

Lomustine Capsules IP 40 mg

BELUSTINE - 40

R, Only

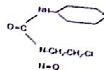
COMPOSITION:

Each capsule contains
Lomustine IP 40 mg
Excipients q.s

Colours: Approved colours used in empty Capsule shell

DESCRIPTION

(Lomustine [CCNU]) Capsules is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1-(2-chloro-ethyl)-3-cyclo-hexyl-1-nitrosourea. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_2O_2$ and a molecular weight of 233.71. It is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). It is relatively insoluble in water (<0.05 mg per mL). It is relatively unionized at a physiological pH. Inactive ingredients in capsules are: magnesium stearate and mannitol. The structural formula is:



Lomustine is available in 40 mg capsules for oral administration.

CLINICAL PHARMACOLOGY

Although it is generally agreed that Lomustine 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 carbamylation of amino acids in proteins.

Lomustine may be given orally. Following oral administration of radioactive Lomustine at doses ranging from 30 mg/m² to 100 mg/m², about half of the radioactivity given was excreted 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, Lomustine 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

Lomustine 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 metastatic, 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

Lomustine 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 Lomustine should not be given more frequently than every 6 weeks.

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 Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

Pulmonary toxicity from Lomustine 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: Pregnancy "Category D". Lomustine can cause fetal harm when administered to a pregnant woman. Lomustine 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.

WARNINGS

(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 Lomustine (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 Lomustine should not be given more frequently than every 6 weeks. 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 Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General: In all instances where the use of Lomustine 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 Lomustine 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.

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 (DLCO) are particularly at risk.

Since Lomustine (Lomustine) Capsules 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: Lomustine 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). Lomustine also affects fertility in male rats at doses somewhat higher than the human dose.

Pregnancy: Pregnancy "Category D". (See WARNINGS.)

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 Lomustine, 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.

Information for the Patient: Patients receiving Lomustine should be given the following information and instructions by the physician:

1. Patients should be told that Lomustine is an anticancer drug and belongs to the group of medicines known as alkylating agents.
2. In order to provide the proper dose of Lomustine, 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 Lomustine 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.

ADVERSE REACTIONS

Hematologic Toxicity: The most frequent and most serious toxicity of Lomustine 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 Lomustine and persists for 1 to 2 weeks. Approximately 65% of patients receiving 130 mg/m² develop white blood counts below 5000 wbc/mm³. Thirty-six percent developed white blood counts below 3000 wbc/mm³. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

Lomustine 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 Lomustine. Onset of toxicity has occurred after an interval of 6 months or longer from the start of therapy with cumulative doses of Lomustine usually greater than 1100 mg/m². 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 Lomustine 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 Lomustine.

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 Lomustine. 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 Lomustine. However, the relationship to medication in these patients is unclear.

OVERDOSAGE

No proven antidotes have been established for Lomustine overdosage.

DOSAGE AND ADMINISTRATION

The recommended dose of Lomustine in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m² as a single oral dose every 6 weeks. In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m² every 6 weeks. When Lomustine 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

Nadir After Prior Dose	
Leukocytes	Platelets
>4000	> 100,000
3000-3999	75,000-99,999
2000-2999	25,000-74,999
<2000	< 25,000

A repeat course of Lomustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm³; leukocytes above 4000/mm³) 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.

STORAGE:

Store protected from light and moisture.

SHELF LIFE:

24 Months

How Supplied

Container of 10 capsules.

Manufactured by:
INTERMED
No. 4, G.K. Industrial Estate, Arcot Road,
Porur, Chennai - 600 116.

Marketed by:
Medi Biotek (India) Pvt. Ltd.,
ISO 9001:2008 Certified Company
4/29, Letangs Road, Vepery,
Chennai - 600 007.