PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrBiCNU*

Carmustine For Injection USP

Lyophilized Powder, 100 mg/vial
Route of Administration: Intravenous Infusion

Antineoplastic Agent

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RECENT MAJOR LABEL CHANGES

4 Dosage Administration, 4.3 Reconstitution	06/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BiCNU (carmustine for injection) is indicated as palliative therapy to surgery and radiotherapy as a single agent or in established combination therapy with other chemotherapeutic agents in the following:

- Brain tumours - glioblastoma, medulloblastoma, astrocytoma and metastatic brain tumours.
- Multiple myeloma - in combination with glucocorticoid such as prednisone.
- 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.
- Non-Hodgkin's lymphomas - 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.
- Tumours of the Gastrointestinal tract.
- Malignant melanoma when used in combination with other antineoplastic drugs.

Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. (see 7.1.3 Pediatrics).

Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to BICNU (carmustine), to other nitrosoureas or to any excipients. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Pregnant women and Breastfeeding (see 7.1.1 Pregnant Women, 7.1.2 Breastfeeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **BICNU (Carmustine for Injection USP) should only be only be used by physicians with special experience in the field of chemotherapy.**
- **BICNU can cause common serious side effects such as**
  - **Severe bone marrow depression or Myelosupression**
  - **Hepatic toxicity**
  - **Severe (end-stage) Renal impairment**
- **Complete blood count, Hepatic and Renal function tests are checked prior to treatment and regularly monitored during therapy**
- **BiCNU should be used with extreme caution in children (<18 years of age) due to high risk of pulmonary toxicity**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Patients with impaired renal function
- Pediatric and Geriatric patients
- In patients with Combination/Concomitant therapy with other myelosuppressive drugs or in whom the bone marrow reserves are depleted.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of BiCNU as a 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 2 successive days.

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

Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose, in both monotherapy as well as in combination therapy with other myelosuppressive medicinal products. The following schedule is suggested as a guide to dosage adjustment: **Table 1**

Nadir After Prior Dose		Percent of Prior Dose to be Given
Leukocytes	Platelets	
> 4000	> 100,000	100%
3000 - 3999	75,000 - 99,999	100%

2000 - 2999	25,000 - 74,999	70%
< 2000	< 25,000	50%

In cases where the nadir after initial dose does not fall in the same row for leucocytes and platelets (e.g. leucocytes >4,000 and platelets <25,000) the value given the lowest percentage of prior dose should be used (e.g. platelets <25,000 then a maximum of 50% of prior dose should be given).

Patients with impaired renal function
In patients with impaired renal function, the dose of carmustine should be reduced depending on the glomerular filtration rate.

Geriatrics (65 years of age)
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 take into consideration concomitant disease or other therapy with other medicinal products.

As elderly patients are more likely to have decreased renal function, care should be taken in selecting the dose, monitoring renal function and reducing the dose accordingly.

Pediatrics (<18 years of age)
Carmustine is contraindicated (see 2 CONTRAINDICATIONS) due to the high risk of pulmonary toxicity (see 8 ADVERSE REACTIONS).

4.3 Reconstitution

Preparation of Intravenous Solutions

Dissolve carmustine (100 mg powder) with 3 mL of the supplied sterile diluent (propylene glycol injection) until clear solution is achieved. If required, stir vigorously to get clear solution.

Use the propylene glycol vial for reconstitution after achieving the room temperature only and use the larger bore size needle (less than 22-gauge needle) to remove the diluent from the vial.

Each mL of the reconstituted stock solution will contain 33.3 mg of carmustine. Reconstitution, as recommended, results in a yellowish solution.

The reconstituted stock solution must be further diluted upto 500 mL either with 0.9% Sodium chloride injection or 5% dextrose injection. The resulting solution contains final concentration of 0.2 mg/mL of Carmustine which must be stored protected from light.

Examine reconstituted vials for crystal formation prior to use. If crystals are observed, they may be re-dissolved by warming the vial to room temperature with agitation. Reconstituted vials should be inspected visually for particulate matter and discoloration prior to administration.

After reconstitution and dilution

After reconstitution as recommended, the reconstituted solution is stable for 480 hours under refrigeration (2°C -8°C) and 24 hours at temperature (25°C ±2°C) in glass container. Examine reconstituted vials for crystal formation prior to use.

The reconstituted diluted solution should be used within 8 hours at 25°C±2°C and protected from light.

The reconstituted diluted solution can be stored in the refrigerator (2-8° C) for 48 hours and, protected from light, for an additional 6 hours at temperature (25°C ± 2°C).

