

BOXED WARNING

BiCNU (carmustine for injection) 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 BiCNU (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 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 **DOSAGE AND ADMINISTRATION**).

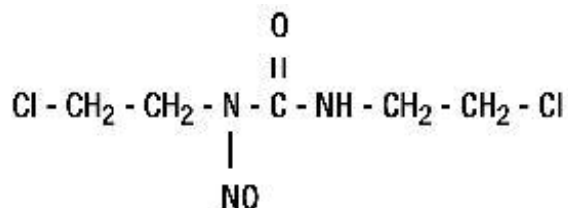
Pulmonary toxicity from BiCNU appears to be dose related. Patients receiving greater than 1400 mg/m² cumulative dose are at significantly higher risk than those receiving less.

Delayed pulmonary toxicity can occur years after treatment, and can result in death, particularly in patients treated in childhood (see **ADVERSE REACTIONS** and **PRECAUTIONS: Pediatric Use**).

DESCRIPTION

BiCNU[®] (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 sterile lyophilized pale yellow flakes or congealed mass with a molecular weight of 214.06. It is highly soluble in alcohol and lipids, and poorly soluble in water. BiCNU is administered by intravenous infusion after reconstitution as recommended.

The structural formula is:



BiCNU is available in 100-mg single dose vials of lyophilized material. Sterile diluent for constitution of BiCNU is co-packaged with the active drug product for use in constitution of the lyophile. The diluent is supplied in a vial containing 3 mL of Dehydrated Alcohol Injection, USP.

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 carbamylation of amino acids in proteins.

Intravenously administered carmustine is rapidly degraded, with no intact drug detectable after 15 minutes. However, in studies with ¹⁴C-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 CO₂. 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 & USAGE

BiCNU (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

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

The bone marrow toxicity of BiCNU 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 BiCNU 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 BiCNU 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).

BiCNU (carmustine for injection) may cause fetal harm when administered to a pregnant woman. BiCNU 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.

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

Injection site reactions may occur during the administration of BiCNU (see ADVERSE REACTIONS: **Other Toxicities**). Given the possibility of extravasation, close monitoring of the infusion site for possible infiltration during drug administration is recommended. A specific treatment for extravasation reactions is unknown at this time.

PRECAUTIONS

GENERAL PRECAUTIONS

In all instances where the use of BiCNU 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 BiCNU 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 (DL_{CO}) are particularly at risk.

Since BiCNU 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 (see **ADVERSE REACTIONS: Hematologic Toxicity**).

CARCINOGENESIS & MUTAGENESIS & IMPAIRMENT OF FERTILITY

BiCNU 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**). BiCNU 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 of the potential for serious adverse events in nursing infants, nursing should be discontinued while taking BiCNU.

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 BiCNU 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 BiCNU 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 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 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.

ADVERSE REACTIONS

Pulmonary Toxicity

Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur

from 9 days to 43 months after treatment with BiCNU and related nitrosoureas. Most of these patients were receiving prolonged therapy with total doses of BiCNU greater than 1400 mg/m². However, there have been reports of pulmonary fibrosis in patients receiving lower total doses. Other risk factors include past history of lung disease and duration of treatment. Cases of fatal pulmonary toxicity with BiCNU have been reported.

Additionally, delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in a long-term study with 17 patients who received BiCNU in childhood and early adolescence (1-16 years) in cumulative doses ranging from 770 to 1800 mg/m² combined with cranial radiotherapy for intracranial tumors. Chest x-rays demonstrated pulmonary hypoplasia with upper zone contraction. Gallium scans were normal in all cases. Thoracic CT scans have demonstrated an unusual pattern of upper zone fibrosis. There was some late reduction of pulmonary function in 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, 8 of 17 died of delayed pulmonary lung fibrosis, including all those initially treated (5 of 17) at less than 5 years of age.

Hematologic Toxicity

A frequent and serious toxicity of BiCNU 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 BiCNU and persists for 1 to 2 weeks. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

BiCNU 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 has been reported in patients following long-term nitrosourea therapy.

Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia. Greater myelotoxicity (e.g., leukopenia and neutropenia) has been reported when carmustine was combined with cimetidine (see **PRECAUTIONS: Drug Interactions**).

Gastrointestinal Toxicity

Nausea and vomiting after intravenous 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.

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 BiCNU.

