

Data Sheet

Name of Medicine

CeeNU
(Iomustine, CCNU)

Presentation

Capsule: 10 mg and 40 mg

Uses

Actions

CeeNU (1-(2-chloroethyl)-3 cyclohexyl-1-nitrosourea) is one of the group of nitrosoureas. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 233.71.

CeeNU is soluble in 10 percent 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 physiological pH.

Inactive ingredients in **CeeNU** are magnesium stearate and mannitol.

Pharmacokinetics

It is generally agreed that **CeeNU** 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 physiological pH, **CeeNU** crosses the blood brain barrier quite effectively. Levels of radioactivity in the cerebrospinal fluid (CSF) are 50 percent or greater than those measured concurrently in plasma.

Indications

CeeNU is indicated as palliative therapy to be employed in addition to other modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

1. Brain Tumours - both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.
2. Hodgkin's Disease - as a secondary therapy.
3. Advanced Lung Carcinoma - for small cell carcinoma **CeeNU** is effective in combination with other appropriate neoplastic agents, particularly cyclophosphamide. Patients who have demonstrated delayed hypersensitivity competence in pretreatment testing are usually more responsive to therapy.

Dosage and Administration

The recommended dose of **CeeNU** in adults and children is 130 mg/ m² as a single dose by mouth every 6 weeks. (see Pharmaceutical Precautions)

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 haematologic toxicity is delayed and cumulative.

Doses subsequent to the initial dose should be adjusted according to the haematologic 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
Leukocytes (/mm ³)	Platelets (/mm ³)	to be Given
>4,000	>100,000	100 percent
3,000-3,999	75,000-99,999	100 Percent
2,000-2,999	25,000-74,999	70 percent
<2,000	<25,000	50 percent

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

Contraindications

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

Warnings and Precautions

CeeNU 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.

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).

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

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 patient should be apprised of the potential hazard to the foetus. 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 leukaemia 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 from **CeeNU** in nursing infants, 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.

Since **CeeNU** may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

Effects on Ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed

Adverse Effects

Gastrointestinal.

Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually last 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** to fasting patients.

Haematologic 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 post-administration 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 percent of patients receiving 130 mg/m² develop white blood counts below 5,000 wbc/mm³. Thirty-six percent developed white blood cell counts below 3,000/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 leukaemia on bone marrow dysplasia have been reported in patients following long term nitrosourea therapy.

Anaemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

Pulmonary Toxicity characterised by pulmonary infiltrates and/or fibrosis have been rarely reported 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 1,100 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 tumours who received related nitrosoureas during their childhood and early adolescence.

Other Toxicities:

Stomatitis, alopecia, anaemia 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.

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.

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**.

Overdose

Accidental overdose with lomustine has been reported, including fatal cases. Accidental overdose has been associated with bone marrow suppression, abdominal pain, diarrhoea, vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath.

There is no specific antidote for overdose with **CeeNU**. In case of overdose, appropriate supportive measures should be taken

Pharmaceutical Precautions

Stability:

When stored in well closed containers at room temperature (25°C), **CeeNU** capsules are stable until the expiration date indicated on the package. Avoid excessive heat over 40°C.

Procedure for Handling and Disposal of Anti-cancer Drugs:

Only the appropriate number of **CeeNU** capsules required for a single administration should be dispensed. Patients should be told that **CeeNU** is taken as a single oral dose and will not be repeated for at least 6 weeks

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.

Care must be taken whenever handling anticancer products. Always take steps to prevent exposure. This includes appropriate equipment, such as, wearing gloves, and washing hands with soap and water after handling such products.

Directions to Pharmacist:

The capsules are to provide enough medication for a single dose. The total dose prescribed by the physician can be obtained (to within 10 mg) by determining the appropriate combination of the 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.

Medicine Classification

Prescription Medicine.

Package Quantities

Capsule: 10 mg and 40 mg x 20's

Further Information

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 anti-cancer 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 colours 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.

Name and Address

Bristol-Myers Squibb (NZ) Limited
Simpson Grierson
88 Shortland Street
Auckland
New Zealand

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