Table 2- Reconstitution

Vial Size	Volume of Diluent to be added to Vial	Approximate Available Volume	Concentration per mL
100 mg powder	3 mL sterile diluent	500 mL (3 mL reconstituted solution plus 497 mL of 0.9% NaCl Injection OR 497 mL 5% Dextrose Injection)	0.2 mg/mL of Carmustine

4.4 Administration

The reconstituted diluted solution should be used intravenously only and should be administered by slow IV infusion over a 1- to 2-hour period, protected from light. Rapid IV infusion in less than one hour may produce intense pain and burning at the site of injection. (See 8 ADVERSE REACTIONS)

The lyophilized dosage formulation contains no preservatives and is not intended as a multiple dose vial. The reconstituted diluted solution in glass or polypropylene containers can be stored in the refrigerator (2-8°C) for 48 hours and, protected from light, for an additional 6 hours at temperature (25°C ± 2°C). (For more information See 11 STORAGE, STABILITY AND DISPOSAL)

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

In the case of overdosage, the patient should be treated symptomatically.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3– Dosage Forms, Strengths, Composition and Packaging:

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (iv)	Lyophilized powder, 100 mg/vial	Powder – no excipients Sterile Diluent- Propylene glycol

BiCNU (carmustine for Injection, USP; DIN: 00297763) is available in a package that includes a 30 mL amber glass vial with butyl rubber **(not made with natural rubber latex)** stopper containing 100 mg of carmustine (powder) and a glass vial containing 3 mL of sterile diluent.

7 WARNINGS AND PRECAUTIONS

Carmustine should only be used by physicians with special experience in the field of chemotherapy.

General

Parenteral administration

The intra-arterial compatibility has not been tested. Severe tissue damage can be expected in case of inadvertent intra-arterial administration. Experimental direct injection of Carmustine to the carotid artery has been associated with ocular toxicity.

During administration of carmustine, administration site reactions may occur. Given the possibility of extravasation, close monitoring of the infusion site is recommended for possible infiltration during administration. A special method for handling extravasation is currently unknown. Accidental contact of the reconstituted infusion solution with the skin has resulted in burns and excessive pigmentation in the affected areas. Local soft tissue toxicity resulting from extravasation of carmustine has been reported. Infiltration of carmustine may cause swelling, pain, erythema, burning, and skin necrosis.

Comorbidities and poor disease status

Patients with comorbidities and poorer disease status are at higher risk for adverse events. This is especially important for elderly patients.

Carcinogenesis and Mutagenesis

BiCNU is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. The benefit to the mother versus the risk of toxicity to the mother and fetus must be carefully weighed. See 16 NON-CLINICAL TOXICOLOGY for discussion on animal data.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed, however, there is a possibility of dizziness as an adverse reaction reported with this medicinal product which may affect the ability to drive and use machines. This medicinal product contains propylene glycol which mimics the similar effects of alcohol in the medicinal product.

Hematologic

Bone marrow toxicity

Delayed and cumulative bone marrow toxicity is a common and severe toxic adverse reaction of Carmustine. Complete blood count should be monitored frequently for at least six weeks after a dose. In case of a decreased number of circulating platelets, leucocytes or erythrocytes either from previous chemotherapy or other cause the dose should be adjusted (see Table 1, 4.2 Recommended Dose and Dosage Adjustment). In addition to this, the liver, kidney and lung function should be examined and monitored regularly during the carmustine therapy. Repeat doses of Carmustine should not to be given more frequently than every six weeks.

The myelosuppression is dose and cumulative dose related, and often biphasic. Thrombocytopenia is generally more pronounced than leukopenia, but both are dose-limiting adverse effects. Anaemia is common but is usually less pronounced. The bone marrow toxicity of Carmustine is cumulative and therefore the dosage adjustment must be considered based on nadir blood counts from prior dose (see 4.2 Recommended Dose and Dosage Adjustment).

Respiratory

Lung toxicity has been observed in up to 30% of patients. The early onset of lung toxicity (within 3 years of treatment) resulted in pulmonary infiltrates and / or pulmonary fibrosis, some of which were fatal. The patients were between 22 months and 72 years old. The risk factors include smoking, respiratory diseases, existing radiographic abnormalities, sequential or simultaneous chest irradiation and the combination with other active substances that can cause lung damage. The incidence of side effects is likely to be dose dependent. Cumulative doses of 1200-1500 mg / m2 have been associated with an increased likelihood of pulmonary fibrosis. Spirometry (FVC, DLCO) should be performed regularly during treatment. Patients who have a baseline value of <70% of the expected forced expiratory vital capacity (FVC) or the carbon monoxide diffusion capacity (DLCO) are particularly at risk.

Cases of very late onset pulmonary fibrosis (up to 17 years after treatment) have been observed in patients who received carmustine in childhood or adolescence.

