



Package leaflet: Information for the user

Carmustine 100 mg Powder and Solvent for Concentrate Solution for Infusion
carmustine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Carmustine is and what it is used for
2. What you need to know before you use Carmustine
3. How to use Carmustine
4. Possible side effects
5. How to store Carmustine
6. Contents of the pack and other information

1. What Carmustine is and what it is used for

Carmustine 100 mg-Powder and solvent for solution for infusion is a medicine which contains carmustine. Carmustine belongs to a group of anticancer substances known as nitrosourea that act by slowing the growth of cancer cells.

Carmustine is indicated in adults in the following malignant neoplasms as a single agent or in combination with other antineoplastic agents and/or other therapeutic measures (radiotherapy, surgery):

- Brain tumours (glioblastoma, Brain-stem gliomas, medulloblastoma, astrocytoma and ependymoma), brain metastases
- Secondary therapy in non-Hodgkin's lymphoma and Hodgkin's disease
- Tumours of gastrointestinal tract or digestive system tract
- Malignant melanoma (skin cancer)
- as conditioning treatment prior to autologous haematopoietic progenitor cell transplantation (HPCT) in malignant haematological diseases (Hodgkin's disease / Non-hodgkin's lymphoma).

2. What you need to know before you use Carmustine Do not use Carmustine:

- if you are allergic to carmustine, other nitrosourea medicines or any of the other ingredients of this medicine (listed in section 6).
- if you suffer from suppression of blood cell formation in the bone marrow and the number of your platelets, white blood cells (leucocytes), or red blood cells (erythrocytes) is therefore reduced, either as a result of chemotherapy or other causes.
- if you suffer from higher-grade kidney dysfunction.
- in children and adolescents.
- if you are pregnant or if you are breast-feeding.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Carmustine.

The major side effect of this medicine is delayed bone marrow suppression, which may show as tiredness, bleeding from the skin and mucous membranes as well as infections and fever due to changes in the blood. Therefore your doctor will monitor blood counts weekly for at least 6 weeks after a dose. At the recommended dosage, courses of Carmustine would not be given more frequently than every 6 weeks. The dosage will be confirmed with the blood count.

Before treatment, your liver and kidney function will be tested and observed regularly during the treatment.

Since the use of Carmustine can lead to lung damage, an X-ray of the chest region and the lung function tests will be conducted before the treatment is started (Please also see the section "Possible side effects").

High-dose treatment with carmustine (up to 600 mg/m²) is only performed in combination with subsequent stem cell transplantation. Such a higher dose can increase frequency or severity of lung, kidney, liver, heart, and gastrointestinal toxicities as well as infections and disturbances in the electrolyte balance (low blood levels of potassium, magnesium, phosphate).

Abdominal pain (neutropenic enterocolitis) may occur as a therapy-related adverse event during treatment with chemotherapeutic agents.

Patients who suffer from multiple conditions simultaneously and have poorer disease status are at higher risk for adverse events. This is especially important for elderly patients. Your doctor will talk to you about the possibility of lung damage and allergic reactions and their symptoms. If such symptoms occur, you should contact your doctor immediately (see section 4).

Children and adolescents

Carmustine must not be used in children and adolescents aged <18 years.

Other medicines and Carmustine

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without prescription, such as:

- Phenytoin, used in epilepsy
- Dexamethasone, used as an anti-inflammatory and immunosuppressive agent
- Cimetidine, used for stomach problems like indigestion
- Digoxin, used if you have abnormal heart rhythm
- Melphalan, an anticancer drug

Carmustine with alcohol

The amount of alcohol in this medicine may alter the effects of other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy and fertility

Carmustine should not be used during pregnancy because it may harm your unborn baby. Therefore this medicine should not normally be administered to pregnant women. If used during pregnancy, the patient must be aware of the potential risk to the unborn baby. Women of childbearing potential are advised to use effective contraception to avoid becoming pregnant whilst being treated

with this medicine and for at least 6 months after treatment.

Male patients should use adequate contraceptives measures during treatment with Carmustine for at least 6 months to prevent their partners becoming pregnant.

Breast-feeding

You should not breast-feed while taking this medicine up to 7 days after treatment. A risk to the newborn/infant cannot be excluded..

Driving and using machines

Carmustine has no or negligible influence on the ability to drive and use machines. You must check with your doctor before driving or operating any tools or machines because the amount of alcohol in this medicine may impair your ability to drive or use machines.

Carmustine contains ethanol (alcohol)

This medicinal product contains 0.57 vol% ethanol (alcohol), which means 7.68 g per dose. This corresponds to 11.32 ml of beer or 4.72 ml wine, per dose.

Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease or epilepsy.

The amount of alcohol in this medicinal product may alter the effects of other medicines.