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

Other Toxicities

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

Rapid intravenous infusion of BiCNU may produce intensive flushing of the skin and suffusion of the conjunctiva within 2 hours, lasting about 4 hours. It is also associated with burning at the site of injection although 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. Neuroretinitis, chest pain, headache, allergic reaction, hypotension, and tachycardia have been reported as part of ongoing surveillance.

OVERDOSAGE

No proven antidotes have been established for BiCNU overdosage.

DOSAGE & ADMINISTRATION

The recommended dose of BiCNU as a single agent in previously untreated patients is 150 to 200 mg/m² intravenously every 6 weeks. This may be given as a single dose or divided into daily injections such as 75 to 100 mg/m² on 2 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.

Doses subsequent to the initial dose should be adjusted according to the hematologic 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/mm ³	Platelets/mm ³	
>4000	>100,000	100%
3000-3999	75,000-99,999	100%
2000-2999	25,000-74,999	70%
<2000	<25,000	50%

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), 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.

Administration Precautions

As with other potentially toxic compounds, caution should be exercised in handling BiCNU and preparing the solution of BiCNU. Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.¹⁻⁴ Accidental contact of reconstituted BiCNU with the skin has caused transient hyperpigmentation of the affected areas. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing BiCNU. If BiCNU lyophilized material or solution contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. More information is available in the references listed below.

Reconstituted solution should only be administered by slow intravenous infusion. Administration of BiCNU over a period of less than 2 hours can lead to pain and burning at the site of injection.

Preparation of Intravenous Solutions

First, dissolve BiCNU with 3 mL of the supplied sterile diluent (Dehydrated Alcohol Injection, USP). Second, aseptically add 27 mL Sterile Water for Injection, USP. Each mL of resulting solution contains 3.3 mg of BiCNU in 10% ethanol. Such solutions should be protected from light.

Reconstitution as recommended results in a clear, colorless to yellowish solution which may be further diluted with 5% Dextrose Injection, USP. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Important Note

The lyophilized dosage formulation contains no preservatives and is not intended for use as a multiple dose vial.

Stability

The unopened vial of the dry drug must be stored in a refrigerator (2°-8°C, 36°-46°F). The diluent vials must be stored in a refrigerator (2°-8°C, 36°-46°F). The recommended storage of unopened BiCNU vials provides a stable product for up to 3 years. After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°-8°C, 36°-46°F). Reconstituted vials should be examined for crystal formation prior to use. If crystals are observed, they may be redissolved by warming the vial to room temperature with agitation.

Vials reconstituted as directed and further diluted to a concentration of 0.2 mg/mL in 5% Dextrose Injection, USP, should be stored at room temperature, protected from light and utilized within 8 hours. Glass containers were used for the stability data provided in this section. Only use glass containers for BiCNU administration.

Important Note

BiCNU has a low melting point (30.5°-32.0°C or 86.9°-89.6°F). Exposure of the drug to this temperature or above will cause the drug to liquefy and appear as an oil film on 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 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.

HOW SUPPLIED

BiCNU[®] (carmustine for injection). Each package includes a vial containing 100 mg carmustine and a vial containing 3 mL sterile diluent.

NDC 23155-261-41

STORAGE

Store product and diluent in a refrigerator (2°-8°C, 36°-46°F).

REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling occupational exposure to hazardous drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm*. 2006;63:1172-1993.
4. Polovich M, White JM, Kelleher LO, eds. 2005. Chemotherapy and biotherapy guidelines and recommendations for practice. 2nd ed. Pittsburgh, PA: Oncology Nursing Society.

To report adverse events and for medical information, please call 1- 866-901-DRUG (3784)

BiCNU & Diluent Manufactured by:
Emcure Pharmaceuticals Ltd.,
Hinjawadi, Pune, India.

Distributed by:
Heritage Pharmaceuticals Inc.

Eatontown, NJ 07724
1.866.901.DRUG (3784)

PACKAGE LABEL PRINCIPAL DISPLAY PANEL - diluent label

NDC 23155-262-31

Rx only

Dehydrated Alcohol Injection, USP

3 mL

Sterile Diluent for BiCNU® (carmustine for injection)

READ ENCLOSED PACKAGE INSERT

STORE IN A REFRIGERATOR (2°-8°C, 36°-46°F).

Manufactured by:
Emcure Pharmaceuticals Ltd.,
Hinjawadi, Pune, India.

Manufactured for:

Heritage Pharmaceuticals Inc.

