PRODUCT INFORMATION

BiCNU®
(Carmustine)

APPROVED NAME

Carmustine.

DESCRIPTION

Carmustine is one of the nitrosoureas. The chemical name is 1, 3-bis(2-chloroethyl)-1-nitrosourea; the structural formula is:

\[
\begin{array}{c}
\text{NO} & \text{O} \\
\mid & \mid \\
\text{Cl} \text{CH}_2 \text{CH}_2 \text{N} \rightarrow \text{C} \rightarrow \text{NHCH}_2 \text{CH}_2 \text{Cl}
\end{array}
\]

Molecular Formula: C_5H_9Cl_2N_3O_2

Carmustine is a pale yellow powder with a molecular weight of 214.06. It is highly soluble in alcohol and poorly soluble in water. It is also highly soluble in lipids. One gram of carmustine is soluble in approximately 250mL of 0.9% saline solution or 80mL of propylene glycol.

PHARMACOLOGY

PHARMACOKINETICS

Distribution

Intravenously administered Carmustine is rapidly degraded, with no intact drug detectable after 15 minutes. However, in studies with C^{14} labelled drug prolonged levels of the isotope were observed in the plasma and tissue, probably representing radioactive fragments of the parent compound.

Because of the high lipid solubility and the relative lack of ionization at a physiological pH, carmustine crosses the blood brain barrier quite effectively. Levels of radioactivity in the CSF are 50% or greater than those measured in plasma.
**Metabolism**

No information.

**Excretion**

Approximately 60 to 70% of a total dose is excreted in the urine in 96 hours and about 10% as respiratory carbon dioxide. The fate of the remainder is undetermined.

**PHARMACODYNAMICS**

**Mechanism of Action**

Carmustine alkylates DNA and RNA and has been shown to inhibit several enzymes by carbamoylation of amino acids in proteins. Carmustine is not cross resistant with other alkylators.

It is thought that the antineoplastic and toxic activities of carmustine may be due to metabolites.

**INDICATIONS**

BiCNU is indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following:

1. Malignant Glioma
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**

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

Should not be given to individuals with decreased circulating platelets, leucocytes, or erythrocytes either from previous chemotherapy or other causes.
WARNINGS

Bone marrow suppression, notably thrombocytopenia and leucopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of carmustine.

BiCNU has been administered directly into the carotid artery; this procedure is investigational and has been associated with ocular toxicity.

Pulmonary toxicity from carmustine appears to be dose related. Patients receiving greater than 1400 mg/m² cumulative dose are at significantly higher risk than those receiving less. Delayed pulmonary toxicity can occur years after treatment, and can result in death, particularly in patients treated in childhood (see Adverse Reactions).

PRECAUTIONS

BiCNU should be administered preferably by individuals experienced in antineoplastic therapy.

It is recommended that liver and renal function tests be monitored.

Patients with pre-existing lung disease are at greater risk of developing carmustine-associated pulmonary toxicity. Thoracic irradiation and other drugs affecting the pulmonary function have also been implicated as predisposing to development of pulmonary toxicity during treatment with carmustine.

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.

Since delayed bone marrow toxicity is the major toxicity, complete blood counts should be monitored frequently for at least 6 weeks after a dose. Repeat doses of BiCNU should not be given more frequently than every 6 weeks.

The bone marrow toxicity of carmustine 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).

Injection site reactions may occur during the administration of BiCNU (see ADVERSE REACTIONS, Other). Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

DRUG INTERACTIONS

BiCNU may need to be used with caution in combination chemotherapy (see ADVERSE REACTIONS).
CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY

Carmustine is carcinogenic in rats and mice, producing a marked increase in tumour incidence in doses approximately those employed clinically.

Nitrosourea therapy does have carcinogenic potential. The occurrence of acute leukaemia and bone marrow dysplasias have been reported in patients following nitrosourea therapy.

USE IN PREGNANCY

Pregnancy Category (Category D)

Safe Use in Pregnancy has not been established. Therefore, the benefit to the mother versus the risk of toxicity to the mother and the fetus must be carefully weighed.

Carmustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to human dose. BiCNU also affects fertility in male rats at doses somewhat higher than the human dose.

USE IN LACTATION

It is not know whether carmustine is excreted in human milk nor whether it has a harmful effect on the newborn. Therefore, administration is not recommended for nursing mothers unless alternative methods of feeding the infant are established.

PAEDIATRIC USE

Safety and effectiveness in children have not been established. Same monitoring and dose modification principles apply as for adults (see ADVERSE REACTIONS).

IMPAIRED HEPATIC FUNCTION

No information available.

IMPAIRED RENAL FUNCTION

No information available.

INSTRUCTIONS TO BE GIVEN TO PATIENT

Patients should be advised to use adequate contraceptive measures during treatment with BiCNU.
ADVERSE REACTIONS

Adverse reactions reported have been grouped by frequency according to the following criteria.

Very common \(\geq 1/10\)
Common \(\geq 1/100\) and \(<1/10\)
Uncommon \(\geq 1/1000\) and \(<1/100\)
Rare \(\geq 1/10000\) and \(<1/1000\)
Very Rare \(<1/10000\)

Haematological

Very common: Myelosuppression (delayed; usually occurs 4 to 6 weeks after drug administration and is dose related). Platelet nadirs occur at 4 to 5 weeks; leucocyte nadirs occur at 5 to 6 weeks post therapy. Thrombocytopenia is generally more severe than leucopenia (both may be dose limiting); anaemia.

Common: Cumulative myelosuppression after repeated doses (manifested by more depressed indices or longer duration of suppression).

Rare: Acute leukaemia and bone marrow dysplasias following long term therapy; thrombosis

Gastrointestinal

Very common: Nausea: vomiting (occurs within 2 hours, usually lasts 4-6 hours and is dose dependant).