Long-term follow-up of 17 patients who survived childhood brain tumors showed that 8 of them died of pulmonary fibrosis. Two of these 8 deaths occurred within the first 3 years of treatment and 6 within 8-13 years of treatment. The mean age (at the time of treatment) of the deceased patients was 2.5 years (1-12 years) and the mean age of the long-term survivors was 10 years (5-16 years). All patients younger than 5 years at the time of treatment died of pulmonary fibrosis. Neither the carmustine dose nor the addition of vincristine or irradiation to the spine had any effect on the fatal outcome.

Pulmonary fibrosis was noted in all remaining survivors who were available for follow-up. The risk-benefit ratio of carmustine therapy must be carefully considered due to the high risk of lung toxicity.

Hepatic/Biliary/Pancreatic

Hepatic necrosis may occur after administration of doses higher than those recommended in the dosage instructions**.**

Monitoring and Laboratory Tests

In addition to Complete Blood Count, hepatic, and renal should also be checked prior to treatment and regularly monitored during therapy (see 8 ADVERSE REACTIONS).

Renal

Renal changes with decrease in kidney size, progressive azotemia, and renal failure have been observed after high cumulative doses and after long-term treatment with carmustine and related nitrosoureas.

Reproductive Health: Female and Male Potential

- **Fertility**

  In animal experiments, carmustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at doses that are equivalent to human doses. BICNU also affects the fertility of male rats at doses slightly higher than the human dose. At doses roughly equivalent to those used in clinical studies, BICNU is carcinogenic in rats and mice by causing a marked increase in the incidence of tumors. See 16 NON-CLINICAL TOXICOLOGY for discussion on animal data.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate data from the use of carmustine in pregnant women. Animal studies have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY). Carmustine must not be used during pregnancy (see 2 CONTRAINDICATIONS).

7.1.2 Breast-feeding

It is not known whether carmustine or metabolites are excreted in breast milk. A risk to the newborn / child cannot be excluded. Due to the potential for serious side effects in the infant, breast-feeding should not be performed during use (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

BiCNU should be used with extreme caution in children due to the high risk of pulmonary toxicity (see 3 SERIOUS WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS).

7.1.4 Geriatrics

No data from clinical studies of BiCNU 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.

BiCNU and its metabolites are 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 (see 4.2 RECOMMENDED DOSE AND DOSAGE ADJUSTMENT).

8 ADVERSE REACTIONS

Summary of the safety profile:

The table includes adverse events that were presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1 % of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse events are included if the incidence is >5 % higher in the treatment group.

High dose is defined as >200 mg/m^2.

Tabulated list of adverse reactions

The following table includes adverse reactions of carmustine listed by MedDRA system organ class and frequency convention presented in order of decreasing seriousness:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to < 1/1,000)

Very rare (<1/10,000)

Not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

MedDRA-System organ class	**Frequency**	**Adverse reactions** Clinically important side effects are in italics in the table
Infections and parasitic diseases	Not known	Opportunistic infections (including fatal ones)
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	Common	Acute leukemia, bone marrow dysplasia; after long-term use.
	Not known	Secondary malignancies
Blood and lymphatic system disorders	Very common	*Myelosuppression (*see 7 WARNINGS AND PRECAUTIONS*)*
	Common	Anaemia
Immune system disorders	Not known	Allergic reaction
Nervous system disorders	Very common	Headache
	Rare	Encephalopathy (high dose therapy and dose limiting)
	Not known	Muscle pain
Eye diseases	Very common	Ocular toxicity, transient conjunctival injection, and blurred vision; Retinal hemorrhage
	Rare	Neuroretinitis
Heart disease	Very common	Hypotension due to alcohol content from diluents (high dose therapy)
	Not known	Tachycardia, anginal pain complaints
Vascular disease	Very common	Phlebitis
	Rare	Veno-occlusive disease (high dose therapy)
Respiratory, thoracic and mediastinal disorders	*Very common*	*Lung toxicity[1] (see 7 WARNINGS AND PRECAUTIONS),*
	Rare	Interstitial fibrosis (at lower doses)
Gastrointestinal disorders	Very common	*Nausea and vomiting[2], frequently appears within 2-4 hours after administration, lasts for 4-6 hours and are dose-related*
	Not known	Neutropenic enterocolitis
Liver and biliary diseases	Common	Hepatotoxicity, reversible, onset with a delay up to 60 days after administration (high-dose therapy and dose-limiting), manifested by a reversible increase in bilirubin, alkaline phosphatase and SGOT.