Eatontown, NJ 07724

1.866.901.DRUG (3784)

NDC 23155-262-31 Rx only		510310086IN02	
Dehydrated Alcohol Injection, USP 3 mL	READ ENCLOSED PACKAGE INSERT	STORE IN A REFRIGERATOR (2°-8°C, 36°-46°F).	 N 3 23155 26231 5
		Manufactured by: Emcure Pharmaceuticals Ltd., Hinjawadi, Pune, India. Manufactured for: Heritage Pharmaceuticals Inc. Eatontown, NJ 07724 1.866.901.DRUG (3784) Mfg.Lic.No. : PD/93 Rev. 10/13	
Sterile Diluent for BiCNU® (carmustine for injection)			Non Varnished Area 17 x 8 mm
		Lot :	Exp. :

PACKAGE LABEL PRINCIPAL DISPLAY PANEL - vial label

NDC 23155-261-31 Rx Only

BiCNU® (carmustine for injection)

100 mg

REFRIGERATE IMMEDIATELY

Wear gloves at all times when handling containers.

STORE IN A REFRIGERATOR (2°- 8°C, 36°- 46°F)

After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°-8°C, 36°-46°F). Reconstituted vials should be examined for crystal formation prior to use.

If crystals are observed, they may be redissolved by warming the vial to room temperature with agitation. Protect from light.

USUAL DOSAGE: Adults - 150 to 200 mg/m², intravenously every 6 weeks. Read enclosed package insert for indications, dosage, directions for use, and precautions.

NOT RETURNABLE.

Manufactured by:

Emcure Pharmaceuticals Ltd.,
Hinjawadi, Pune, India.

Manufactured for:

Heritage Pharmaceuticals Inc.

Eatontown, NJ 07724

1.866.901.DRUG (3784)

NDC 23155-261-31 **Rx only**

BiCNU[®]
(carmustine for injection)

100 mg

REFRIGERATE IMMEDIATELY

Wear gloves at all times when handling containers.

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Emcure Pharmaceuticals Ltd.,
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Manufactured for:
Heritage Pharmaceuticals Inc.
Eatontown, NJ 07724
1.866.901.DRUG (3784)
Mfg.Lic.No. : PD/93
Rev. 10/13

510310085IN02

Heritage[®]

Lot: _____
Exp. : _____

Non Varnished Area
30.5 x 10 mm



PACKAGE LABEL PRINCIPAL DISPLAY PANEL - carton

NDC 23155-261-41

Rx only

BiCNU[®] (carmustine for injection)

100 mg AND DILUENT

REFRIGERATE IMMEDIATELY

Wear gloves at all times when handling containers.

STORE IN A REFRIGERATOR

(2°- 8°C, 36°- 46°F)

NOT RETURNABLE.

BiCNU & Diluent Manufactured by:

Emcure Pharmaceuticals Ltd.,

Hinjawadi, Pune, India.

Distributed by:

Heritage Pharmaceuticals Inc.

