AUSTRALIAN PRODUCT INFORMATION – CEENU® (LOMUSTINE)

1 NAME OF THE MEDICINE

Lomustine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules containing 10 mg and 40 mg of lomustine.

Lomustine (CeeNU) is an antitumour agent, cancer chemotherapeutic agent, cytotoxic agent and alkylating agent. Lomustine is a yellow powder, very slightly soluble in water (0.5mg/mL); slightly soluble in propylene glycol (0.7mg/mL) and polysorbate 80 (2.5mg/mL); soluble in absolute alcohol (70mg/mL).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsule containing 10mg lomustine are white, marked CPL 3030/10mg.

Capsule containing 40mg lomustine are white/dark green, marked CPL 3031/40mg.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CeeNU may be used for the treatment of:

1. Brain tumours (primary and secondary).

2. Hodgkin's disease (as secondary therapy).

Lomustine is used in addition to appropriate surgical and/or radiotherapeutic procedures or as a component of various chemotherapeutic regimens in the palliative treatment of primary and metastatic brain tumours.

CeeNU containing combinations should be used as alternative therapy in the treatment of disseminated Hodgkin's disease in patients refractory to other established treatment regimens.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

The recommended dose of CeeNU is 130mg/m^2 as a single dose by mouth every 6 weeks.

In individuals with compromised bone marrow function, the dose should be reduced to 100mg/m^2 every six weeks.

A repeat course of CeeNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm^3, leucocytes above 4,000/mm^3). Blood counts should be monitored weekly and repeat courses should not be given before six weeks because the haematological 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 by the manufacturer as a guide to dosage adjustment.

Table 1 - Guide to dosage adjustment

CeeNU 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 drugs, the doses should be adjusted accordingly.

Paediatric use

As for adults.

Use in elderly

No specific recommendations are made, but as excretion of CeeNU metabolites is predominantly renal, severely impaired renal function could predispose to increased toxicity.

Hepatic Impairment

The hepatic excretion of lomustine metabolites is minor and there are no clear indications that toxicity is altered in patients with impaired liver function.

Renal Impairment

The predominantly renal excretion of lomustine metabolites suggest that severe renal insufficiency could predispose to increased toxicity.

INFORMATION FOR THE PATIENT

1. 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.

2. Patients should be told that CeeNU is given as a single oral dose and will not be repeated for at least six weeks. Capsules should be taken on an empty stomach.

3. Patients should be told that nausea and vomiting usually last less than 24 hours; it is extremely important to ensure that the capsules have not been vomited. Loss of appetite may last for several days.

4. 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

Hypersensitivity

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

Severe myelosuppression

CeeNU is contraindicated in patients with marked myelosuppression.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

CeeNU should be used in approved institutions and be administered by individuals experienced in the use of antineoplastic therapy.

Delayed haematological toxicity

Since the major toxicity is delayed bone marrow suppression, notably thrombocytopenia and leucopoenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, blood counts should be monitored weekly for at least 6 weeks after a dose (see 4.8 Adverse effects (Undesirable effects)). At the recommended dosage, courses of CeeNU should not be given more frequently than 6 weekly.

Pulmonary fibrosis

Respiratory symptoms indicative of pulmonary fibrosis may not appear for several months following initiation of treatment with CeeNU. Withdrawal of the drug does not arrest fibrotic degeneration, and a number of deaths from acute respiratory failure have occurred. Pulmonary toxicity appears to be dose related.

Pulmonary Function

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.

Myelosuppression

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

Secondary malignancies

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

Bone marrow toxicity

The bone marrow toxicity of lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see **Table 1 Guide to dosage adjustment** under 4.2 Dose and method of administration).

Live virus vaccines

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.

Use in hepatic impairment

Animal studies revealed delayed liver damage evidenced by the sudden marked elevation of transaminase, alkaline phosphatase and BSP values. The reversibility of such toxicity has not been demonstrated and regular liver function tests should be carried out during therapy.

Use in renal impairment

Evidence of renal toxicity has been observed in dogs and monkeys manifested by elevated BUN. Chronic renal failure has been reported with lomustine administration (see 4.8 Adverse effects (Undesirable effects)). Renal function tests should be monitored periodically.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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).

Food

It is reported that administration of lomustine on an empty stomach reduces the incidence of nausea and vomiting.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

CeeNU 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.

Dispense only a single dose to patient.