Hepatic

Uncommon: Elevated transaminases, alkaline phosphatase and bilirubin.

Rare: Fatal hepatic toxicity (cumulative doses over 1200-1500mg/m²) has occurred.

Renal

Uncommon: Decrease in kidney size; progressive azotaemia; renal failure.

Pulmonary

Common: Pulmonary infiltrates and/or fibrosis (high cumulative dose greater than 1400mg/m²). This toxicity has occurred from 9 days to 43 months after treatment. In a long-term study of 17 patients who survived childhood brain tumors, very delayed onset pulmonary toxicity occurring up to 15 years after treatment with BiCNU has been reported. These children ranged between 2 and 16 years of age when treated with BiCNU at doses of 800 mg/m² or above. All received cranial irradiation and most received spinal radiotherapy. Chest X-rays and CT scans have demonstrated upper-zone fibrotic changes primarily. All children exhibited reduced pulmonary function and the toxicity was shown to be progressive, resulting in death in approximately 50% of cases. Severity was related to age at treatment with five children treated at age less than 5 years having died of pulmonary fibrosis.

Uncommon: Pulmonary fibrosis (low cumulative dose).
**Ophthalmic**
Rare : Neuroretinitis; suffusion of conjunctiva (from rapid IV infusion)

**Skin and Appendages**
Uncommon : Facial flushing; burning at site of injection; hyperpigmentation from accidental skin contact, extravasation*.

**Cardiovascular**
Uncommon : Hypotension; tachycardia; chest pain.

**Hypersensitivity**
Uncommon : Allergic reactions.

**Neurological**
Uncommon : Headache

* Complications reported for extravasation included local soft tissue toxicity, swelling, pain, erythema, burning sensation, and skin necrosis.

**DOSAGE**

BiCNU is administered by slow intravenous infusion. BiCNU SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION

The recommended dose of BiCNU as single agent in previously untreated in patients is 200 mg/m² intravenously every 6 weeks. This may be given as a single dose or divided into daily injections such as 100 mg/m² on successive days. When BiCNU is used in combination with other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted, the doses should be adjusted accordingly.

A repeat course of BiCNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm³; leucocytes above 4,000/mm³); this usually occurs within 6 weeks. Blood counts should be monitored frequently and repeat courses should not be given before 6 weeks because of delayed toxicity.

In view of the cumulative dose-related toxicity which occurs with BiCNU the total dose administered should not exceed 1500 mg/m², unless the expected benefits outweigh the high risk of toxicity, especially pulmonary (see under ADVERSE REACTIONS).

Doses subsequent to the initial dose should be adjusted according to the haematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:
Nadir After Prior Dose                      Percentage of Prior Dose to be Given

<table>
<thead>
<tr>
<th>Leucocytes/mm³</th>
<th>Platelets/mm³</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;4,000</td>
<td>&gt;100,000</td>
<td>100 percent</td>
</tr>
<tr>
<td>3,000-3,999</td>
<td>75,000-99,999</td>
<td>100 percent</td>
</tr>
<tr>
<td>2,000-2,999</td>
<td>25,000-74,999</td>
<td>70 percent</td>
</tr>
<tr>
<td>&lt;2,000</td>
<td>&lt;25,000</td>
<td>50 percent</td>
</tr>
</tbody>
</table>

Preparation of Intravenous Solutions:

To facilitate reconstitution, allow BiCNU and the supplied sterile diluent (absolute ethanol) to come to controlled room temperature (15°C to 30°C) before mixing. Dissolve BiCNU completely with 3 mL of the supplied sterile diluent and then aseptically add 27 mL of Sterile Water for Injection to the alcohol solution. Each mL of the resulting solution will contain 3.3 mg of carmustine in 10 percent ethanol having pH of 5.6 to 6.0 (Solution in the ethanol must be complete before sterile water for Injection is added). Accidental contact of reconstituted BiCNU with the skin has caused transient hyper pigmentation of the affected areas. If BiCNU lyophilized material or solution contact the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

Reconstitution as recommended results in a clear, colourless to light yellow solution which may be further diluted with either Sodium Chloride for Injection or 5 percent Dextrose for Injection. The reconstituted solution should be used intravenously only and should be administered by IV drip over a 1 to 2 hour period. Injection of BiCNU over shorter periods of time may produce intense pain and burning at the site of injection.

Use only glass containers for preparation and administration.

Important Note:

The lyophilized dosage formulation contains no preservatives, use once only immediately after dilution and discard any residue.

STORAGE

Unopened vials of the dry powder should be shipped and stored under refrigeration (2°C-8°C). Do not freeze. Shelf life is 36 months.

Important Note:

Carmustine has a low melting point (approximately 30.5°C - 32.0°C). Exposure of the drug to this temperature or above will cause the drug to liquify and appear as an oil film in the bottom of the vials. This is a sign of decomposition and vials should be discarded.

The stability of reconstituted solutions has not been demonstrated and their use should be commenced immediately after preparation.
Poisoning and Overdosage

No information is available relating to carmustine poisoning in humans. Treatment will be mainly supportive. Haematological and gastrointestinal toxic effects are expected to be the principal manifestations of carmustine overdosage.

PRESENTATION

BiCNU (carmustine). Each carton contains a vial containing 100 mg carmustine and a vial containing 3 mL sterile diluent. BiCNU is a lyophilized powder, pale yellow in an amber glass vial. Diluent is clear sterile ethanol in a clear glass vial – AUST R 19243.

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DATE OF APPROVAL

Shelf-life extension approved: September 1995
Safety amendments approved by Therapeutic Goods Administration: October, 1998
Alternate manufacturing site for diluent approved 3rd March 2009
Safety Related Notification: 20th July 2010

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