**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

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 substances 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)
- Hodgkin's disease (lymphoid tumour)
- Non-Hodgkin's lymphomas (lymphoid tumour)
- Tumours of gastrointestinal tract or digestive system tract
- Malignant melanoma (skin cancer)

Carmustine is also used as a conditioning therapy before transplantation of your own blood stem cells (autologous stem cell transplantation) in malignant hematological diseases of the lymphatic system (Hodgkin's lymphoma and non-Hodgkins 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).
- 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 severe kidney function impairment
- if age of the patient is less than 18 years of age
- 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.

Inform your physician immediately if you experience any of the following symptoms:
- Signs of infection (fever, persistent sore throat)
- Enhanced tendency to bruising/bleeding
- Unusual tiredness
- Accelerated/throbbing heartbeat

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

**Gastrointestinal** symptoms in the form of vomiting and nausea may occur during therapy.

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 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 **lungs, kidneys, 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) 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).

Women and male of child bearing potential should use effective contraception while on treatment and for at least 6 months after treatment (Please also see the section " Pregnancy, breast-feeding and fertility"

**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
- Dexamethasone, use as an anti-inflammatory and immunosuppressive agent
- Methotrexate, cyclophosphamide, procarbazine, chlormethine (nitrogen mustard), fluorouracil, vinblastine, actinomycin (dactinomycin), bleomycin, doxorubicin (adriamycin) used for treatment of various types of cancers.

**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. Women of child bearing potential should use effective contraception to avoid becoming pregnant while on treatment and for at least 6 months after treatment.

Male patients should use adequate contraceptive measures during treatment with Carmustine for at least 6 months 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 seven days after completion of treatment. A risk to the newborn/infant cannot be excluded.

**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 as dizziness is an adverse reaction reported with this medicine which may impair your ability to drive or use machines.

Carmustine contains propylene glycol
Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects.

Do not use this medicine in children less than 5 years old.

Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are 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.

**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 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 autologous stem 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 over a one to two hour period. 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.

**Use in children and adolescents (age <18 years)**
Carmustine cannot be used in children and adolescents due to high risk of lung toxicity.

**Use in elderly**
Carmustine can be used with caution in elderly patients. The kidney function will be carefully monitored.

**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)
- Ataxia (lack of voluntary coordination of muscle movements)
- Dizziness
- Headache
- Transient redness in the eye, blurred vision, retinal bleeding, inflammation of the iris and optic nerve
- Hypotension (fall in blood pressure) with 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 (blood cancer) 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; 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 veins in the liver become blocked. The following symptoms are possible: fluid accumulation in the abdomen, enlargement of the spleen, severe bleeding of the esophagus, yellowing of skin and the white skin of the eyes;
- Breathing problems due to a type of lung disease in which lung tissue is scarred (interstitial fibrosis) (with lower doses); symptoms may include dry cough, shortness of breath, fatigue, weight loss
- Kidney problems
- Gynecomastia (breast growth in males)
    - Bleeding in the gastrointestinal tract
    - inflammation of the optic nerve and adjacent retina in the eye
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**Very rare** (may affect up to 1 in 10,000 people).
- inflammatory process that causes a blood clot to form and block one or more veins, usually in legs. The affected vein might be near the surface of your skin or deep within a muscle (thrombophlebitis).

**Not known** (frequency cannot be estimated from the available data)
- Muscule 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 heartbeat, chest pain
- Allergic reaction
- Disturbances in electrolyte balance (low blood levels of potassium, magnesium, phosphate).
- Abdominal pain (neutropenic enterocolitis).
- A decrease in renal volume, progressive accumulation of certain metabolic products in the blood (azotemia) and kidney failure were observed after high cumulative doses and after long-term treatment with Carmustine and other nitrosoureas. Renal damage was also observed after lower total doses

**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
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie
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 as recommended, Carmustine for injection is stable for 480 hours under refrigeration (2°C -8°C) and 24 hours at room temperature (25°C ±2°C) in glass container. 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.

From a microbiological point of view, the reconstituted solution should be used immediately.

