Data Sheet

Name of Medicine

CeeNU
(lomustine, 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 C9H16C1N3O2 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 hematologic response should be checked prior to the next dose and the dose adjusted accordingly. The following schedule is suggested as a guide to dosage adjustment.

<table>
<thead>
<tr>
<th>Nadir After Prior Dose</th>
<th>Percentage of Dose to be Given</th>
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</thead>
<tbody>
<tr>
<td><strong>Leukocytes (/mm³)</strong></td>
<td><strong>Platelets (/mm³)</strong></td>
</tr>
<tr>
<td>≥4,000</td>
<td>≥100,000</td>
</tr>
<tr>
<td>3,000-3,999</td>
<td>75,000-99,999</td>
</tr>
<tr>
<td>2,000-2,999</td>
<td>25,000-74,999</td>
</tr>
<tr>
<td>&lt;2,000</td>
<td>&lt;25,000</td>
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</tbody>
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When CeeNU is used in combination with myelosuppressive drugs, the doses should be adjusted accordingly.

CeeNU v 5.0
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).

Concomitant use of CeeNU with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction of the vaccine virus because normal defence mechanisms may be suppressed by CeeNU. Vaccination with a live vaccine in a patient taking CeeNU may result in severe infection. Patient’s antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought (see Drug Interactions).
**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.

CeeNU can have a mutagenic effect. Men treated with CeeNU are therefore advised not to father children during treatment and for up to 6 months afterwards, and to seek advice regarding sperm conservation before the start of treatment given the possibility of irreversible infertility caused by CeeNU therapy.

**Nursing Mothers:**
Due to the lipophilic nature of CeeNU, it is likely to be excreted in breast milk; however, such has not yet been confirmed. As a risk to the nursing child potentially exists, a decision should be made whether to discontinue breastfeeding or to discontinue CeeNU therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for 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.

**Drug Interactions**

**Medicinal products:** There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients (see Warnings and Precautions).

**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.

Decreases in haematocrit, mild anaemia. When lomustine therapy is continued for longer than 1 year, refractory anaemia and thrombocytopenia are common. Mild pancytopenia has also been reported after lomustine treatment.

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 20 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.

Chronic renal failure has been reported with lomustine administration. Renal function tests should be monitored periodically.

**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.

Because of the lipophilic nature of the drug, the product is not dialyzable.

**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 20s

**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.

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