Eatontown, NJ 07724

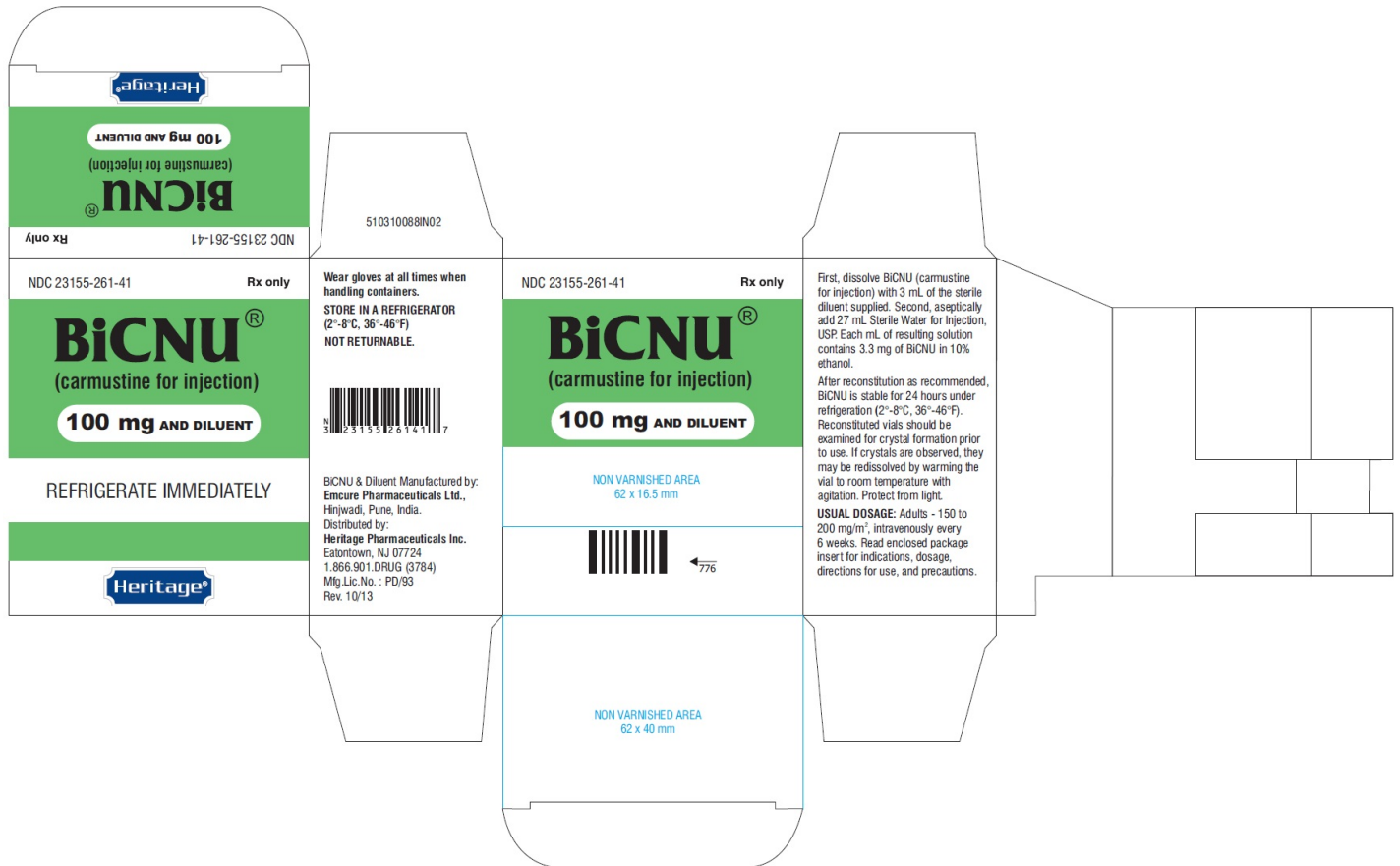
1.866.901.DRUG (3784)

First, dissolve BiCNU (carmustine for injection) with 3 mL of the sterile diluent supplied. Second, aseptically add 27 mL Sterile Water for Injection, USP. Each mL of resulting solution contains 3.3 mg of BiCNU in 10% ethanol.

After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°- 8°C, 36°- 46°F). Reconstituted vials should be examined for crystal formation prior to use. If crystals are

observed, they may be redissolved by warming the vial to room temperature with agitation. Protect from light.

USUAL DOSAGE: Adults - 150 to 200 mg/m², intravenously every 6 weeks. Read enclosed package insert for indications, dosage, directions for use, and precautions.



BICNU

carmustine kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:23155-261
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:23155-261-41	1 in 1 CARTON		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	30 mL
Part 2	1 VIAL	3 mL

Part 1 of 2

BICNU

carmustine injection, powder, lyophilized, for solution

Product Information**Route of Administration**

INTRAVENOUS

DEA Schedule**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
CARMUSTINE (CARMUSTINE)	CARMUSTINE	100 mg in 30 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		30 mL in 1 VIAL, SINGLE-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA017422	04/04/2013	

Part 2 of 2**DEHYDRATED ALCOHOL**

alcohol injection

Product Information**Route of Administration**

INTRAVENOUS

DEA Schedule**Inactive Ingredients**

Ingredient Name	Strength
ALCOHOL	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		3 mL in 1 VIAL		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA017422	04/04/2013	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA017422	04/04/2013	

Labeler - Heritage Pharmaceuticals Inc. (780779901)

Registrant - Emcure Pharmaceuticals Limited (916921919)

Establishment

Name	Address	ID/FEI	Business Operations
Emcure Pharmaceuticals Limited		862602830	ANALYSIS(23155-261), LABEL(23155-261), MANUFACTURE(23155-261), PACK(23155-261)

Revised: 11/2013

Heritage Pharmaceuticals Inc.