MedDRA-System organ class	Frequency	Adverse reactions Clinically important side effects are in italics in the table
Skin and subcutaneous tissue disorders	Very common	Dermatitis when applied topically, gets better with reduced concentration of the compound product; Hyperpigmentation, temporary, in the case of accidental skin contact.
	Common	Reaction at the injection site
	Not known	Risk of extravasation: Vesicant
Kidney and urinary tract disorders	Rare	*Renal toxicity (increased at high cumulative doses).*
Reproductive system and breast disorders	Rare	Gynecomastia
	Not known	Infertility, teratogenesis
General disorders and administration site conditions	Common	Burning sensation at the injection site
	Very rare	Thrombophlebitis

[1] At post-marketing clinical follow-up, the pulmonary toxicity was also manifested as pneumonitis and interstitial lung disease

[2] Prior administrations of antiemetic and sedatives is effective in diminishing and sometimes preventing this adverse event

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Cimetidine

Concomitant use leads to delayed, major, suspected, increased carmustine toxic effect (due to the inhibition of carmustine metabolism) or increased myelotoxicity (e.g. leukopenia and neutropenia).

9.2 Drug-Food Interactions

Not applicable

9.3 Drug-Herb Interactions

Not applicable

9.4 Drug-Laboratory Test Interactions

Not applicable

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Carmustine (1,3-bis (2-chloroethyl) -1-nitrosourea) is a cell-cycle phase nonspecific antineoplastic agent of the nitrosourea type, which exerts tumour cytotoxicity via multiple mechanisms. As an

alkylating agent, it can alkylate reactive sites on nucleoproteins, thus interfering with DNA and RNA synthesis and DNA repair. It is able to form interstrand crosslinks in DNA, which prevents DNA replication and transcription. In addition, carmustine is known to carbamoylate lysine residues on proteins causing irreversible inactivation of enzymes including glutathione reductase. The carbamoylating activity of carmustine is generally considered less significant than the alkylating activity in its action on tumours, but carbamoylation may serve to inhibit DNA repair.

10.2 Pharmacodynamics

The antineoplastic and toxic activities of carmustine may be due to its metabolites. Carmustine and related nitrosoureas are unstable in aqueous solutions and degrade spontaneously to reactive intermediates that are capable of alkylation and carbamoylation. The alkylating intermediates are believed to be responsible for the antitumor effect of carmustine. However, opinion is divided over the role of the carbamoylating intermediates as mediators of the biological effects of the nitrosoureas. On one hand, their carbamoylating activity was reported to contribute to the cytotoxic properties of their parent drugs by inhibiting DNA repair enzymes. On the other hand, it has been speculated that the carbamoylating species may mediate some of toxic effects of carmustine.

Carmustine crosses the blood-brain barrier readily because of its lipophilic nature.

10.3 Pharmacokinetics

Distribution

Intravenously administered Carmustine is rapidly degraded, with no drug intact detectable after 15 minutes. Because of the good lipid solubility and the lack of ionization at the physiological pH, Carmustine is very well transferred through the blood-brain barrier. Levels of radioactivity in the CSF are at least 50 % higher than those measured concurrently in plasma. The kinetic of carmustine in humans is characterized by a two-chamber model. After the intravenous infusion over 1 hour, the carmustine-plasma level drops in a biphasic manner.

Biotransformation

It is presumed that the metabolites of carmustine causes its antineoplastic and toxic activity.

Elimination

Approximately 60-70 % of a total dose is excreted in the urine in 96 hours and about 10 % as respiratory CO2. The fate of the remainder 20-30 % is undetermined.

11 STORAGE, STABILITY AND DISPOSAL

The solution for infusion is unstable in polyvinyl chloride (PVC) containers. The carmustine solution can be administered from **glass bottles or polypropylene container only**, using PVC-free infusion set.

This medicinal product must not be mixed with other medicinal products except those mentioned (See 4.3 RECONSTITUTION).

The unopened vials containing the dry powder should be transported and stored at refrigerated temperature (2 to 8˚C). Alternatively, BICNU can be transported on dry ice and then stored at

refrigerated temperature (2˚C to 8˚C). The recommended storage conditions for the unopened vials will prevent significant decomposition until the expiry date stated on the package. The lyophilized product does not contain any preservatives and is only suitable for single use.

Physical phenomena ranging from pointed flakes to a rigid mass can occur in the unopened vial without any decomposition of the active ingredient carmustine. The storage of carmustine at 27˚C or higher temperatures leads to the liquefaction of the substance, because carmustine has a low melting point (approx. 30.5˚ C to 32.0˚C). A film of oil will appear on the bottom of the vial as a sign of disintegration. These may no longer be used. If it is unclear whether the product has been adequately refrigerated when the product is received, the larger vial in each individual carton should be inspected immediately. To check, the vial is held in bright light. Carmustine appears as a very small amount of dry flakes or as a dry, rigid mass. If so, BICNU is suitable for use and should be refrigerated immediately. Glassware was used for the stability data reported in this section. Only glass vessels should therefore be used for production and application.

