Space for Ups. No.

Space for Edge code

PMO-xxxx

Package Leaflet

Onfola

Carmustine for Injection USP, 100 mg/vial

amneal®

==========

1. NAME OF THE MEDICINAL PRODUCT

Onfola (Carmustine for Injection USP, 100 mg/vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 100 mg carmustine.

Each vial of solvent contains 3 ml dehydrated alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Lyophilized pale yellow flakes or congealed mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Onfola is indicated as palliative therapy as a single agent or in established combination therapy in the following:

- Brain tumors glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors.
- Multiple myeloma in combination with prednisone.
- Relapsed or refractory Hodgkin's lymphoma in combination with other approved drugs.
- Relapsed or refractory Non-Hodgkin's lymphomas in combination with other approved drugs.

4.2 Posology and method of administration

Posology

The recommended dose of carmustine for injection as a single agent in previously untreated patients is 150 mg/m^2 to 200 mg/m^2 intravenously every 6 weeks. Administer as a single-dose or divided into daily injections such as 75 mg/m^2 to 100 mg/m^2 on two successive days. Lower the dose when carmustine for injection is used with other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted. Administer carmustine for injection, for the duration according to the established regimen. Premedicate each dose with anti-emetics.

Adjust doses subsequent to the initial dose 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*	
> 4,000	> 100,000	100%
3,000 to 3,999	75,000 to 99,999	100%
2,000 to 2,999	25,000 to 74,999	70%
< 2,000	< 25,000	50%

The hematologic toxicity can be delayed and cumulative. Monitor blood counts weekly. Do not administer a repeat course of carmustine for injection until circulating blood elements have returned to acceptable levels (platelets above 100 Gi/L, leukocytes above 4 Gi/L and absolute neutrophil count above 1 Gi/L). The usual interval between courses is 6 weeks.

Evaluate renal function prior to administration and periodically during treatment. For patients with compromised renal function, monitor for toxicity more frequently. Discontinue carmustine for injection if the creatinine clearance is less than 10 mL/min. Do not administer carmustine for injection to patients with compromised renal function. Monitor transaminases and bilirubin periodically during treatment (see section 4.8.1).

Method of Administration:

Administer reconstituted solution by slow intravenous infusion over at least two hours. Administration of carmustine for injection over a period of less than two hours can lead to pain and burning at the site of injection. Monitor the injected area during the administration. The rate of administration of the intravenous infusion should not be more than 1.66 mg/m^2/min.

See section 6.4 for special precautions for storage and section 6.6 for special precautions for disposal <and other handling> of the injection. Carmustine for injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.

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

Accidental contact of reconstituted carmustine for injection with the skin has caused transient hyperpigmentation of the affected areas. Wear impervious gloves to minimize the risk of dermal exposure impervious gloves when handling vials containing carmustine for injection. Immediately wash the skin or mucosa thoroughly with soap and water if carmustine for injection lyophilized material or solution contacts the skin or mucosa.

4.3 Contraindications

Carmustine for injection is contraindicated in patients with previous hypersensitivity to carmustine for injection or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Myelosuppression

Bone marrow toxicity is a dose-limiting, common and severe toxic effect of carmustine for injection occurring 4 to 6 weeks after drug administration (thrombocytopenia occurs at about 4 weeks post-administration persisting for 1 to 2 weeks; leukopenia occurs at 5 to 6 weeks after a dose of carmustine for injection persisting for 1 to 2 weeks; thrombocytopenia is generally more severe than leukopenia; anemia is less frequent and less severe compared to thrombocytopenia and/or leukopenia) Complete blood count should therefore be monitored weekly for at least six weeks after a dose. Repeat doses of carmustine for injection should not be given more frequently than every six weeks. The bone marrow toxicity of carmustine for injection is cumulative and therefore the dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see section 4.8.1). Greater myelotoxicity (e.g., leukopenia and neutropenia) has been reported when carmustine was combined with cimetidine (see section 4.5).

