNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm³; leukocytes above 4,000/mm³). Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

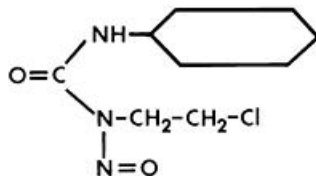
Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

Nadir After Prior Dose		Percentage of Prior Dose to be Given
Leukocytes	Platelets	
> 4000	> 100,000	100%
3000 - 3999	75,000 - 99,999	100%
2000 - 2999	25,000 - 74,999	70%
< 2000	< 25,000	50%

When CeeNU is used in combination with myelosuppressive drugs, the doses should be adjusted accordingly.

PHARMACEUTICAL INFORMATION

Chemistry:



Trade Name: CeeNU

Proper Name: Lomustine

Chemical Name: 1-(2-chloroethyl)-3 cyclohexyl-1-nitrosourea

Molecular Formula: C₉H₁₆ClN₃O₂

Molecular Weight: 233.71

Description: Yellow powder. Soluble in 10% ethanol (0.05 mg/mL) and in absolute alcohol (70 mg per mL). It is relatively insoluble in water (<0.05 mg/mL). It is relatively un-ionized at a physiological pH.

STABILITY

Unopened bottles of CeeNU (lomustine-CCNU) capsules are stable for 36 months at room temperature.

Storage: PROTECT FROM LIGHT. Avoid excessive heat (over 40°C).

AVAILABILITY

The capsules of CeeNU (lomustine-CCNU) are prepared in three dosage strengths: 10 mg, 40 mg, and 100 mg.

All capsules contain mannitol and magnesium stearate as inert ingredients. A desiccant packet is enclosed in each bottle of capsules.

CeeNu capsules are available as follows:

- 10 mg in amber bottles of 20 capsules
- 40 mg in amber bottles of 20 capsules
- 100 mg in amber bottles of 20 capsules

HANDLING AND DISPOSAL

1. Preparation of CeeNU (Iomustine-CCNU) should be done in a vertical laminar flow hood (Biological Safety Cabinet - class II)
2. CeeNU capsules should not be placed in automated counting machines. The counting and pouring of CeeNU should be done carefully and the equipment used should be rinsed with water and then thoroughly cleaned with detergent and water.
3. Personnel handling CeeNU should wear gloves, safety glasses, a mask and disposable protective clothing.
4. Vials and other materials which have come in contact with CeeNU should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.
5. Personnel regularly involved in the preparation and handling of CeeNU should have bi-annual blood examinations.

PHARMACOLOGY

The following is a summary of the data provided by the studies indicated in the attached list of references.

Kline et al used a biological procedure for the determination of drug levels of CeeNU (Iomustine-CCNU). The biological target was L1210 leukemia. A dose response curve was determined for the drug when given simultaneously with the inoculation of a designated number of leukemia cells, using % of cures and median survival time as the parameters of response. The drug was also administered at a series of time intervals prior to the inoculation of leukemia cells and the dose level equivalence at the time of leukemic inoculation was estimated by reference of the observed therapeutic response to that obtained for the standard curve. The curve for percentage retention of administered CeeNU had a shallow slope and the half-life of the drug in the host was estimated to be 94 minutes.

Oliverio et al studied the metabolic fate of CeeNU using the ^{14}C label in each of three positions of the molecule; the ethyl, carbonyl, and cyclohexyl moieties. In rodents, 24 hours after intraperitoneal or oral dose of the ethyl or cyclohexyl labelled CeeNU, 75% of the radioactivity appeared in the urine, while about 10-20% of carbonyl or ethyl labelled CeeNU was expired as $^{14}\text{CO}_2$. In dogs and monkeys, CeeNU was also rapidly degraded and excretion of ^{14}C was primarily in the urine. Plasma levels of ^{14}C fell off rapidly in the first hour followed by a slower disappearance. After an intravenous injection, the CSF/plasma ratio of ethyl labelled CeeNU was three, while that for the cyclohexyl-labelled moiety was unity. This agrees with the observation that the cyclohexyl portion of the molecule is 60% plasma protein bound while the ethyl portion is not bound. The results support the suggested intermediate formation of an isocyanate moiety during the degradation of nitrosoureas *in vivo*. The identified metabolites and cyclohexylisocyanate were inactive against L-1210.

