

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 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 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 effective 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 have Carmustine

Do not use Carmustine

- if you are allergic to carmustine 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 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, lung and kidney function will be tested and observed regularly during treatment.

Since the use of Carmustine can lead to lung damage, an X-ray of the chest region and lung function tests will be conducted before 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).

Stomach pain (neutropenic enterocolitis) can occur as therapy-related adverse event upon treatment with chemotherapeutic agents.

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 medicine

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 contraceptive measures while on treatment with Carmustine and for at least 6 months after treatment to prevent their partners becoming pregnant.

Breast-feeding

You must not breast-feed while taking this medicine and 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 alcohol (ethanol)

This medicine contains 2.37 g of alcohol (ethanol) per vial, which is equivalent to 33.86 mg/kg. The amount in maximum dose (600 mg/m²) of this medicine to 640 ml of beer or 256 ml of wine.

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, or breast-feeding 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.

Because this medicine is usually given slowly over 1-2 hours, the effects of alcohol may be reduced.

3. How to use Carmustine

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

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 daily infusions such as 75 to 100 mg/m² on two successive days. Dosage will also depend on whether Carmustine is given with other anti-cancer medicines.

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 (intravenously) over a one- to two-hour period protected from light. The duration 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.

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 concern about the amount of medicine that you received.

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 a 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 due to retinal bleeding;
- Hypotension (fall in blood pressure);
- 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
- 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). Symptoms may include bleeding from the gums, bone pain, fever, frequent infections, frequent or severe nosebleed, lumps caused by swollen lymph nodes in and around the neck, underarm, abdomen or groin, pale skin, shortness of breath, weakness, fatigue or a general decrease in energy;
- Anaemia (decrease in the amount of red blood cells in the blood);
- Encephalopathy (disorder of brain). Symptoms may include muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures;
- Anorexia;
- Constipation;
- Diarrhoea;
- Inflammation of the mouth and lips;
- Reversible liver toxicity in high-dose therapy. 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) where very small (microscopic) veins in the liver are blocked. Symptoms may include: fluid accumulation in the abdomen, enlargement of spleen, severe bleeding of the oesophagus, yellow-colouring of skin and whites of the eyes;
- Breathing problems caused by interstitial fibrosis (with lower doses);
- Kidney problems;
- Gynecomastia (breast growth in males)

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

- Muscular pain;
- Seizures (fits) including status epilepticus;

- Tissue damage due to leakage in injection area;
- Infertility;

Carmustine has been shown to adversely affect the development of unborn babies

- Electrolyte abnormalities (and disturbances in the electrolyte balance (low blood levels of potassium, magnesium, phosphate))

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 HPRA Pharmacovigilance, website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Carmustine

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

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 label and carton after EXP. The expiry date refers to the last day of that month.

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

Keep the vials in the outer carton in order to protect from light.

After reconstitution (reconstituted stock solution)

Chemical and physical in-use stability of reconstituted stock solution has been demonstrated for 24 hours at 2 to 8°C.

After dilution (solution after dilution for infusion)

Chemical and physical in-use stability of solution after dilution for infusion in 500 ml sodium chloride solution for injection or 5% glucose solution for injection and stored in a glass or polypropylene container has been demonstrated for 4 hours at 20 to 25°C, protected from light. These solutions will also remain stable for 24 hours** in a refrigerator (2 to 8 °C) and a further 3 hours at 20 to 25 °C, protected from light.

From a microbiological point of view, unless the method of opening, reconstitution and 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 user.

The solution must be protected from light until the end of administration.

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.

**24 hours in-use storage time of final diluted solution is the total time, carmustine is in solution including the time it is reconstituted using 3 ml of ethanol and 27 ml of water for injections.

6. Contents of the pack and other information

What Carmustine contains

The active substance is carmustine.

Each 30 ml vial of powder for concentrate for solution for infusion contains 100 mg carmustine. Each vial of solvent contains 3 ml of ethanol anhydrous.

After reconstitution with the solvent provided and dilution in 27 ml of sterile water, one ml of solution contains 3.3 mg of carmustine.

Other excipients:

- Powder: No excipients.
- Solvent: Ethanol anhydrous.

What Carmustine looks like and contents of the pack

Carmustine is a powder and solvent for concentrate for solution for infusion. The Pale yellow dry flakes or dry congealed mass is in a amber glass vial (30 ml) sealed with a grey bromobutyl rubber stopper and aluminium seal having polypropylene cap.

The solvent is a clear colourless liquid in a clear glass vial (5 ml) sealed with a fluorotec coated butyl rubber stopper with an aluminium seal having polypropylene cap.

