WAYMADE PLC

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UK 675-7165-02

WAYMADE PLC

Package leaflet: Information for the user

Carmustine Waymade 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 Waymade is and what it is used for

Carmustine Waymade is a medicine which contains carmustine as active ingredient. 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;
- as conditioning treatment prior to autologous haematopoietic progenitor cell transplantation (HPCT) in malignant haematological diseases (Hodgkin's disease / Non-hodgkin's lymphoma).
- Multiple myeloma (malignant tumor developing from bone marrow) – in combination with glucocorticoid such as prednisone.

2. What you need to know before you use Carmustine Waymade

Do not use Carmustine Waymade:
- if you are allergic to carmustine or to any ingredient of this medicine (listed in section 6);
- if you suffer from suppression of blood cell formation in the bone marrow and the number of your platelets, white blood cells (leucocytes), or red blood cells (erythrocytes) is therefore reduced, either as a result of chemotherapy or other causes;
- if you suffer from higher-grade kidney dysfunction;
- in children and adolescents;
- if you are pregnant or breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Carmustine Waymade.

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 Waymade 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 Waymade 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 Waymade (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 Waymade must not be used in children and adolescents below 18 years of age.

Other medicines and Carmustine Waymade
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 Waymade 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 Waymade should not be used during pregnancy because it may harm your unborn baby. Therefore, this medicine should not normally be administered to pregnant women. If used during pregnancy, the patient must be aware of the potential risk to the unborn baby. Women of childbearing potential are advised to use effective contraception to avoid becoming pregnant whilst being treated with this medicine and for at least 6 months after treatment.

Male patients should use adequate contraceptives measures during treatment with Carmustine Waymade 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 Waymade 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 Waymade contains ethanol anhydrous (alcohol)
This medicine contains 2.4 g of alcohol (ethanol) in one vial, corresponding to 7.68 g at the maximum dose (320 mg). The amount of alcohol in the maximum dose (200 mg / m² in patients weighing 70 kg) of this medicine corresponds to the amount contained in 192 ml of beer or 76.8 ml of wine. Because this medicine is usually given slowly over 6 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 Waymade

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

This medication is for intravenous infusion.

Adults
Dosage is based on your medical condition, body size and response to treatment. It is usually given at least every 6 weeks. The recommended dose of Carmustine Waymade 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 Waymade is given with other anticancer medicines.

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

The recommended dose of Carmustine Waymade 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 Waymade is given into a vein by a drip (intravenously) over a one to two hours 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.

If you use more Carmustine Waymade 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 a severe allergic reaction.

Carmustine Waymade 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 the Yellow Card Scheme website: 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 Waymade

This medicine will be stored by your doctor or healthcare professional.

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated

WAYMADE PLC			
Product Name	Carmustine		Colours Used
PIP Code	UK 675-7165-02	■	Black
Old PIP Code	GB 674-9618-PIL		
Variaion No.	Drehm address update - impacting revision date		
Customer	Waymade PLC		
Market	UK		
Language	English		
Size	297 x 320 mm (PIL)		
Min. Font Size	8		
Version No.	2 (Page 2 of 2)		
Date	08/11/24		
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on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep both the vials (active and solvent) in the outer carton in order to protect from light.

After reconstitution and dilution
After reconstitution, Carmustine Waymade is stable for 24 hours under refrigeration (2°C – 8°C), stored in a glass container and protected from light.

The reconstituted solution further diluted with either 500 ml of Sodium Chloride 9 mg/ml (0.9%) solution or 500 ml of Dextrose 50 mg/ml (5%) solution in glass or polypropylene container. It should be stored at room temperature, protected from light and utilized within 4 hours. These solutions are also stable for 24 hours under refrigeration (2°C – 8°C) and an additional 6 hours at room temperature and 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 Waymade contains
The active substance is carmustine.
Each vial of powder for concentrate for solution for infusion contains 100 mg carmustine. After reconstitution and dilution, one ml of solution contains 3.3 mg carmustine.
- Excipients:
- Powder: No excipients.
- Solvent: Ethanol anhydrous.

What Carmustine Waymade looks like and contents of the pack
One pack of Carmustine Waymade is a powder and solvent for concentrate for solution for infusion contains one vial with 100 mg of powder of Carmustine and one vial of 3 ml of solvent, Ethanol anhydrous.

The powder is lyophilized pale yellow flakes or congealed mass supplied in an amber glass vial.
The solvent is a colourless clear liquid supplied in a clear glass vial.

Lyophilized pale yellow flakes or congealed mass for reconstitution.
Appearance of solution: The reconstituted solution is a clear, colourless to light yellowish solution.

Powder: Type I amber glass vial (30 ml) with a grey 20 mm bromobutyl rubber stopper with a blue flip-off matte top seal.

Solvent: Type I glass vial (5 ml) with a grey 13 mm chlorobutyl rubber stopper and sealed with blue flip-off matte top seal.

Marketing Authorization Holder and Manufacturer

Marketing Authorization Holder
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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 Carmustine Waymade powder for concentrate for solution for infusion contains no preservative and is not intended as 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 dry flakes or dry congealed mass. 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 and every vial in the carton. For verification, hold the vial in bright light.

Reconstitution and dilution for the powder for concentrate for solution for infusion:
Dissolve the 100 mg Carmustine Waymade powder for concentrate for solution for infusion with 3 ml of the supplied sterile refrigerated ethanol anhydrous solvent provided in the carton. Carmustine must be completely dissolved in ethanol anhydrous before sterile water for injections is added. Then aseptically add 27 ml of sterile water for injections to the alcohol solution. The 30 ml stock solution needs to be mixed thoroughly. Reconstitution, as recommended, results in a clear, colourless to light yellowish solution.

Examine reconstituted vials for crystals formation prior to use. If crystals are observed, they may be re-dissolved by warming the vial to room temperature with agitation. After reconstitution, Carmustine is stable for 24 hours under refrigeration (2°C – 8°C), stored in a glass container and protected from light.

The reconstituted solution must be further diluted with either 500 ml of Sodium Chloride solution 9 mg/ml (0.9%) or 500 ml of Dextrose 50 mg/ml (5%) solution. The reconstituted and diluted solution (i.e ready-to-use solution) should be mixed for at least 10 seconds before administration. The ready to use solution should be stored at room temperature in a glass or polypropylene container, protected from light and utilized within 4 hours. These solutions are also stable for 24 hours under refrigeration (2°C – 8°C) and an additional 6 hours at room temperature protected from light.

The pH and osmolarity of ready-to-use solutions for infusion:
The pH of ready-to-use solutions for infusion is 4.0 to 6.8.

Method of administration
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 and administration. Administration of the infusion should be performed using a PVC free PE infusion set or containers. During administration of the medicinal product, the container shall be of suitable glass ware or polypropylene container only. Ensure that the polypropylene containers used are PVC and DEHP free. Carmustine has a low melting point (30.5°C – 32.0°C or 86.9°F – 89.6°F). Exposure of this drug to this temperature or above will cause the drug to liquefy and appears as an oil film on the vials. This is a sign of decomposition and vials should be discarded.

Infusion of Carmustine Waymade 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 Waymade 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 Waymade 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 Waymade 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 6 weeks. Blood counts should be monitored frequently and repeat courses should not be given before 6 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:

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 tumour 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 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 dose reduced according to this.

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

Compatibility/Incompatibility with containers
The intravenous solution is unstable in polyvinyl chloride containers. Do not use PVC containers. The Carmustine solution can be administered from glass ware or polypropylene container only. Ensure polypropylene containers used are PVC free and DEHP free.