BRISTOL LABORATORIES
ONCOLOGY PRODUCTS

Rx Only

CeeNU®
(lomustine)
Capsules

WARNINGS

CeeNU (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 CeeNU (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 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**).

DESCRIPTION

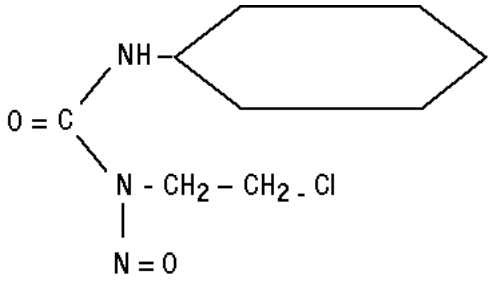
CeeNU® (lomustine) (CCNU) is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea. It is a yellow

powder with the empirical formula of $C_9H_{16}ClN_30_2$ and a molecular weight of 233.71. CeeNU is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). CeeNU is relatively insoluble in water (<0.05 mg per mL).

It is relatively unionized at a physiological pH.

Inactive ingredients in CeeNU capsules are: magnesium stearate and mannitol.

The structural formula is:



CeeNU is available in 10 mg, 40 mg and 100 mg capsules for oral administration.

CLINICAL PHARMACOLOGY

Although it is generally agreed that CeeNU alkylates DNA and RNA, it is not cross resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins.

CeeNU may be given orally. Following oral administration of radioactive CeeNU at doses ranging from 30 mg/m^2 to 100 mg/m^2, about half of the radioactivity given was excreted in the urine in the form of degradation products within 24 hours.

The serum half-life of the 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 physiological pH, CeeNU crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50% or greater than those measured concurrently in plasma.

INDICATIONS AND USAGE

CeeNU has been shown to be useful as a single agent in addition to other treatment modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

Brain tumors—both primary and metastic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Hodgkin's Disease—secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

CONTRAINDICATIONS

CeeNU should not be given to individuals who have demonstrated a previous hypersensitivity to it.

WARNINGS

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 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**).

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 Category D

CeeNU can cause fetal harm when administered to a pregnant woman. CeeNU is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

In all instances where the use of CeeNU is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of CeeNU therapy should be carried out with caution and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

Information for the Patient

Patients receiving CeeNU should be given the following information and instructions by the physician:

1. Patients should be told that CeeNU is an anticancer drug and belongs to the group of medicines known as alkylating agents.

2. In order to provide the proper dose of CeeNU, patients should be aware that there may be two or more different types and colors of capsules in the container dispensed by the pharmacist.

3. Patients should be told that CeeNU is given as a single oral dose and will not be repeated for at least 6 weeks.

4. Patients should be told that nausea and vomiting usually last less than 24 hours, although loss of appetite may last for several days.

5. If any of the following reactions occur, notify the physician: fever, chills, sore throat, unusual bleeding or bruising, shortness of breath, dry cough, swelling of feet or lower legs, mental confusion, or yellowing of eyes and skin.

Laboratory Tests

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 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 may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

Carcinogenesis, Mutagenesis, Impairment of Fertility

CeeNU is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans (see **ADVERSE REACTIONS**). CeeNU also affects fertility in male rats at doses somewhat higher than the human dose.

Pregnancy

Pregnancy "Category D" — See **WARNINGS** section.

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.

Pediatric Use

See **ADVERSE REACTIONS: Pulmonary Toxicity**, and **DOSAGE AND ADMINISTRATION** sections.

Geriatric Use

No data from clinical studies of CeeNU 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.

CeeNU 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.

ADVERSE REACTIONS

Hematologic Toxicity

The most frequent and most serious toxicity of CeeNU is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadministration and persists for 1 to 2 weeks. Leukopenia occurs at 5 to 6 weeks after a dose of CeeNU and persists for 1 to 2 weeks. Approximately 65% of patients receiving 130 mg/m^2 develop white blood counts below 5000 wbc/mm^3. Thirty-six percent developed white blood counts below 3000 wbc/mm^3. 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.

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 6 months or longer from the start of therapy with cumulative doses of CeeNU usually greater than 1100 mg/m^2. There is one report of pulmonary toxicity at a cumulative dose of only 600 mg.

Delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who received related nitrosoureas in childhood and early adolescence (1-16 years) combined with cranial radiotherapy for intracranial tumors. There appeared to be some late reduction of pulmonary function of all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study of carmustine, all those initially treated at less than five years of age died of delayed pulmonary fibrosis.

Gastrointestinal Toxicity

Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect. Nausea and vomiting can also be reduced if CeeNU is administered to fasting patients.

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.

Nephrotoxicity

Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with CeeNU. Kidney damage has also been reported occasionally in patients receiving lower total doses.

Other Toxicities

Stomatitis, alopecia, optic atrophy, and visual disturbances such as blindness, 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.

OVERDOSAGE

No proven antidotes have been established for CeeNU overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose of CeeNU in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m^2 as a single oral dose every 6 weeks. In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m^2 every 6 weeks. When CeeNU is used in combination with other myelosuppressive drugs, the doses should be adjusted accordingly.

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 %

A repeat course of CeeNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm^3; leukocytes above 4000/mm^3) and this is usually in 6 weeks. Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

HOW SUPPLIED

The dose pack of CeeNU® (lomustine) NDC 0015-3034-10 Capsules contains:

2—100 mg capsules (Green/Green)

2—40 mg capsules (White/Green)

2—10 mg capsules (White/White)

Stability

CeeNU Capsules are stable for the lot life indicated on package labeling when stored at room temperature in well closed containers. Avoid excessive heat (over 40° C, 104° F).

Directions to the Pharmacist

The dose pack contains a total of 300 mg and will provide enough medication for titration of a single dose. The total dose prescribed by the physician can be obtained (to within 10 mg) by determining the appropriate combination of the enclosed capsule strengths.

The appropriate number of capsules of each size should be placed in a single vial to which the patient information label (gummed label provided) explaining the differences in the appearance of the capsules is affixed. Each color-coded capsule is imprinted with the dose in milligrams.

A patient information sticker, to be placed on dispensing container, is enclosed.

Also available: Individual bottles of 20 capsules each.

NDC 0015-3032-20—100 mg capsules (Green/Green)

NDC 0015-3031-20—40 mg capsules (White/Green)

NDC 0015-3030-20—10 mg capsules (White/White)

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1–7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

References:

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253 (11): 1590-1592.

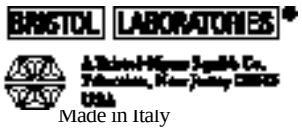
3. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.

5. Jones, RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center, Ca—*A Cancer Journal for Clinicians* 1983; (Sep./Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK PRACTICE GUIDELINES). *Am J Health-Syst Pharm* 1996; 53:1669–1685.



Revised _____