Package leaflet: Information for the user

Carmustine 50 mg powder and solvent for concentrate for solution for infusion
Carmustine 300 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 Carmustine is given to you
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 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 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/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).

Stomach pain (neutropenic enterocolitis) can occur as therapy-related adverse reaction 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.

<u>Pregnancy and fertility</u>
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.

The fertility of male patients may be affected by treatment with Carmustine. You should seek adequate counselling regarding fertility/family planning before initiating treatment with Carmustine.

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 ethanol (alcohol)
This medicine contains 2.37 g of alcohol (ethanol) per vial for 50 mg strength and 7.11 g of alcohol (ethanol) per vial for 300 mg strength, which is equivalent to 25.596 g per maximal dose (600 mg/m^2 in 70 kg patient). The amount in maximal dose of this medicine is equivalent to 640 ml beer or 256 ml 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.

Recommended dose for 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 daily infusions 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 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/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

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 you 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;
- Any signs of infection
- 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.

<u>After reconstitution (reconstituted stock solution)</u>
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 sodium chloride solution for injection or 5% glucose solution for injection at final concentration of 0.2 mg/ml 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 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.

**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 ethanol and water for injections.

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

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 protect the environment.

6. Contents of the pack and other information

What Carmustine contains
The active substance is carmustine.

Carmustine 50 mg
One 20 ml vial of powder for concentrate for solution for infusion contains 50 mg carmustine. One 5 ml vial of solvent contains 3 ml of ethanol anhydrous.

Carmustine 300 mg
One 100 ml vial of powder for concentrate for solution for infusion contains 300 mg carmustine. One 10 ml vial of solvent contains 9 ml of ethanol anhydrous.

Once the solution is reconstituted with the solvent provided and further diluted with sterile water, one ml of solution will contain 3.3 mg of carmustine.

The other ingredients are:
- 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 powder is pale yellow dry flakes or dry powder is in amber glass vial sealed with rubber stopper and aluminium seal having polypropylene cap.

The solvent is a clear colourless liquid in clear glass vial sealed with rubber stopper and aluminium seal having polypropylene cap.

Pack sizes: Pack contains 1 vial of 50 mg powder and 1 vial of 3 ml solvent
Pack contains 10 vials of 50 mg powder and 10 vials of 3 ml solvent
Pack contains 1 vial of 300 mg powder and 1 vial of 9 ml solvent
Pack contains 10 vials of 300 mg powder and 10 vials of 9 ml solvent

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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. Lutomierska 50,
95-200 Pabianice, Poland

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

Accord Healthcare Single Member S.A.
64th Km National Road Athens,
Lamia, Schimatari, 32009, Greece

This medicinal product is authorised in the Member States of the European Economic Area under the following names:

Name of the Member state	**Name of the medicine**
Finland	Carmustine 50 mg Kuiva-aine ja liuotin välikonsentraatiksi infuusionestettä varten, liuos Carmustine 300 mg Kuiva-aine ja liuotin välikonsentraatiksi infuusionestettä varten, liuos
Austria	Carmustine 50 mg Pulver und Lösungsmittel für ein Konzentrat zur Herstellung einer Infusionslösung Carmustine 300 mg Pulver und Lösungsmittel für ein Konzentrat zur Herstellung einer Infusionslösung
Germany	Carmustine 50 mg Pulver und Lösungsmittel für ein Konzentrat zur Herstellung einer Infusionslösung Carmustine 300 mg Pulver und Lösungsmittel für ein Konzentrat zur Herstellung einer Infusionslösung
Denmark	Carmustine 50 mg pulver og solvens til koncentrat til infusionsvæske, opløsning Carmustine 300 mg pulver og solvens til koncentrat til infusionsvæske, opløsning
Norway	Carmustine
Sweden	Carmustine 50 mg pulver och vätska till koncentrat till infusionsvätska, lösning Carmustine 300 mg pulver och vätska till koncentrat till infusionsvätska, lösning
France	Carmustine 50 mg Poudre et solvant pour solution à diluer pour perfusion Carmustine 300 mg Poudre et solvant pour solution à diluer pour perfusion

Spain	Carmustine 50 mg polvo y disolvente para concentrado para solución para perfusión Carmustine 300 mg polvo y disolvente para concentrado para solución para perfusión
Italy	Carmustine
Portugal	Carmustine
Ireland	Carmustine 50 mg powder and solvent for concentrate for solution for infusion Carmustine 300 mg powder and solvent for concentrate for solution for infusion
Poland	Carmustine

This leaflet was last revised in March 2026

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 carmustine powder for concentrate for solution for infusion contains no preservative and is not intended as a multiple dose vial. 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 dry frozen product does not contain any preservatives and is suitable only for one use. The lyophilisate can appear as a fine powder, however handling can cause it to appear as a heavier and lumpier lyophilisate than as a powdery lyophilisate due to the mechanical instability of the freeze drying cake. The presence of an oily film can be an indication of melting of the medicinal product. Such products are not accepted for use due to the risk of temperature excursions to more than 30°C. This medicinal product 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 vial in the carton. For verification, hold the vial in bright light.

Reconstitution and dilution of the powder for concentrate for solution for infusion
Dissolve carmustine (powder) with the required quantity of 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. Then aseptically add required quantity of sterile water for injection to the alcohol solution. The stock solution needs to be mixed thoroughly.

Powder vial	**Solvent vial (ethanol)**	**Required volume of solvent (ethanol)**	**Required volume of water for injection.**	**Concentration of stock solution**
50 mg	3 ml	1.5 ml	13.5 ml	3.3 mg/ml
300 mg	9 ml	9 ml	81 ml	3.3 mg/ml

One ml of the reconstituted stock solution contains 3.3 mg carmustine in 10% ethanol. Reconstitution, as recommended, results in a clear, colourless to yellowish stock solution, practically free from visible particles, which should be further diluted immediately to required quantity of either sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection to get final concentration of 0.2 mg/ml. The diluted solution (i.e. the ready-to-use solution) should be mixed for at least 10 seconds before administration. The Ready-to-Use solution should be administered over 1-2 hours.

The pH and osmolality of diluted ready-to-use solutions for infusion are
pH: 3.2 to 7.0 diluted in sodium chloride 9 mg/ml (0.9%) or 5% glucose solution for injection.
Osmolality: 340 to 400 mOsmol/l (diluted in glucose 50 mg/ml [5%] solution for injection or sodium chloride 9 mg/ml [0.9%] solution for injection).

Method of administration
For Intravenous use after reconstitution and dilution.
The reconstituted and diluted solution (i.e. ready-to-use solution) must be given intravenously and should be administered by intravenous drip over a one- to two-hour period. Administration of the infusion should be performed using a PVC free PE infusion set. During administration of the medicinal product, the glass or polypropylene container shall be used. Further, the ready-to-use solution needs to be protected from light (e.g. using alu-foil wrapped around the container of the

ready-to-use solution) and preferably kept at temperatures below 20-25°C as Carmustine degrades faster at higher temperatures.

Infusion of Carmustine over shorter periods of time may produce intense pain and burning at the site of injection. The injected area should be monitored during the administration.

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/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 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).

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/m^2 intravenously.

Special populations

Paediatric population

Carmustine is contraindicated in children and adolescents aged <18 years.

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.