After reconstitution and dilution

After reconstitution as recommended, the reconstituted solution is stable for 480 hours under refrigeration (2°C -8°C) and 24 hours at temperature (25°C ±2°C) in glass container. Examine reconstituted vials for crystal formation prior to use. If crystals are observed, they may be re-dissolved by warming the vial to room temperature with agitation. Keep the vials in the outer carton in order to protect from light.

The reconstituted diluted solution (See 4.3 RECONSTITUTION, 4.4 ADMINISTRATION) should be used within 8 hours at 25℃±2℃ and protected from light.

The reconstituted diluted solution can be stored in the refrigerator (2-8° C) for 48 hours and, protected from light, for an additional 6 hours at temperature (25°C ± 2°C).

The solution should be protected from light until end of administration. The appearance of reconstituted diluted solution is clear, pale yellowish solution free from visible particles.

Do not use this drug after the expiry date which is stated on the label and carton after expiry. The expiration date refers to the last day of that month.

12 SPECIAL HANDLING INSTRUCTIONS

Each pack contains 1 vial with 100 mg powder (amber glass bottle type I with butyl rubber stopper) and 1 vial (transparent glass bottle type I) with 3 ml sterile solvent.

Carmustine should only be used by doctors who have experience in tumor therapy.

For single use only. Use only clear and colorless to light yellow solutions. Only use glass containers for the production and application.

The precautionary measures required for handling cytostatics must be strictly observed. Various guidelines have been published on this subject. There is no general agreement that the practices recommended in these guidelines are necessary or appropriate.

Accidental contact of the finished infusion solution with the skin has caused burns and excessive pigmentation in the affected areas. If BICNU lyophilisate or solution comes into contact with the skin or mucous membrane, the skin or mucous membrane should be washed thoroughly with water immediately.

To minimize the risk of dermal exposure, impervious gloves should always be worn when handling BICNU dry ampoules with solvent. This includes all handling of the preparation in clinics, pharmacies, storage rooms, home care wards. In addition, during unpacking and inspection, during transport within a building and during the preparation and administration of the dose.

Guidelines for the safe handling and disposal of antineoplastic agents must be observed.

SPECIAL INSTRUCTIONS: Handling and Disposal

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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

Personnel preparing BiCNU should wear safety glasses and disposable gowns and masks. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing BiCNU lyophilized 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.

1. Preparation of BiCNU should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. All needles, syringes, vials and other materials which have come in contact with BiCNU should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the Manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

3. Personnel regularly involved in the preparation and handling of BiCNU should have bi-annual blood examinations.

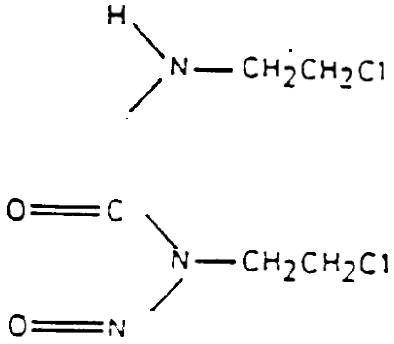
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Trade Name: BiCNU
Proper Name: Carmustine
Chemical Name: 1,3 Bis (2-chloroethyl)-1-nitrosourea

Structural Formula:



Molecular Formula: $C_5H_9N_3O_2Cl_2$

Molecular Weight: 214.06

Physicochemical properties: BiCNU, (carmustine) is a nitrosourea which comes in the form of thin, lacy, brittle, pale yellow flakes having a melting point of 30.5 - 32.0°C. It is light sensitive and vesicant and decomposes readily at room temperature. It is poorly soluble in water and in saline; quite soluble in propylene glycol; soluble in 50% alcohol and highly soluble in lipids.

It is most stable at pH 4, but in more acidic as well as in aqueous solutions of pH greater than 7, it is short lived.

14 CLINICAL TRIALS

Not applicable.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

PHARMACOLOGY

ANIMAL

Plasma Level

After a single IV injection of 10 mg/kg in the dog, the plasma level of intact carmustine reaches a peak level of 30 mcg/mL with a half-life of less than 15 minutes. The same half-life has also been found in the mouse. It is interesting to note that plasma samples taken as early as 5 minutes after oral or parenteral administration in the monkey did not contain intact carmustine.

In the monkey, the half-life of ^{14}C labeled carmustine and its degradation products as determined by 14C counts is prolonged up to 22 hours after a single IV injection of 10 mg/kg.

One minute after IV infusion, intact carmustine could be detected in the CSF of the dog and it reaches 48% of the plasma concentration after equilibration.

Following IV injection, intact carmustine was not characterized in the CSF of the monkey.