Pulmonary Toxicity

Cases of fatal pulmonary toxicity with carmustine for injection have been reported. Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur from 9 days to 43 months after treatment with carmustine for injection and related nitrosoureas. Pulmonary toxicity from carmustine for injection is dose-related. Patients receiving greater than 1,400 mg/m^2 cumulative dose are at significantly higher risk than those receiving less. However, there have been reports of pulmonary fibrosis in patients receiving lower total doses. Interstitial fibrosis (with lower doses) occurred rarely. Additionally, delayed onset pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients who received carmustine for injection (in cumulative doses ranging from 770 mg/m^2 to 1,800 mg/m^2 combined with cranial radiotherapy for intracranial tumors) in childhood and early adolescence. Other risk factors include past history of lung disease and duration of treatment. Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) are particularly at risk.

Administration Reactions

Injection site reactions may occur during the administration of carmustine for injection. Rapid intravenous infusion of carmustine for injection 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. 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.

Carcinogenicity

Long-term use of nitrosoureas, such as carmustine for injection, has been reported to be associated with the development of secondary malignancies. Carmustine was carcinogenic when administered to laboratory animals (see section 5.3). Nitrosourea therapy, such as carmustine for injection, has carcinogenic potential in humans. Patients treated with carmustine for injection should be monitored long-term for development of second malignancies.

Ocular Toxicity

Carmustine for injection has been administered through an intraarterial intracarotid route; this procedure is investigational and has been associated with ocular toxicity. Safety and effectiveness of the intra-arterial route have not been established.

Embryo-Fetal Toxicity

Carmustine was embryotoxic in rats and rabbits and teratogenic in rats when given in doses lower than the maximum cumulative human dose based on body surface area. There are no adequate and well-controlled studies in pregnant women. Advise pregnant women of the potential risk to the fetus (see section 4.6). Advise females of reproductive potential to use highly effective contraception during and after treatment with carmustine for injection, for at least 6 months after therapy. Advise males of reproductive potential to use effective contraception during and after treatment with carmustine for injection, for at least 3 months after therapy (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Other Drugs on Carmustine for Injection

Cimetidine

Greater myelosuppression (e.g., leukopenia and neutropenia) has been reported when oral cimetidine has been co-administered with carmustine. Consider alternative drugs to cimetidine.

Phenobarbital

Phenobarbital induces the metabolism of carmustine and may compromise antitumor activity of carmustine for injection. Consider alternative drugs to phenobarbital.

Effects of Carmustine for Injection on Other Drugs

Phenytoin

Carmustine for injection when co-administered with phenytoin may reduce phenytoin serum concentrations. Consider alternative drugs to phenytoin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

Carmustine for injection can cause fetal harm when administered to a pregnant woman based on the mechanism of action (see section 5.1) and findings in animals. Limited available data with carmustine for injection use in pregnant women are insufficient to inform a drug-associated risk of major birth defects and miscarriage. Carmustine was embryotoxic in rats and rabbits and teratogenic in rats (thoracoabdominal closure, neural tube, and eye defects and malformations of the skeletal system of the fetus) when given in doses lower than the maximum cumulative human dose based on body surface area. Consider the benefits and risks of carmustine for injection, for the mother and possible risks to the fetus when prescribing carmustine for injection to a pregnant woman.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Intraperitoneal (IP) administration of carmustine to pregnant rats 14 days prior to mating and during the period of organogenesis at cumulative doses ≥ 26 mg/kg (158 mg/m^2), approximately 0.1 times the maximum cumulative human dose of 1,400 mg/m^2, resulted in pre-implantation loss, increased resorptions (including completely resorbed litters), and reduced the number of live births in the presence of maternal toxicity.

Carmustine administered IP to pregnant rats during the period of organogenesis at cumulative doses ≥ 4 mg/kg (24 mg/m^2), approximately 0.02 times the maximum cumulative human dose based on a mg/m^2 basis, resulted in reduced fetal weight and various malformations, which included thoracoabdominal closure defects, neural tube defects, and eye defects, including microphthalmia/anophthalmia, and skeletal anomalies in the skull, sternebra, vertebrae and ribs, and reduced skeletal ossification) in the presence of maternal toxicity. Embryo-fetal death was observed at cumulative doses ≥ 8 mg/kg (48 mg/m^2), approximately 0.03 times the maximum cumulative human dose on a mg/m^2 basis. Intravenous (IV) administration of carmustine to rats at a cumulative dose of 50 mg/kg (300 mg/m^2), approximately 0.2 times the maximum cumulative human dose on a mg/m^2 basis, during the last quarter of pregnancy resulted in the death of offspring within 4 months. Carmustine administered IV to rabbits during the period of organogenesis resulted in spontaneous abortions in mothers and growth defects in the fetus, mainly at cumulative doses ≥ 13 mg/kg (156 mg/m^2), approximately 0.1 times the maximum cumulative human dose on a mg/m^2 basis.

