Package leaflet: Information for the user

Carmustine 100 mg powder and solvent for concentrate for 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 or 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

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

Carmustine is used as palliative therapy (relieving and preventing the suffering of patients) as a single agent or in established combination therapy with other approved anticancer substances in certain types of cancers, like:
- brain tumours; glioblastoma, medulloblastoma, astrocytoma and metastatic brain tumours.
- multiple myeloma (malignant tumour developing from bone marrow).
- secondary therapy in non-Hodgkin's lymphoma and Hodgkin's disease.
- as conditioning treatment prior to autologous haematopoietic progenitor cell transplantation (HPCT) in malignant haematological diseases (Hodgkin's disease / Non-Hodgkin's lymphoma).
- tumours of gastrointestinal tract or digestive system tract.
- malignant melanoma (skin cancer).

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).
- Carmustine should not be used in patients who have reduced number of blood platelets (thrombocytes), white blood cells (leucocytes) or red blood cells (erythrocytes), either as a result of chemotherapy or from 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.

Since the major side effect of this medicine is delayed bone marrow suppression, 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 (Please also see the section "Possible side effects").

High–dose treatment with carmustine (up to 600 mg/m^2) 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 therapy 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).

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.
- Cimetidine, used for stomach problems like indigestion.
- Digoxin, used if you have abnormal heart rhythm.
- Melphalan, an anticancer drug.

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 avoid becoming pregnant whilst being treated with this medicine.
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 must not breast-feed while taking this medicine.

Driving and using machines
The effect of this medicine on your ability to drive and use machines is not known. 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 medicine contains 2.4 g of alcohol (ethanol) in each reconstituted vial. The amount of alcohol in one reconstituted vial of this medicine is equivalent to 60 ml of beer or 24 ml of wine. Because this medicine is usually given slowly over 1-2 hours, the effects of alcohol may be reduced.

The amount of alcohol in this medicine can affect your ability to drive or use machines. This is because it may affect your judgement and how fast you react.
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 agents.
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/m^2 intravenously every 6 weeks. This may be given as a single dose or divided into two daily injections such as 75 to 100 mg/m^2 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/m^2 intravenously.

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

Route of administration

Carmustine is given into a vein by a drip over a one- to two-hour period protected from light. 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 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 medicine, 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);
- 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);
- Respiratory disorders (lung related disorders) with breathing problems;
- 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 leukaemias 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, 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;
- 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 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 white skin 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 tumours (cancers caused by radiation or chemotherapy);
- Seizures (fits) including status epilepticus;
- Tissue damage due to leakage in injection area;
- Infertility;
- Impairment of embryo/foetus development in pregnant women;
- Any signs of infection;
- Fast heartbeat, 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: http://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.

Store and transport refrigerated (2°C – 8°C).

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

This medicine will be stored by your doctor or health care professional.

After reconstitution and dilution
After reconstitution, Carmustine is stable for 24 hrs in a refrigerator (2ºC – 8ºC) protected from light.

The reconstituted solution should be further admixed with 500 ml sodium chloride (0.9%) solution or 500 ml glucose (5%) solution. These solutions are stable up to 4 hours at room temperature (20°C-25°C) protected from light and also at 24 hrs at 2°C -8°C protected from light.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist or doctor how to throw away medicines you no longer use. These measures will help 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 anhydrous ethanol.
After reconstitution with the solvent provided and further dilution with 27 ml of sterile water, one ml of solution contains 3.3 mg carmustine.

- The other excipients are:

Powder: No excipients.
Solvent: anhydrous ethanol.

What Carmustine looks like and contents of the pack

Carmustine is a powder and solvent for concentrate for solution for infusion.
The powder is pale yellow flakes or congealed mass supplied in amber glass vial (30 ml) stoppered with bromobutyl rubber stopper and sealed with aluminium flip off seal having polypropylene disc.
The solvent is a colourless clear liquid supplied in a clear glass vial (5 ml) stoppered with bromobutyl rubber stopper and sealed with aluminum seal having polypropylene disc.

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

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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. The medicinal product is for single use only. It should be handled with caution and avoid skin contact with the medicinal product. Reconstitution and further dilutions should be carried out under aseptic conditions.

By following the recommended storage conditions it is possible to avoid any decomposition of the unopened vial until the date of expiry mentioned on the packaging.

The storage of carmustine at 27°C or higher temperature can lead to liquefaction of the substance, since carmustine has a low melting point (ca. 30.5°C to 32.0°C). An indication of the decomposition is the appearance of an oil film at the bottom of the vial. This medicine should not be used any further. When you are not clear about the fact whether the product is adequately cooled, then you should immediately inspect each and every vial in the carton. For verification, hold the vial in bright light.

Reconstitution and dilution for each vial of the powder for concentrate for solution for infusion should be prepared as follows
Dissolve carmustine (100 mg powder) with 3 ml of the supplied sterile solvent 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 the reconstituted stock solution will contain 3.3 mg of carmustine in 10% ethanol and have a pH of 4.0 to 6.8.

Reconstitution, as recommended, results in a clear colourless to yellowish solution.

The 30 ml stock solution is to be diluted immediately by adding the 30 ml stock solution to either 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection, or 500 ml 5% glucose solution for injection.

Method of administration:

Carmustine is for intravenous use after reconstitution and further dilution.
Reconstitution and dilution with the sterile solvent provided (3 ml vial) and sterile water for injection (27 ml), results in a clear colourless to yellowish stock solution. This stock solution has to be further diluted with 500 ml with sodium chloride 9 mg/ml (0.9%) solution for injection, or 500 ml with 5% glucose solution for injection. The resulting ready-to-use solution for infusion should be administered immediately by intravenous drip over a one- to two-hour period, protected from light. The duration of infusion should not be less than one hour, otherwise it leads to burning and pain in the injected area. The injected area should be monitored during the administration.

There is no general limit to the duration of use of carmustine therapy. In case the tumour remains incurable or some serious or intolerable side effects appear, the carmustine therapy must be terminated.

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

Posology and laboratory investigations

Initial doses

The recommended dose of Carmustine as a single agent in previously untreated patients is 150 to 200 mg/m^2 intravenously every 6 weeks. This may be given as a single dose or divided into daily infusions such as 75 to 100 mg/m^2 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/ mm^3, leukocytes above 4,000/ mm^3), 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.

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

Special populations

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.
Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored.
In elderly patients the incidence of stomatitis (oral mucositis) is higher when high dose of carmustine is administered.

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

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.