

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BiCNU, 100 mg, Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 100 mg carmustine.

Each vial of diluent contains 3 mL dehydrated alcohol (equivalent to 2.37 g).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder for reconstitution.

BiCNU (1,3-bis (2-chloroethyl)-1-nitrosourea) is one of the nitrosoureas. It 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

1. Primary Brain tumours - glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumours.
2. Multiple Myeloma - in combination with prednisone.
3. Menigeal Leukaemia - BiCNU should be used in patients who have not responded to intrathecal administrations of methotrexate.
4. 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.
5. Malignant Melanoma (disseminated) - BiCNU should be used in combination with other active chemotherapeutic agents.
6. 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.
7. Other Solid Tumours; Gastrointestinal Carcinoma, Breast Carcinoma - BiCNU has been used in combination with other therapeutic agents only after other conventional methods have failed.

4.2 Dose and method of administration

Dose

Adults

The recommended dose of BiCNU as single agent in previously untreated 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 two successive days. When BiCNU is used in combination with other myelo suppressive 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; leukocytes 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 Undesirable effects).

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
Leukocytes	Platelets	
>4000	>100,000	100 percent
3000-3,999	75,000-99,999	100 percent
2,000-2,999	25,000-74,999	70 percent
<2,000	<25,000	50 percent

Paediatric population

BiCNU should be used with extreme caution in children due to the high risk of pulmonary toxicity.

Method of Administration

BiCNU is administered by slow intravenous infusion.

BiCNU SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS 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. Rapid IV infusion of BiCNU may produce intensive flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting 4 hours.

Preparation of Intravenous Solutions

To facilitate reconstitution, allow BiCNU and the supplied sterile diluent (absolute ethanol) to come to controlled room temperature (15° 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 BiCNU in 10 percent ethanol having a 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 hyperpigmentation of the affected areas. If BiCNU lyophilized material or solution contacts 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.

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.

4.3 Contraindications

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

BiCNU should not be given to individuals with decreased circulating platelets, leukocytes, or erythrocytes either from previous chemotherapy or other causes.

4.4 Special warnings and precautions for use

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

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 carmustine.

Since delayed bone marrow toxicity is a 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 BiCNU is cumulative, and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see dosage adjustment table under Dose and method of administration).

BiCNU induced pulmonary toxicity has been reported to occur with a frequency ranging up to 30% but may be as high as 100% in children. Early onset pulmonary toxicity usually occurs within 3 years of therapy and is characterized by pulmonary infiltrates and/or fibrosis, and cases of fatal pulmonary toxicity have occurred. Cases of late pulmonary fibrosis, occurring up to 17 years after treatment, have also been reported. Age of onset has been reported from 1 year and 10 months to 72 years of age.

Risk factors include smoking, the presence of a respiratory condition, pre-existing radiographic abnormalities, sequential or concomitant thoracic irradiation, previous thoracic irradiation, and association with other agents that cause lung damage. The incidence appears to be dose related with total cumulative doses of 1200-1500mg/m² being associated with increased likelihood of lung fibrosis. 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.

In a recent long-term follow-up of 17 patients who survived childhood brain tumors, eight (47%) died of lung fibrosis. Of these eight deaths, two occurred within 3 years of treatment, and six occurred 813 years after treatment. Of the patients who died, the median age at treatment was 2.5 years (ranging from 1-12); the median age of the long term survivors was 10 years (5-16 years at treatment). All five patients treated below the age of 5 years have died of pulmonary fibrosis. In this series, dose of BiCNU did not influence fatal outcome nor did co-administration of vincristine or spinal irradiation. Of the remaining survivors available for follow-up, evidence of slowly progressive lung fibrosis was detected in all patients.

The risks and benefits of BiCNU therapy must be carefully considered, especially in young patients, due to the extremely high risk of pulmonary toxicity.

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 (DL_{CO}) are particularly at risk.

Injection site reactions may occur during the administration of BiCNU (see Undesirable effects). 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.

Paediatric Use

BiCNU should be used with extreme caution in children due to the high risk of pulmonary toxicity (see Special warnings and precautions for use).

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

BiCNU has been administered through an intraarterial intracarotid route; this procedure is investigational and has been associated with ocular toxicity.

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

4.5 Interaction with other medicines and other forms of interaction

No information available.

4.6 Fertility, pregnancy and lactation

Use in pregnancy (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 foetus must be carefully weighed.

Use in lactation

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 from BiCNU in nursing infants, nursing should be discontinued while using BiCNU.

