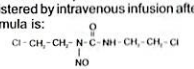
For the use of Registered Medical Practitioner or a Hospital only

ONCOMA

CAROMA
Carmustine for Injection USP - 100 mg (Lyophilized)

COMPOSITION
Each vial contains:
Carmustine USP - 100 mg
DESCRIPTION
Carmustine for Injection is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1,3-bis(2-chloroethyl)-1-nitrosourea. It is white to yellowish lyophilized mass or powder with a molecular weight of 214.06. It is highly soluble in alcohol and lipids, and poorly soluble in water. Carmustine for Injection is administered by intravenous infusion after reconstitution as recommended.
The structural formula is:



Carmustine for Injection is available in 100 mg single dose vials of lyophilized material.
CLINICAL PHARMACOLOGY
Although it is generally agreed that carmustine 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 carbamoylation of amino acids in proteins.
Intravenously administered carmustine is rapidly degraded, with no intact drug detectable after 15 minutes. However, in studies with C14-labeled drug, prolonged levels of the isotope were detected in the plasma and tissue, probably representing radioactive fragments of the parent compound.
It is thought that the antineoplastic and toxic activities of carmustine may be due to metabolites. Approximately 60% to 70% of a total dose is excreted in the urine in 96 hours and about 10% as respiratory CO_2. The fate of the remainder is undetermined.
Because of the high lipid solubility and the relative lack of ionization at physiological pH, carmustine crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are ≥50% of those measured concurrently in plasma.
INDICATIONS
Carmustine for Injection is indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following:
1. Brain tumors - glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.
2. Multiple myeloma - in combination with prednisone.
3. Hodgkin's disease - as 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.
4. Non-Hodgkin's lymphomas as secondary therapy in combination with other approved drugs for patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

CONTRAINDICATIONS
Carmustine for Injection 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 Carmustine for Injection should not be given more frequently than every 6 weeks.
The bone marrow toxicity of Carmustine for Injection is cumulative; 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 Carmustine for Injection appears to be dose related. Patients receiving greater than 1400 mg/m2 cumulative dose are at significantly higher risk than those receiving less. Additionally delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who received Carmustine for Injection in childhood and early adolescence (see ADVERSE REACTIONS).
Long-term use of nitrosoureas has been reported to be associated with the development of secondary malignancies.
Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).
Carmustine for Injection may cause fetal harm when administered to a pregnant woman. Carmustine for Injection has been shown to be embryotoxic in rats and rabbits and teratogenic in rats when given in doses 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.
Carmustine for Injection has been administered through an intraarterial intracarotid route; this procedure is investigational and has been associated with ocular toxicity.
PRECAUTIONS
General
In all instances where the use of Carmustine for Injection 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 Carmustine for Injection 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 Carmustine for Injection may cause liver dysfunction, it is recommended that liver function tests be monitored.
Renal function tests should also be monitored periodically.
Drug Interactions
Greater myelotoxicity (e.g., leukopenia and neutropenia) has been reported when carmustine was combined with cimetidine.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carmustine 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). Carmustine also affects fertility in male rats at doses somewhat higher than the human dose.
Pregnancy
Pregnancy Category D: See WARNINGS section.
Nursing Mothers
It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse events in nursing infants, nursing should be discontinued while taking Carmustine.
Pediatric Use
Safety and effectiveness in children have not been established. Delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in a long-term study of patients who received Carmustine in childhood and early adolescence (1-16 years). Eight out of the 17 patients (47%) who survived childhood brain tumors, including all the 5 patients initially treated at less than 5 years of age, died of pulmonary fibrosis. Therefore, the risks and benefits of Carmustine therapy must be carefully considered, due to the extremely high risk of pulmonary toxicity. (See ADVERSE REACTIONS: Pulmonary Toxicity.)
Geriatric Use
No data from clinical studies of Carmustine for Injection are available for patients 65 years of age and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Carmustine for Injection and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.