Keep the vials in the outer carton in order to protect from light. The reconstituted stock solution must be further diluted to 500 ml with 0.9 % sodium chloride for injection or 5% dextrose for injection, in glass or polypropylene containers, is physically and chemically stable for 8 hours at 25°C ± 2°C when protected from light. These solutions are also stable upto 48 hours under refrigeration (2°-8°C) and an additional 6 hours at 25°C ± 2°C, when protected from light.

The solution should be protected from light until 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.

Each vial of powder for concentrate for solution for infusion contains 100 mg carmustine.
Each vial of solvent contains 3 ml of anhydrous propylene glycol.
After reconstitution with the solvent provided, one mL of solution contains 33.3 mg carmustine.

- The other excipients are:

Powder: No excipients.
Solvent: propylene glycol.

**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 and is supplied in a type I amber glass vial (30 ml) with a dark grey bromobutyl rubber stopper and sealed with a polypropylene cap.
The solvent is a clear, colourless, viscous liquid and is supplied in a type I clear glass vial (5 ml) with a grey bromobutyl rubber stopper and sealed with a polypropylene cap.

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

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder
Tillomed Pharma GmbH
Mittelstraße 5/5a
12529 Schönefeld Germany

Manufacturer
MIAS Pharma Limited
Suite 2, Stafford House, Strand Road
Portmarnock, Co. Dublin
Ireland

Tillomed Malta Limited,
Malta Life Sciences Park,
LS2.01.06 Industrial Estate,
San Gwann, SGN 3000, Malta

**This medicinal product is authorised in the Member States of the EEA under the following names:**

| | |
|---|---|
| Belgium: | Carmustine Tillomed 100 mg poudre et solvant pour solution à diluer pour perfusion |
| Czech Republic: | Carmustine Zentiva |
| Denmark: | Carmustin Macure |
| Finland: | Carmustine Macure 100 mg kuiva-aine ja liuotin välikonsentraatiksi infuusionestettä varten, liuos |
| Greece: | Carmustine /Tillomed 100 mg κόνις και διαλύτης για συμπύκνωμα για διάλυμα προς έγχυση |
| Hungary: | Carmustine Zentiva 100 mg por és oldószer oldatos infúzióhoz való koncentrátumhoz |
| Ireland: | Carmustine 100 mg powder and solvent for concentrate for solution for infusion |
| Italy: | BICNU |
| Lithuania: | Carmustine Zentiva 100 mg milteliai ir tirpiklis infuzinio tirpalo koncentratui |
| Netherlands: | Carmustine Glenmark 100 mg poeder en oplosmiddel voor concentraat voor oplossing voor infusie |
| Norway: | Carmustine Macure |
| Poland: | Carmustine Zentiva |
| Portugal: | Carmustine Tillomed 100 mg pó e solvente para concentrado para solução para perfusão |
| Slovakia: | Carmustine Zentiva |
| Slovenia: | Karmustin Tillomed 100 mg prašek in vehikel za raztopino za infundiranje |
| Sweden: | Carmustine Macure |

**This leaflet was last revised in 11/2023**

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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 diluent (Propylene Glycol injection) until clear solution is achieved. If required, stir vigorously to get clear solution. Use the propylene glycol vial for reconstitution after achieving the room temperature only and use the larger pore size needle (below 22-gauge needle) to remove the diluent from the vial.
Each ml of the reconstituted stock solution will contain 33.3 mg of carmustine.

Reconstitution, as recommended, results in a yellowish solution.

The reconstituted solution must be further diluted to 500 ml either with 0.9 % Sodium chloride injection, or 5% dextrose injection.
The resulting solution contains final concentration of 0.2 mg/mL of Carmustine which must be stored protected from light.

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. Reconstituted vials should be inspected visually for particulate matter and discoloration prior to administration.

Method of administration:

For Intravenous use after reconstitution and dilution.

The reconstituted and diluted solution should be administered immediately as an intravenous infusion over 1-2 hours, protected from light. The duration of infusion should not be less than one hour, otherwise it leads to burning and pain at the injected area. The injected area should be monitored during the administration. Administration should be finalised within 3 hours from reconstitution/dilution of the medicinal product.

Administration of the infusion should be performed using a PVC free PE infusion set.

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 |

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 $mg/m^2$ 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.