- If you have epilepsy or liver problems, talk to your doctor or pharmacist before taking this medicine.
- The amount of alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.
- If you are pregnant, talk to your doctor or pharmacist before taking this medicine.
- If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

3. How to use Carmustine

Carmustine will always be given to you by a healthcare professional with experience in the use of anticancer medicines.

This medication is for intravenous infusion.

Adults

Dosage is based on your medical condition, body size and response to treatment. It is usually given at least every 6 weeks. The recommended dose of Carmustine 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 two daily injections such as 75 to 100 mg/m² on two successive days. Dosage will also depend on whether Carmustine is given with other anti-cancer drugs.

Doses will be adjusted according to how you respond to the treatment.

The recommended dose of carmustine given in combination with other chemotherapeutic agents before haematopoietic progenitor cell transplantation is 300 – 600 mg/m² intravenously.

Your blood count will be monitored frequently to avoid toxicity in your bone marrow and the dose adjusted if necessary.

Route of administration

Following reconstitution and dilution carmustine is given into a vein by a drip over a one to two hour period. The time of infusion should not be less than one hour to avoid burning and pain at the injected area. The injected area will be monitored during the administration.



The following information is intended for healthcare professionals only:

This information is a short description of preparation and/or handling, incompatibilities, posology of the medicine, overdose or monitoring measures and laboratory investigations based on the current SmPC.

The lyophilized dosage formulation contains no preservative and is not intended as multiple dose vial. Reconstitution and further dilutions should be carried out under aseptic conditions

Preparation of intravenous solution:

Dissolve carmustine with 3 ml of the supplied sterile diluent and then aseptically add 27 ml of sterile water for injection to the alcohol solution. The 30 ml stock solution needs to be mixed thoroughly.

Each ml of resulting solution will contain 3.3 mg of carmustine in 10% ethanol and have a pH of 4.0 to 6.8.

Method of administration:

Carmustine is for intravenous use after reconstitution and further dilution.

Reconstitution as recommended results in a clear colourless solution which may be further diluted to 500 ml sodium chloride for injection, or 5% glucose for injection. The reconstituted solution must be given intravenously and should be administered by i.v. drip over one to two hour period. Injection of Carmustine over shorter periods of time may produce intense pain and burning at the site of injection.

NOTE: Reconstituted vials stored under refrigeration 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.

Carmustine has a low melting point (approximately 30.5-32.0° C or 86.9-89.6° F). Exposure of this drug to this temperature or above will cause the drug to liquefy and appear as an oil film in the bottom of the vials. This is a sign of decomposition and vials should be discarded.

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. Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.
9. Any unused product or waste material should be disposed of in accordance with local requirements for biohazardous waste

Posology and laboratory investigations

Initial doses

The recommended dose of Carmustine 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 infusions such as 75 to 100 mg/m² on two successive days.

When Carmustine is used in combination with other myelosuppressive medicinal products or in patients in whom bone marrow reserve is depleted, the doses should be adjusted according to the haematologic profile of the patient as shown below.

Monitoring and subsequent doses

A repeat course of Carmustine 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 six weeks. Blood counts should be monitored frequently and repeat courses should not be given before six weeks because of delayed hematologic toxicity.

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The duration of the treatment is determined by the doctor and may vary for each patient.

Use in elderly

Carmustine can be used with caution in elderly patients. The kidney function will be carefully monitored. In elderly patients, the occurrence of inflammation of mucous membranes of mouth (oral mucositis) is higher when high dose of carmustine is given.

If you use more Carmustine than you should

As a doctor or nurse will be giving you this medicine, it is unlikely that you will receive an incorrect dose. Tell your doctor or nurse if you have any concerns about the amount of medicine that you receive.

If you have any further questions on the use of this product, ask your doctor or pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately if you notice any of the following:

Any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body), and feeling you are going to faint. These may be signs of severe allergic reaction.

Carmustine may cause the following side effects:

Very common (may affect more than 1 in 10 people)

- Delayed myelosuppression (decrease in blood cells in bone marrow); which can increase the chance of infections if white blood cells are decreased.
- Ataxia (lack of voluntary coordination of muscle movements);
- Dizziness;
- Headache;
- Transient redness in the eye, blurred vision, retinal bleeding;
- Hypotension (fall in blood pressure) in high-dose therapy;
- Phlebitis (inflammation of the veins) associated with pain, swelling, redness, tenderness;
- Respiratory disorders (lung related disorders) with breathing problems;
- This medicine may cause severe (possibly fatal) lung damage. Lung damage may occur years after treatment. Tell your doctor immediately if you experience any of the following symptoms:
- shortness of breath, persistent cough, chest pain, persistent weakness/tiredness.
- Severe nausea and vomiting; beginning within 2-4 hours of administration and lasting for 4-6 hours;
- When used on the skin, inflammation of the skin (dermatitis)
- Accidental contact with skin may cause transient hyperpigmentation (darkening of an area of skin or nails)