Lactation

Risk Summary

There is no information regarding the presence of carmustine in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse events (e.g., carcinogenicity and myelosuppression) in nursing infants, nursing should be discontinued while taking carmustine for injection.

Females and Males of Reproductive Potential

Contraception

Advise female patients to avoid pregnancy during treatment with carmustine for injection because of the risk of fetal harm (see section 4.6).

Advise female patients of reproductive potential to use highly effective contraception during and for up to six months after completion of treatment.

Advise males with female sexual partners of reproductive potential to use effective contraception during carmustine for injection treatment and for at least three months after the final dose of carmustine for injection (see section 5.3).

Infertility

Based on nonclinical findings, male fertility may be compromised by treatment with carmustine for injection (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been undertaken on the consequences the medicine on the competency to drive and the ability to operate machines. However the possibility will have to be taken into consideration, that the alcohol quantity in these pharmaceutical medicines can impair the competency to drive and the ability to operate machines.

4.8 Undesirable effects

4.8.1 Adverse reactions

The following serious adverse reactions are described elsewhere in the labeling:

- Myelosuppression (see section 4.4)
- Pulmonary toxicity (see section 4.4)
- Administration Reactions (see section 4.4)
- Carcinogenicity (see section 4.4)
- Ocular Toxicity (see section 4.4)

The following adverse reactions associated with the use of carmustine for injection were identified in clinical studies. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac Disorders

Tachycardia and chest pain

Eye Disorders

Conjunctival edema, conjunctival hemorrhage, blurred vision and loss of depth perception

Gastrointestinal Toxicity

Nausea, vomiting, anorexia, and diarrhea

Hepatotoxicity
Increased transaminase, increased alkaline phosphatase, increased bilirubin levels

Infections and Infestations
Opportunistic infection (including with fatal outcome)

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)
Acute leukemia, bone marrow dysplasias

Nephrotoxicity
Progressive azotemia, decrease in kidney size, renal failure

Nervous System Disorders
Headaches, encephalopathy, and seizures

Pulmonary Toxicity
Pneumonitis, interstitial lung disease

Reproductive System and Breast Disorders
Gynecomastia

Skin and Subcutaneous Tissue Disorders
Burning sensation, hyperpigmentation, swelling, pain, erythema, skin necrosis, alopecia, allergic reaction

Vascular Disorders
Veno-occlusive disease

4.8.2 Clinical Studies Experience (upon request from any regulatory Authority in GCC)

4.8.3 Post-marketing Experience (upon request from any regulatory Authority in GCC)

To reports any side effect(s):

Saudi Arabia:

- The National Pharmacovigilance Centre (NPC):
  - SFDA Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: https://ade.sfda.gov.sa/

4.9 Overdose

The main result of overdose is myeloablation. No proven antidotes have been established for carmustine for injection overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antineoplastic medicine, alkylating agent, nitrosourea
ATC Code: L01AD01

Mechanism of Action

The mechanism of action of carmustine is not fully understood. While carmustine alkylates DNA and RNA, it is not cross-resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins. The metabolites may contribute to antitumor activity and toxicities of carmustine.

Pharmacodynamics

The exposure-response relationship for efficacy or safety is unknown.

5.2 Pharmacokinetic properties

Distribution

Carmustine crosses the blood-brain barrier. Levels of radioactivity in the CSF are greater than or equal to 50% of those measured concurrently in plasma.

Elimination

Following a short intravenous infusion, the reported elimination half-life ranges from 15 minutes to 75 minutes.

Metabolism

Carmustine may be inactivated through denitrosation reactions catalyzed by both cytosolic and microsomal enzymes, including NADPH and glutathione-S-transferase.