Studies with ^{14}C labeled carmustine showed that in the dog, after a 10 mg/kg IV injection, radioactivity enters the CSF rapidly and reaches 18% of the plasma level one minute following drug administration. Equilibration occurs by 15 minutes and the concentration of carmustine reaches about 60% that of plasma.

In the monkey, 15 minutes after IV injection, the level of carmustine in the CSF was 73% that of plasma and after 90 minutes as high as 90%.

Urinary Excretion

Ten minutes after a single intravenous injection in the dog, intact carmustine begins to appear in the urine. The excretion reaches a peak at about 2 hours and then gradually tapers off until 3 hours later. Nevertheless, in no case is the total amount of unchanged carmustine excreted in 4 hours in excess of 0.1% of the dose.

In mice, the urinary excretion of ^{14}C carmustine is fast. For instance, 4 hours after a 10 mg/kg IV injection it reached 62% of the administered dose. This excretion is initially faster after intraperitoneal administration than subcutaneous or oral, but after 24 hours no significant differences are noted between the different dose routes: the excretion level being close to 80%.

In the monkey, 48 hours after a 10 mg/kg IV injection of ^{14}C carmustine, an average of 68% of ^{14}C radioactivity is recovered in the urine. Further urinary excretion is minimal after 48 hours.

In the dog, the urinary excretion is rather slow with 16% in 2 hours and 30% in 6 hours after a 10 mg/kg IV dose of ^{14}C carmustine.

Pulmonary Excretion

Expired CO_2 was collected from mice given an intraperitoneal dose of ^{14}C labeled carmustine. The 24 hours' recovery of ^{14}C CO_2 accounted for an average of 8.5% of the radioactive dose. After IV administration into monkeys no more than 2% of the dose was collected as $^{14}CO_2$.

HUMAN

Protein Binding

The average extent of binding of carmustine with human plasma proteins is about 80% at 0°C. (The experiments were carried out at 0°C because of the extreme instability of carmustine in plasma).

Plasma Level

Plasma samples taken as early as 5 minutes after oral or parenteral drug administration did not contain intact carmustine. Plasma levels of the radioactivity were prolonged with a half-life of about 34 hours for the orally and 67 hours for the intravenously administered ^{14}C carmustine.

C.S.F.

After IV administration of ^{14}C carmustine, radioactive 14C was found in the CSF of man equilibrating with plasma radioactivity in about 1 hour showing 97 and 30% of plasma level in 2 men, respectively.

Urinary Excretion

Extremely small amounts of intact carmustine were detected in urine samples collected at one-half hour following drug administration (IV or oral). After the second half hour urine samples did not contain unaltered carmustine.

Urinary excretion of the radioactivity was strikingly similar in all patients regardless of the route of administration (IV or oral) and quite comparable to monkeys. By 96 hours, an average of 65% of the isotope had been recovered in the urine.

Pulmonary Excretion

Over 24 hours, the radioactivity excretion of ^{14}C carmustine as $^{14}CO2$ was approximately 10% of the dose after oral administration and 6% when given IV. Although carmustine is well absorbed after oral, intraperitoneal and subcutaneous administration, it is mainly used by the intravenous route. The active moiety of carmustine is still unknown but the high degradation rate of carmustine in plasma suggests that the biological activity as well as the delayed toxicity of carmustine are related at least partly to its degradation products. The in vitro decomposition of carmustine has been studied quite extensively. However, to date, nothing is known on its biodegradation except for the fact that part of it is excreted as CO_2 as determined with ^{14}C labeled carmustine.

TOXICOLOGY

Acute Toxicity

LD_{50} of carmustine was established in the rat and the mouse after different administration routes.

Species	Dose Range (mg/kg)	Route	Calculation of LD_{50} Based on Observations period of	LD_{50} (mg/kg)
Mouse	25.1 - 79.4	IV	21 days	45
Mouse	50.0 - 60.0	IM	48 days	23
Mouse	15.9 - 100.0	Oral (methyl-cellulose)	21 days	42
Mouse	20.0 - 112.0	IP	25 days	45
Rat	14.0 - 50.0	IV	23 days	20
Rat	10.0 - 39.8	Oral	23 days	20
Rat	10.0 - 39.8	Oral in saline	23 days	20

It is interesting to note the similarities between the IV and oral route toxicity both in the mouse and the rat.

Delayed toxic manifestations of carmustine have been shown in various animals including the mouse, rat, dog and monkey. They involve chronologically the following systems:

Hematopoietic System

Initially carmustine deletes the several hematopoietic elements of the marrow and lymphoidal components of the spleen and nodes resulting in marked and prolonged (2-3 weeks) leukopenia and thrombocytopenia. Marrow depression was reversible if the animal survived.