Carcinogenicity, mutagenicity, impairment of fertility

Carmustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. Carmustine also affects fertility in male rats at doses somewhat higher than the human dose. Carmustine is carcinogenic in rats and mice, producing a marked increase in tumour incidence in doses approximating those employed clinically.

4.7 Effects on ability to drive and use machines

No information available.

4.8 Undesirable effects

Haematopoietic

The most frequent and most serious toxicity of BiCNU is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose-related. Platelet nadirs occur at 4 to 5 weeks; leukocyte nadirs occur at 5 to 6 weeks post therapy. Thrombocytopenia is generally more severe than leukopenia, however, both may be dose limiting toxicities. Anaemia also occurs, but is generally less severe.

BiCNU may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.

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

Gastrointestinal

Nausea and vomiting after IV administration of BiCNU are noted frequently. This toxicity appears within 2 hours of dosing, usually lasting 4 to 6 hours, and is dose-related. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect.

Hepatic

When high doses of BiCNU have been employed, a reversible type of hepatic toxicity manifested by increased transaminase, alkaline phosphatase and bilirubin levels, has been reported in a small percentage of patients.

Pulmonary

Pulmonary toxicity is also manifested as pneumonitis and interstitial lung disease in postmarketing experience. (see Special warnings and precautions for use).

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 BiCNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

Cardiovascular

Hypotension, tachycardia.

Other

Burning at the site of injection is common but true thrombosis is rare. Local soft tissue toxicity has been reported following extravasation of BiCNU. Infiltration of BiCNU may result in swelling, pain, erythema, burning sensation and skin necrosis.

Accidental contact of reconstituted BiCNU with the skin has caused burning and hyperpigmentation of the affected areas.

Rapid IV infusion of BiCNU may produce intensive flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting about 4 hours.

Neuroretinitis has been reported.

Chest pain, headache, allergic reactions have been reported.

4.9 Overdose

For information on the management of overdose, contact the New Zealand Poison Information Centre on 0800 POISON or 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotheapeutic group: Antineoplastic medicine, alkylating agent, nitrosourea,
ATC code: L01AD01

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 BiCNU may be due to metabolites.

The oncolytic effect of carmustine is considered in part to be due to the inhibition of the synthesis of DNA and RNA by preventing the synthesis of purine nucleosides and their conversion to components of DNA. In addition carmustine interferes selectively with the utilisation of histidine or histidine metabolites.

5.2 Pharmacokinetic properties

Distribution

Intravenously administered BiCNU is rapidly degraded, with no intact drug detectable after 15 minutes. However, in studies with C14 -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, BiCNU crosses the blood brain barrier quite effectively. Levels of radioactivity in the CSF are 50 percent or greater than those measured concurrently in plasma.

Metabolism

No information.

Excretion

Approximately 60 to 70 percent of a total dose is excreted in the urine in 96 hours and about 10 percent as respiratory CO₂. The fate of the remainder is undetermined.

5.3 Preclinical safety data

None.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dehydrated Alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Products should be stored at 2°C – 8°C. (Refrigerate. Do not freeze).

The unopened vial may have a physical appearance ranging from lacy flakes to a congealed mass, with no evident degradation of the carmustine active ingredient. Do not use if product has liquified.

After reconstitution as recommended, the reconstituted solution should be used immediately and any residue discarded. Only use glass containers for BiCNU preparation and administration.

Important Note

BiCNU 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. If there is a question of adequate refrigeration upon receipt of this product, immediately inspect the larger vial in each individual carton. Hold the vial to a bright light for inspection. The BiCNU will appear as a very small amount of dry flakes or dry congealed mass. If this is evident, the BiCNU is suitable for use and should be refrigerated immediately.

6.5 Nature and contents of container

Each package includes a vial containing 100 mg carmustine, a pale yellow powder for reconstitution, and a vial containing 3 ml sterile diluent. Diluent is clear sterile ethanol in a clear glass vial.

6.6 Special precautions for disposal

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.

To minimise the risk of dermal exposure, always wear impervious gloves when handling vials containing BiCNU (carmustine) powder for injection. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Australia

Sponsor: Emcure Pharmaceuticals Pty Ltd.

Distributed by: Luminarie Pty Ltd

Baulkham Hills NSW 2153

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New Zealand

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9. DATE OF FIRST APPROVAL

17 April 1975

10. DATE OF REVISION OF THE TEXT

29 April 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
1	Sponsor company name and address details updated
2	Typo error and text formatting to be done
3	Change in distributor details