Common (may affect up to 1 in 10 people)

- Acute leukemias and bone marrow dysplasias (abnormal development of the bone marrow) following long term use; The following symptoms may occur: bleeding gums, bone pain, fever, frequent infections, frequent or severe nosebleeds, lumps due to swollen lymph nodes in and around the neck, underarm, forearm, abdomen, or groin, pale skin, shortness of breath, weakness, fatigue, or general lack of energy;
- Anaemia (decrease in the amount of red blood cells in the blood);
- Encephalopathy (disorder of brain) in high-dose therapy. Symptoms may include muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures;;
- Loss of appetite (anorexia);
- Constipation;
- Diarrhoea;
- Inflammation of the mouth and lips;
- Reversible liver toxicity in high-dose therapy, delayed up to 60 days after administration. This can result in increased liver enzymes and bilirubin (detected by blood tests);
- Alopecia (loss of hair);
- Flushing of the skin;
- Reactions on the injection site

Rare (may affect up to 1 in 1,000 people)

- Veno-occlusive disease (progressive blockage of the veins) in high-dose therapy; in which very small (microscopic) veins in the liver become blocked. The following symptoms are possible: fluid accumulation in the abdomen, enlargement of the spleen, severe bleeding of the oesophagus, yellowing of skin and the whites of the eyes;
- Breathing problems due to a type of lung disease in which tissue is scarred (interstitial fibrosis) (with lower doses);
- Kidney problems;
- Gynecomastia (breast growth in males)
- Inflammation of the optic nerve and adjacent retina in the eye
- Bleeding in the gastrointestinal tract

Very rare (may affect up to 1 in 10,000 people)

- Inflammation of the vein wall with associated thrombosis (thrombophlebitis)

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

- Allergic reactions
- Muscular pain;
- Secondary tumors (cancers caused by radiation or chemotherapy).
- Seizures (fits) including status epilepticus;
- Tissue damage due to leakage in injection area;
- Infertility;
- Impairment of embryo/fetus development in pregnant women
- Any signs of infection
- Fast heart beat, chest pain
- Disturbances in electrolyte balance (low blood levels of potassium, magnesium, phosphate).
- Abdominal pain (neutropenic enterocolitis).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Carmustine

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Unopened vials: Store in a refrigerator (2°C – 8°C)

Store in the original pack in order to protect from light.

After reconstitution and dilution (as recommended):

The reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

The diluted solutions of drug product is physically compatible and chemically stable over a period of 8 hours at room temperature (20°C-25°C) and upto 24 hours at refrigerated temperature (2°C-8°C) followed by 6 hours stored at room temperature (20°C-25°C).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information What Carmustine contains

– The active substance is carmustine.

Each vial of powder for concentrate for solution for infusion contains 100 mg carmustine. Each vial of solvent contains 3 ml of Ethanol, anhydrous.

The other excipients are:

Powder: No excipients. Solvent: Anhydrous ethanol

What Carmustine looks like and contents of the pack

Powder and solvent for concentrate for solution for infusion.

Powder

30ml Type-I Moulded Amber glass vial with 20mm neck finish, stoppered with 20mm grey bromobutyl rubber stopper and sealed with aluminum seal having polypropylene disc.

Solvent

10ml Type-I Tubular clear glass vial with 13mm neck finish, stoppered with 13mm grey chlorobutyl rubber stopper and sealed with aluminum seal having polypropylene disc.

Pack sizes: 1 vials

One pack contains one vial of 100 mg powder and one vial with of 3 ml solvent.

Marketing Authorisation Holder

Eugia (UK) Ltd
Ares Block
Odyssey Business Park West End Road
South Ruislip HA4 6QD United Kingdom

Manufacturer

APL Swift Services (Malta) Limited HF26, Hal Far Industrial Estate, Hal Far, Birzebbugia, BBG 3000, Malta

Or

Milpharm Limited
Ares Block, Odyssey Business Park, West End Road,
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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		Percentage of prior dose to be given, %
Leucocytes/ 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

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).

Conditioning treatment prior to SCT

Carmustine is given in combination with other chemotherapeutic agents in patients with malignant haematological diseases before SCT at a dose of 300 - 600 mg/m² intravenously.

Special populations

Patients with impaired renal function

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

Elderly

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 therapy with other medicinal products. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored and the dose reduced according to this.

Children and Adolescents

Carmustine is contraindicated in children and adolescents aged <18 years (see section 4.3) due to the high risk of pulmonary toxicity (see Section 4.4).

Compatibility/ Incompatibility with Containers

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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.