Use in pregnancy (Category D)

Safety in pregnancy has not been established. Lomustine has been shown to be carcinogenic, embryotoxic and teratogenic in animal studies. Lomustine must also be regarded as a potential mutagen. Therefore, the drug should not be used in pregnant women, or those likely to become pregnant, unless the expected benefit outweighs any potential risk.

Use in lactation.

Some lomustine metabolites are excreted in breast milk and may be harmful in young children (see 4.6 Fertility, Pregnancy and Lactation: Use in Pregnancy). Therefore it should not be given to nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

More Common Reactions:

Gastrointestinal

Nausea and vomiting occur in 45 to 100% of patients within 45 minutes to 6 hours after ingestion of an oral dose of lomustine. Although these symptoms are not severe and usually abate within 24 hours, they may persist up to 36 hours and are often followed by 2 to 3 days of anorexia. The frequency and duration of these effects can be reduced by fasting or by administration of antiemetics. Clinical

pharmacological studies indicated that the nausea and vomiting occur after drug absorption has taken place. It appears to be a CNS mediated effect of lomustine.

Haematological

Myelosuppression. The major and dose limiting side effect of lomustine is delayed haematological toxicity. Leucopoenia occurs at about 6 weeks after a dose of lomustine and persists for 1 to 2 weeks. Approximately 65% of patients develop white blood counts below 5,000 wbc/mm^3 and 36% develop white blood counts below 3,000 wbc/mm^3.

Thrombocytopenia occurs at about 4 weeks after a dose of lomustine and persists for 1 to 2 weeks. Lomustine may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.

Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

The occurrence of acute leukaemia and bone marrow dysplasias have been reported in patients following long term nitrosourea therapy.

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

Less Common Adverse Effects:

Biochemical abnormalities

Elevation of liver function test results.

Dermatological

Alopecia.

Gastrointestinal

Stomatitis.

Anaemia

General

Patients who receive myelosuppressive drugs experience an increased frequency of infections as well as possible haemorrhagic complications.

Haematological and reticuloendothelial

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.

Hepatic

Hepatic toxicity, manifested by transient elevation of transaminase, alkaline phosphatase and bilirubin levels, has been reported in a small percentage of patients receiving CeeNU.

Nervous System

Disorientation, lethargy, ataxia, dysarthria.

Renal

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

Serious or Life-threatening Adverse Effects:

Myelosuppression

The delayed onset of myelosuppression demands the utmost care by the prescriber in monitoring the patient's haematology, selecting the appropriate interval between doses and deciding the actual dose to be administered. There is considerable risk of prolonged or fatal myelosuppression if such care is not taken.

Infection and haemorrhagic complications

As these complications are potentially fatal, the patient should be instructed to notify the physician if fever, sore throat, or unusual bleeding or bruising occurs.

Pulmonary toxicity

Pulmonary toxicity characterised by pulmonary infiltrates and/or fibrosis have been rarely reported with lomustine. Onset of toxicity has occurred after an interval of six months or longer from the start of therapy with cumulative doses of lomustine usually greater than 1100 mg/m^2. There is one report of pulmonary toxicity at a cumulative dose of only 600mg. 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 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 dialysable.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

A single definitive molecular mechanism of action for lomustine is not apparent. It may act by the following possible mechanisms:

1. Alkylation of nucleic acids.
2. Carbamoylation of proteins.
3. Interference with enzyme activation (histidine metabolism, forminotransferase, DNA polymerase, NAD-ase).

Lomustine is labile and after oral administration no intact drug is detectable in plasma. Highly reactive intermediates, which bind to macromolecules, are formed rapidly. How the nature and selectivity of these intermediates relate to antitumour activity and toxicity is poorly understood. The overall result is thought to be the inhibition of both DNA and RNA synthesis. Cross resistance between lomustine and carmustine has occurred.

Clinical trials

Systemic screening of synthetic components at the National Cancer Institute in the US was carried out in the fifties, using animal tumours (Sarcoma 181, Carcinoma 755 and Leukaemia L1210). Activity against leukaemia L1210 was demonstrated for 1-methyl-1-nitroso-3-guanidine (MNNG) in 1959. Following this, structurally related compounds were evaluated, including the nitrosourea class. 1-methyl-1-nitrosourea (MNU) was found to be more effective than MNNG. It was also found to be lipid soluble, making it effective against L1210 in the CNS.

Bioavailability

Bioavailability is difficult to define as lomustine is labile and undergoes rapid decomposition. Furthermore the active moiety is unknown.