Studies conducted to determine the effects of NSC 79037 in polyethoxylated vegetable oil and normal saline (ratio of 1:9) applied topically to the hamster cheek pouch revealed no thromboembolism at concentrations 2.5 mg/ml. The only effect produced with this concentration was a slight decrease in the rate of venule and arteriole blood flow in 1/6 hamsters and a slight to moderate decrease in the venule flow of a second animal. Administration of a concentration at 0.625 mg/ml or the vehicle alone produced no detectable effect.

No thromboembolism was observed in the hamster cheek pouch microcirculation after single intrajugular injections of CeeNU in polyethoxylated vegetable oil and normal saline at doses ranging from 0.3125 to

20.0 mg/kg. However, a dosage of 0.625, 1.25, 2.5, 5.0, 10.0 or 20.0 mg/kg produced a decrease in cheek pouch venule blood flow varying from slight to moderate-severe. A slight to moderate-severe decrease in blood flow was also noted in the arterioles at drug levels ranging from 1.25 to 20 mg/kg with some vasoconstriction recorded at the 3 highest levels. At 20.0 mg/kg WBC stickiness was reported only once. The "no effect" level appeared to be 0.3125 mg/kg. Injection of the vehicle alone at volumes equivalent to those employed with 2.5, 5.0, 10.0, and 20.0 mg/kg drug dosages produced some vasoconstriction and a decrease in the rate of arteriole and venule blood flow. Microcirculation appeared normal when the vehicle alone was injected at a volume equivalent to that of a 1.25 mg/kg drug dosage. A mean recovery time of 17 minutes (5-35) was required for normal flow after intravenous injection in hamsters treated with the drug, compared to a mean recovery period of 6 minutes (2-10) in those receiving only the polyethoxylated vegetable oil and saline vehicle. It was concluded that cardiovascular effects observed were, in part, due to the vehicle employed.

Comparison of mortality levels in mice and rats for single oral doses of BicNU and CeeNU on a mg/kg, mg/m², or mmole/kg basis revealed that BicNU was twice as toxic as CeeNU.

TOXICOLOGY

The toxicity of CeeNU (Iomustine-CCNU) was investigated primarily by the Mason Research Institute under contract with the National Cancer Institute. The parenteral toxicity of CeeNU may be summarized as follows:

a) Single Dose (IV infusion):

- Dog: Maximum tolerated dose (MTD) - 0.625 mg/kg
 Primary toxicity = Depressed hematopoiesis, lymphoid tissue.
 Secondary toxicity - Delayed hepatotoxicity
- Rhesus Monkey: MTD = 1.25 mg/kg
 Primary toxicity = nephrotoxicity
 Secondary toxicity - Depressed hematopoiesis, hepatotoxicity.

b) Multiple Dose (IV infusion):

- Dog: 2 or 3 doses of 1.25 mg/kg given at weekly intervals = cumulative hepatotoxicity.

The toxicity of CeeNU given orally may be summarized as follows:

a) Single Dose (capsules)

- Dog: MTD = 2.0 mg/kg

b) Multiple Dose (capsules - dog, gavage - monkey)

- Dog: MTD - 0.65 mg/kg/day x 14
Rhesus Monkey: MTD = 0.15 mg/kg/day x 14

c) Delayed Hepatotoxicity (capsules)

- Dog: A single oral dose of 4 mg/kg produced hepatotoxicity that persisted for 2-3 months after drug treatment.

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