Liver

Although delayed toxicities are commonly seen after exposure of experimental animals to alkylating agents, carmustine has shown striking delayed hepatic toxic manifestations ranging from 14 to 119 days.

After a single oral dose of carmustine in rats, the hepatic function was assessed by a series of standard techniques. By 1 week, all doses of carmustine prolonged pentobarbital hypnosis and BSP retention, later, elevations of serum bilirubin appeared, but these were delayed by as long as 63 days at the lowest dose. Serum bilirubin was direct-reacting at early stages but later shifted to indirect-reacting coincidental with a reduction of BSP retention.

Histopathologic study revealed early pericholangitis and necrosis of bile ductules. Later biliary hyperplasia and cirrhosis developed. These findings disclose a unique ability of carmustine to produce a prolonged and progressive bimodal toxicity resulting in hyperbilirubinemia. These

toxic manifestations were also coupled with an increase in ALT and AST as well as alkaline phosphatase.

Renal

Renal damage without distinctive kidney pathology was reflected by elevated BUN in the monkey and the dog following oral or IV dosage of carmustine.

Others

It may be noted that weight loss during treatment with carmustine was often seen and it appears that this is a manifestation of distinct toxic effects of carmustine. Pertinent to that observation is the finding that carmustine causes a significant reduction in glucose (54.4%) and water (50.0%) absorption from the gut.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBiCNU
Carmustine For Injection USP

Read this carefully before you start taking BiCNU and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BiCNU.

Serious Warnings and Precautions

- **BiCNU** should only be prescribed by doctors who are experienced in the use of drugs to treat cancer.
- Your healthcare professional should do some blood tests on you regularly. This will check your liver and kidney health, as well as your blood cell count.
- **BiCNU** may cause the following serious side effects:
    - **Myelosuppression** (a large decrease in the production of blood cells and platelets by the bone marrow). This includes **Thrombocytopenia** (low blood platelets), **leukopenia** (low white blood cells) and **anemia** (low red blood cells). You should not get a dose of BiCNU more often than every 6 weeks. Your healthcare professional will do blood tests for at least 6 weeks after a dose. They will also check your liver, kidney and lung health.
    - **Liver problems.** High doses of BiCNU might cause liver damage.
    - **Kidney problems.** Decrease in kidney size, kidney damage and failure can happen after high doses and long-term treatment with BiCNU.
- **BiCNU** should be used in children (less than 18 years old) with extreme caution due to high risk of **pulmonary fibrosis** (lung damage).

See the Serious side effects and what to do about them table, below, for more information on these serious side effects.

What is BiCNU used for?

BiCNU is used as palliative therapy (to relieve and prevent suffering) by itself or with other anti-cancer drugs in patients with:

- Brain cancers:
    - astrocytoma, ependymoma, glioblastoma (brain or spinal cord tumors)
    - brain stem glioma (brain stem tumor)
    - medulloblastoma (cerebellum brain tumor)
    - metastatic brain tumors (tumors that spread outside of the brain)
- Blood cancers:
    - Multiple myeloma, with another drug like prednisone.

    - Hodgkin's lymphoma, with or without other anti-cancer drugs
    - Non-Hodgkin's lymphoma, with or without other anti-cancer drugs
- Digestive system cancers (gastrointestinal tract tumors)
- A type of skin cancer like Malignant melanoma, with other anti-cancer drugs

How does BiCNU work?

BiCNU contains carmustine which is a type of drug of drug called an alkylating agent. Carmustine helps stop cancer cells from dividing which helps slow the growth of cancer cells.

What are the ingredients in BiCNU?

Medicinal ingredients: Carmustine

Non-medicinal ingredients (sterile diluent): Propylene glycol

BiCNU comes in the following dosage forms:

Lyophilized Powder, 100 mg / vial

Do not use BiCNU if:

- You are allergic to carmustine, other nitrosourea preparations or any of the other ingredients in this medicine.
- You have bone marrow problems causing:
    - Low levels of blood platelets (thrombocytes), white blood cells (leukocytes) or red blood cells (erythrocytes)
- You have severe kidney problems.
- You are pregnant or breastfeeding.
- You are less than 18 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BiCNU. Talk about any health conditions or problems you may have, including if you:

- Smoke
- Have or had lung problems
- Have or had serious kidney problems
- Have or had x-ray or CT scan results that are not normal
- Have or had radiation therapy on your chest
- Had chemotherapy in the past
- Are 65 years old or older

Other warnings you should know about:

- **Injection site reaction:** BiCNU might leak out while you are receiving it. This might cause swelling, pain, rash, burning and infections around the area. Your healthcare professional will monitor you for signs and symptoms of a leak around the injection site.