Excretion

Approximately 60% to 70% of a total dose is excreted in the urine within 96 hours. Approximately 10% is eliminated as respiratory CO_2.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carmustine is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans (see section 4.8.1).

Carmustine was mutagenic and clastogenic in multiple *in vitro* and *in vivo* genetic toxicology studies.
Male rats treated with carmustine at cumulative doses ≥ 36 mg/kg (216 mg/m^2), approximately 0.15 times the maximum cumulative human dose on a mg/m^2 basis, showed decreases in reproductive potential when mated with untreated female rats (e.g., decreased implantations, increased resorption rate, and a decrease in viable fetuses).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dehydrated Alcohol (Ethanol Absolute) USP

Tert-Butanol HP IH

6.2 Incompatibilities

The intravenous solution is unstable in polyvinyl chloride container. DO NOT USE PVC Containers.

Administer carmustine for injection solution from the glass bottles or polypropylene container only. Ensure the polypropylene containers used are PVC free and DEHP free.

6.3 Shelf life

2 Years

After reconstitution as recommended, carmustine for injection, USP is stable for 24 hours under refrigeration 2° to 8°C (36° to 46°F) in glass container.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

Store the unopened vial of the dry drug in a refrigerator 2° to 8°C, (36° to 46°F). Store the diluent vials in a refrigerator 2° to 8°C, (36° to 46°F). The recommended storage of unopened carmustine for injection vials provides a stable product for up to 18 months.

Carmustine for injection has a low melting point (30.5° to 32.0°C or 86.9° to 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 carmustine for injection will appear as a very small amount of dry flakes or dry congealed mass. If this is evident, the carmustine for injection is suitable for use and should be refrigerated immediately.

6.5 Nature and contents of container

Each carton contains 1 vial Carmustine for Injection USP, 100 mg and 1 vial Sterile Diluent for Carmustine for Injection, USP, 3 mL.

6.6 Special precautions for disposal <and other handling>

Preparation of Intravenous Solution

- Dissolve carmustine for injection with 3 mL of the supplied sterile diluent (Dehydrated Alcohol Injection, USP).
- Aseptically add 27 mL Sterile Water for Injection, USP.
  - Each mL of resulting solution contains 3.3 mg of carmustine for injection in 10% ethanol. Such solutions should be protected from light.
  - The reconstituted solution is a clear, colorless to yellowish solution.
- Once reconstituted, the solution must be further diluted with Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
  - 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.
  - Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
  - After reconstitution as recommended, carmustine for injection is stable for 24 hours under refrigeration 2° to 8°C, (36° to 46°F) in glass container. Examine reconstituted vials 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 with 500 mL Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, in glass or polypropylene containers to a concentration of 0.2 mg/mL, should be stored at room temperature, protected from light and utilized within 8 hours. These solutions are also stable 24 hours under refrigeration 2° to 8°C, (36° to 46°F) and an additional 6 hours at room temperature protected from light.

Important Note

Carmustine for injection has a low melting point (30.5° to 32.0°C or 86.9° to 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 carmustine for injection will appear as a very small amount of dry flakes or dry congealed mass. If this is evident, the carmustine for injection is suitable for use and should be refrigerated immediately.

Guidelines for the safe handling of the antineoplastic agents

1. Trained personnel should reconstitute the drug.

2. This should be performed in a designated area.

3. Adequate protective gloves should be worn.

4. Precautions should be taken to avoid the drug accidentally coming into contact with eyes. In the event of contact with the eyes, flush with copious amount of water and/or saline.

5. The cytotoxic preparation should not be handled by pregnant staff.

6. Adequate care and precaution should be taken in the disposal of items (syringes, needles etc.) used to reconstitute cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000°C. Liquid waste may be flushed with copious amounts of water.

7. The work surface should be covered with disposable plastic-backed absorbent paper.

8. Any unused product or waste material should be disposed of in accordance with local requirements for biohazardous waste

7. MARKETING AUTHORIZATION HOLDER

Amneal Pharmaceuticals of New York LLC

8. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

9. DATE OF REVISION OF THE TEXT

Iss. 04-2025-00

10. DOSIMETRY

Not Applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not Applicable