

DATA SHEET

1 PRODUCT NAME

CeeNU® 10 mg capsules.

CeeNU® 40 mg capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CeeNU 10 mg capsules

Each capsule contains 10 mg of lomustine.

Excipients with known effect:

Each capsule contains 213.87 mg of mannitol.

CeeNU 40 mg capsules

Each capsule contains 40 mg of lomustine.

Excipients with known effect:

Each capsule contains 278.40 mg of mannitol.

Mannitol 213.87 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, 10mg (white, marked CPL 3030/10mg)

Capsules, 40mg (white/dark green, marked CPL 3031/40mg)

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

The recommended dose of CeeNU in adults and children is 130 mg/m² as a single dose by mouth every 6 weeks. (see Directions to Pharmacists below).

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 > 100,000/mm³; leukocytes > 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.

Nadir After Prior Dose		Percentage of Dose to be Given
Leukocytes (/mm ³)	Platelets (/mm ³)	
≥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 medicines, the doses should be adjusted accordingly.

Directions to Pharmacists:

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.

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.

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.

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 medicine 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 4.8 Undesirable effects). 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 4.2 Dose and method of administration).

Caution should be used in administering CeeNU to patients with decreased circulating platelets, leukocytes, or erythrocytes (see 4.2 Dose and method of administration).

Pulmonary toxicity from CeeNU appears to be dose related (see 4.8 Undesirable effects).

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 4.8 Undesirable effects).

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 4.5 Interactions with other medicines and other forms of interaction).

Since CeeNU may cause liver dysfunction, it is recommended that liver function tests be monitored periodically (see 4.8 Undesirable Effects).

Renal function tests should also be monitored periodically.

4.5 Interaction with other medicines and other forms of interaction

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 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

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 medicine is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this medicine, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable 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 medicine 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Accidental overdose with CeeNU (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 medicine, the product is not dialyzable.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nitrosoureas, ATC Code: L01AD02.

5.2 Pharmacokinetic properties

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 medicine 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.

5.3 Preclinical safety data

Carcinogenesis

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.

Impairment of Fertility

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

Mutagenesis

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Magnesium stearate
Mannitol
Opacode black S-1-27794
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Stored at or below 25°C, protect from light. Store 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.

6.5 Nature and contents of container

Bottle, HDPE with PP child resistant closure containing 20 capsules.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of anti-cancer medicines should be considered. Several guidelines on this subject have been published. Any unused medicine or waste material should be disposed of in accordance with local requirements.

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.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Bristol-Myers Squibb (NZ) Limited
Private Bag 92518
Auckland 1141

Tel: Toll free 0800 167 567

9 DATE OF FIRST APPROVAL

17/7/1980

DATE OF REVISION OF THE TEXT

29 December 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Updated to SmPC style format.

CeeNU® is a registered trademark of Bristol-Myers Squibb Company.