- **Lung problems:** BiCNU can cause **pulmonary fibrosis** (lung damage). Your healthcare professional will do tests to check on your lung health during treatment. Lung damage can happen up to 17 years after treatment with BiCNU and can cause death.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Check-ups and testing: You will have regular visits with your healthcare professional before and during your treatment. They will check your blood, liver and kidney health.

Pregnancy and breastfeeding:

Female patients

- Do not take BiCNU if you are pregnant. It may harm your unborn baby.
- If you are able to become pregnant:
  - Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with BiCNU.
- Do not breastfeed while you are taking BiCNU.

Children: BiCNU should not be used in children due to high risk of lung damage.

Geriatric patients: Your healthcare professional might start you off with a lower dose especially if you have other diseases or are taking other drugs. There also might be a higher risk of liver, kidney, heart problems for elderly patients.

Driving and using machines: BiCNU is mixed with a liquid called propylene glycol. Before you drive or do tasks that require special attention, wait until you know how you respond to BiCNU. Check with your healthcare professional before driving or operating machines since BiCNU can cause dizziness. This may impair your ability to drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BiCNU:

- A medicine used to lower stomach acid called cimetidine

How to take BiCNU:

- BiCNU will be given to you by a healthcare professional.
- The powder is first mixed into a solution. This solution is then given to you through a vein by a drip over a one to two-hour period.
- BiCNU is given into a vein by a drip over a one to two-hour period. The injected area will be monitored during the administration.

Usual dose:

- The dose you will receive will depend on your disease and will be measured based on your body size. The dosage will also depend on whether BiCNU is given with other anti-cancer drugs.
- BiCNU is usually given at least every 6 weeks. Your healthcare professional will do blood tests to check your blood health during treatment.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you experience serious side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much BiCNU, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

- BiCNU needs to be given on a fixed schedule. Talk to your healthcare professional if you have missed a treatment.

What are possible side effects from using BiCNU?

These are not all the possible side effects you may have when taking BiCNU. If you experience any side effects not listed here, tell your healthcare professional.

- Headache
- Severe nausea and vomiting
- Rash, itchy skin (when used on the skin)
- Darkening of an area of skin or nails with accidental skin contact
- Breast growth in males
- Muscle pain
- Tissue damage due to leakage in injection area
- Fast heartbeat, chest pain

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Eye disorders: blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids,		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
decreased sharpness of vision, eye irritation, blocked eye veins			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
Lung problems including Interstitial lung disease, pneumonitis, pulmonary fibrosis (diseases that inflame or scar lung tissue): shortness of breath when rest that gets worse with exertion, dry cough, wheezing, cough and chest tightness accompanied by fever and more phlegm, persistent weakness / tiredness		√	
Myelosuppression including leukopenia, thrombocytopenia (a large decrease in the production of blood cells and platelets by the bone marrow): bleeding, bruising, chills, fatigue, fever, infections, weakness, shortness of breath or other signs of infection		√	
Thrombophlebitis, Phlebitis (swelling of a vein): pain, tenderness, redness or swelling		√	
COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		√	
Bone marrow dysplasia or **Acute Leukaemia** (a group of		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
diseases in which the body produces large numbers of abnormal blood cells, blood cancer): Fever, infection, bruising or bleeding easily, breathlessness, blood in urine or stool, bleeding gums, bone pain, frequent or severe nosebleeds, lumps due to swollen lymph nodes in and around the neck, forearm, abdomen, or groin, pale skin, shortness of breath, weakness, fatigue, or general lack of energy;			
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		√	
Injection Site Reactions: blistering, itching, pain, redness, swelling, discoloration, severe skin damage, tenderness, burning/warmth in the area around the injection		√	
RARE			
Encephalopathy (brain disorder): muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures		√	
Kidney problems (damage to the kidneys): back and abdominal pain, change in the colour of urine (pale or dark) decrease in amount of urine		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
produced, pain or discomfort when urinating, swelling of the legs and ankles.			
Neuroretinitis (eye disorder): painless decrease in vision, decreased color vision		√	
UNKNOWN			
Hypersensitivity (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes		√	
Infection: fever and chills, nausea, vomiting, diarrhea, generally feeling unwell		√	
Neutropenic enterocolitis (inflammation of the intestines): abdominal pain, diarrhea, results in nausea, vomiting		√	
Secondary malignancies (cancers caused by radiation or chemotherapy)		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Your healthcare professional will store and throw away this drug (unopened vial, reconstituted and reconstituted diluted solutions)
- Do not use this drug after the expiry date which is stated on the label and carton after expiry. The expiration date refers to the last day of that month.
- Keep out of reach and sight of children.

If you want more information about BiCNU:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.marcanpharma.com, or by calling 1-855-627-2261.

This leaflet was prepared by Marcan Pharmaceuticals Inc.

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