5.2 PHARMACOKINETIC PROPERTIES

Lomustine rapidly decomposes under physiological conditions and no intact drug has been detected in serum after oral administration in humans. Pharmacokinetic studies have used radioactively labelled (C^{14}) lomustine, with the label in either the chloroethyl, carboxyl or cyclohexyl groups.

Absorption

Average peak plasma levels occur at 4 hours, 1 hour and 3 hours respectively for the chloroethyl, carboxyl and cyclohexyl C^{14}-labelled moieties. The extent of absorption was difficult to assess but approximately 60% of the radioactivity administered was recovered in the urine by 48 hours. No data are available on the site or mechanism of absorption, or the effect of blood, other drugs or excipients in the formulation, on absorption of lomustine.

Distribution

The volume of distribution, organ accumulation etc. for this drug is unknown. CSF levels of the labelled chloroethyl moiety have been studied. Peak CSF levels coincide with peak plasma levels. CSF levels were about 30% of plasma levels and the half-life in CSF was 6 hours. No intact drug was detected in the CSF.

Metabolism

Lomustine decomposes under physiological conditions (half-life of 53 minutes in phosphate buffer, pH 7.4, 37^{o}C). The in vivo site of decomposition (bowel, lumen, plasma, liver etc.) is not known. Decomposition products include cyclohexylamine, cyclohexylisocyanate and N, N'-dicyclohexylurea. The disappearance of radioactivity from plasma for the chloroethyl-labelled moiety followed a single phase half-life of 72 hours. The cyclohexyl and carboxyl moieties had two-fold plasma disappearance half-lives of 4 and 5 hours respectively and 50 and 27 hours respectively. Prolonged plasma half-lives are thought to reflect a combination of protein binding and enterohepatic circulation of metabolites.

Excretion

Approximately 60% of the radioactivity administered was recovered in the urine by 48 hours and excretion of radioactivity was virtually complete within 72 hours. About 50 to 60% of radioactivity excreted was recovered during the first 12 hours. No intact drug was detected in the urine. In animals, less than 5% of the drug was excreted in the faeces.

Protein-binding

Radiolabelled metabolites bind to proteins. There is no specific information on binding to plasma proteins, strength of binding and displacement by other drugs.

Clinical Implications of Pharmacokinetic Data

The predominantly renal excretion of the drug metabolites suggests that severe renal insufficiency could predispose to increased toxicity.

The high lipid solubility and the relative lack of ionisation at a physiological pH enables lomustine to cross the blood-brain barrier effectively. This is the rationale for its use in brain tumours. The prolonged half-life of the radioactively labelled metabolites may be an explanation for the delayed onset of myelosuppression.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

Lomustine 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol
Magnesium stearate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

CeeNu 10 mg and 40 mg are supplied in HDPE bottle with polypropylene child resistant cap containing 20 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

PROCEDURES FOR HANDLING AND DISPOSAL OF ANTICANCER 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 anticancer drugs should be followed, according to published guidelines. In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

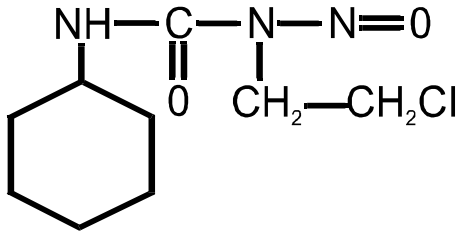
Care must be taken whenever handling cytostatic products. Always take steps to prevent exposure, this includes appropriate equipment, such as, wearing gloves, and washing hands with soap and water after handling such products.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemically, lomustine is similar to the other nitrosoureas carmustine (BiCNU) and semustine (methyl CCNU) and, as well, to Streptozotocin. Biologically, lomustine has some comparability to the alkylating agents.

The chemical name for Lomustine is 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea with the structural formula:



Molecular Formula:

$C_9H_{16}N_3O_2Cl$

Molecular Weight:

233.69

CAS number

13010-47-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave,
Victoria 3170, Australia.
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL (ARTG ENTRY)

30 September 1991.

10 DATE OF REVISION OF THE TEXT

20 November 2020.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2 QUALITATIVE AND QUANTITATIVE COMPOSITION	Remove 100 mg strength.
3 PHARMACEUTICAL FORM	Remove 100 mg strength.
6.5 Nature and contents of container	Remove 100 mg strength.

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