Pack sizes: Pack contains 1 vial of 100 mg powder and 1 vial of 3 ml solvent
Pack contains 10 vials of 100 mg powder and 10 vials of 3 ml solvent

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Accord Healthcare Ireland Limited
Euro House, Euro Business Park,
Little Island, Cork, T45 K857,
Ireland

Manufacturer

Accord Healthcare Polska Sp.z o.o.
ul. Lutomska 50,
95-200 Pabianice, Poland

Or

Laboratori Fundació Dau
C/ C, 12-14 Pol. Ind.
Zona Franca, Barcelona, 08040, Spain

Or

Accord Healthcare B.V.
Winthontlaan 200, 3526KV Utrecht
The Netherlands

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Name of the Member State	Name of the medicine
Cyprus	Carmustine Accord
Czech Republic	Carmustine Accord
Germany	Carmustine Accord 100 mg Pulver und Lösungsmittel für ein Konzentrat zur Herstellung einer Infusionslösung
Denmark	Carmustine Accord
Estonia	Carmustine Accord
Spain	Carmustine Accord 100 mg polvo y disolvente para concentrado para solución para perfusión

Name of the Member State	Name of the medicine
Finland	Carmustine Accord 100 mg Kuiva-aine ja liuotin välikonsentraatiksi infuusionestettä varten, liuos
France	Carmustine Accord 100 mg Poudre et solvant pour solution à diluer pour perfusion
Ireland	Carmustine 100 mg powder and solvent for concentrate for solution for infusion
Italy	Carmustina Accord
Malta	Carmustine 100 mg powder and solvent for concentrate for solution for infusion
The Netherland	Carmustine Accord 100 mg poeder en oplosmiddel voor concentraat voor oplossing voor infusie
Norway	Carmustine Accord
Poland	Carmustine Accord
Portugal	Carmustina Accord
Sweden	Carmustine Accord 100 mg pulver och vätska till koncentrat till infusionsvätska, lösning
United Kingdom (Northern Ireland)	Carmustine 100 mg powder and solvent for concentrate for solution for infusion

This leaflet was last revised in May 2023

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.

Carmustine is a powder and solvent for concentrate for solution for infusion contains no preservative and is not intended as multiple dose vial. 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.

Storing carmustine at 28 °C or higher can cause liquefaction of the substance as the melting point of carmustine is low (about 28.0 to 29.0 °C). When inspected in bright light, the oily film seen at the bottom of the vial is a sign of deterioration. Deteriorated medicinal product must not be used. Flakes with sharp edges and solid mass may be visible in unopened vials without carmustine having been decomposed.

Reconstitution and dilution of the powder for concentrate for solution for infusion

Dissolve carmustine (100 mg powder) with 3 ml of the supplied sterile refrigerated ethanol solvent in the primary packaging (brown glass vial). Carmustine must be completely dissolved in ethanol before sterile water for injections is added. The dilution of the powder may take three minutes. Then aseptically add 27 ml of sterile water for injection to the alcohol solution. The 30 ml stock solution needs to be mixed thoroughly.

One ml of the reconstituted stock solution contains 3.3 mg carmustine in 10% ethanol, and the pH of the solution is 4.0 to 6.8.

Reconstitution, as recommended, results in a yellowish solution, practically free from visible particles.

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.

By reconstituting the powder with the sterile solvent (3 ml vial) provided, a solution has to be prepared by adding additional 27 ml sterile water for injections, resulting in a yellowish stock solution. The stock solution must be further diluted with 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection, or with 500 ml of 5% glucose solution for injection.

The resulting ready-to-use solution for infusion should then be given 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 to avoid burning and pain in the injection area. The injected area should be monitored during the administration.

Pregnant personnel should not handle this medicine.

The instructions for safe handling and discarding of antineoplastic agents must be followed.

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 haematologic toxicity.

Doses subsequent to the initial dose should be adjusted according to the haematologic 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

<i>Nadir after prior dose</i>		<i>Percentage of prior dose to be given</i>
<i>Leucocytes/mm³</i>	<i>Platelets/mm³</i>	
> 4,000	> 100,000	100%
3,000 – 3,999	75,000 - 99,999	100%
2,000 – 2,999	25,000 - 74,999	70%
< 2,000	< 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).

There are no limits for the period of application of carmustine therapy. In case the tumor remains incurable or some serious or intolerable adverse reactions appear, the carmustine therapy must be terminated.

Conditioning treatment prior to HPCT

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

Special populations

Paediatric population

Carmustine must not be used in children aged <18 years because of safety concerns.

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

Renal impairment

For patients with renal impairment the dose of Carmustine should be reduced if the glomerular filtration rate is reduced.

Compatibility/incompatibility with containers

The intravenous solution is unstable in polyvinyl chloride containers. All plastic coming into contact with the carmustine solution for infusion (e.g. infusion set, etc.) should be PVC-free polyethylene plastic, otherwise glass ware should be used.