ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carmustine medac 100 mg powder and solvent for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for solution for infusion contains 100 mg carmustine.

After reconstitution and dilution (se section 6.6), one ml of solution contains 3.3 mg carmustine.

Excipient with known effect
Each ampoule of solvent contains 3 ml ethanol anhydrous (that is equivalent to 2.37 g).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion.

Powder: almost white to light yellow lyophilizate or powder.

Solvent: colourless clear liquid.

The pH and osmolarity of ready-to-use solutions for infusion are:
pH 4.0 to 5.0 and 385-397mOsm/l (if diluted in glucose 50 mg/ml [5%] solution for injection), and
pH 4.0 to 6.8 and 370-378mOsm/l (if diluted in sodium chloride 9 mg/ml [0.9%] solution for injection).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 the gastrointestinal tract,
- Malignant melanoma in combination with other antineoplastic medicinal products.
- as conditioning treatment prior to autologous haematopoietic progenitor cell transplantation (HPCT) in malignant haematological diseases (Hodgkin’s disease / Non-hodgkin’s lymphoma).

4.2 Posology and method of administration

Carmustine medac must be administered only by specialists experienced in the field of chemotherapy and under appropriate medical supervision

Posology

Initial doses
The recommended dose of Carmustine medac 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 medac 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 medac 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 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 dose adjustment:

Table 1

Nadir after prior dose		*Percentage of prior dose to be given*
Leucocytes/mm^3	*Platelets/mm^3*	
>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/m^2 intravenously.

Special populations

Paediatric population
Carmustine is contraindicated in children and adolescents aged <18 years (see section 4.3)

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 take into consideration 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 medac should be reduced if the glomerular filtration rate is reduced.

Method of administration
Carmustine medac is for intravenous use after reconstitution and further dilution.

By reconstituting the powder with the solvent provided, a solution has to be prepared by adding additional 27 ml water for injections. Reconstitution and dilution, as recommended, results in a clear, colourless to light yellow stock solution which has to be further diluted with 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection, or glucose 50 mg/ml (5%) solution for injection.

The resulting ready-to-use solution for infusion should then be administered immediately by intravenous drip over a one- to two-hour period protected from light. The duration of infusion should not be less than one hour, otherwise it leads to burning and pain in the injected area. The injected area should be monitored during the administration.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance, to other nitrosoureas or to any of the excipients listed in section 6.1.
- Severe bone marrow depression.
- Severe (end-stage) renal impairment.
- Children and adolescents
- Breast-feeding.

4.4 Special warnings and precautions for use

Pulmonary toxicity characterised by pulmonary infiltrates and/or fibrosis has been reported to occur with a frequency ranging up to 30%. This may occur within 3 years of therapy and appears to be dose related with cumulative doses of 1,200-1,500 mg/m^2 being associated with increased likelihood of lung fibrosis. Risk factors include smoking, the presence of a respiratory condition, pre-existing radiographic abnormalities, sequential or concomitant thoracic irradiation and association with other agents that cause lung damage. Baseline pulmonary function studies and chest X-ray should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70% of the predicted forced vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) are particularly at risk.

An increased risk for pulmonary toxicities upon treatment with conditioning regimes and HPCT for females has been reported. So far, this increased risk is described for the treatment itself including conditioning regimes without carmustine (e.g. TBI or busulfan-cyclophosphamide) or with carmustine (BEAM: carmustine, etopside, cytarabine and melphalan or CBV: cyclophosphamide, carmustine and etoposide).

High-dose therapy with carmustine (especially with 600 mg/m^2) prior to haematopoietic stem cell transplantation has been shown to increase the risk for incidence and severity of pulmonary toxicities. Therefore, in patients with other risks for pulmonary toxicities, use of carmustine needs to be weighed against the risks.

Upon high-dose therapy with carmustine, the risk and severity for infections, cardiac, hepatic, gastrointestinal, and renal toxicity, diseases of the nervous system and electrolyte abnormalities (hypokalemia, hypomagnesemia and hypophosphatemia) rises.

Patients with comorbidities and worse disease status have a higher risk for adverse reactions. This needs to be respected especially for elderly patients.

Hepatic and renal function should also be checked prior to treatment and regularly monitored during therapy (see section 4.8).

Neutropenic enterocolitis can occur as therapy-related adverse reaction upon treatment with chemotherapeutic agents.

Carmustine is carcinogenic in rats and mice at doses less than the recommended human dose based on body surface area (see section 5.3).

Bone marrow toxicity is a common and severe toxic adverse reaction of carmustine. Complete blood count should be monitored frequently for at least six weeks after a dose. In case of a decreased number of circulating platelets, leucocytes or erythrocytes either from previous chemotherapy or other cause the dose should be adjusted, see Table 1, section 4.2. Liver, kidney and lung function should be checked and monitored regularly during therapy (see section 4.8). Repeat doses of Carmustine medac should not be given more frequently than every six weeks. The bone marrow toxicity of carmustine is cumulative and therefore the dose adjustment must be considered on the basis of nadir blood counts from prior doses (see section 4.2).

Direct administration of carmustine into the carotid artery is regarded as experimental and has been associated with ocular toxicity.

A dose of 600 mg/mg^2 of this medicine administered to an adult weighing 70 kg would result in exposure to 370 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 61.7 mg/100 ml. For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects. Because this medicine is usually given slowly over 6 hours, the effects of alcohol may be reduced.

4.5 Interaction with other medicinal products and other forms of interaction

Phenytoin and dexamethasone
In combination with chemotherapeutic medicinal products reduced activity of antiepileptic medicinal products must be anticipated.

Cimetidine
Concomitant use with cimetidine leads to delayed, major, suspected, increased carmustine toxic effect (due to the inhibition of carmustine metabolism).

Digoxin
Concomitant use with digoxin leads to delayed, moderate, suspected, decreased effect of digoxin (due to the decreased digoxin absorption).

Melphalan
Concomitant use with melphalan leads to increased risk of pulmonary toxicity.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Women should use effective contraception to avoid becoming pregnant while on treatment and for at least 6 months after treatment.

Male patients should be advised to use adequate contraceptive measures while on treatment with carmustine and for at least 6 months after treatment.

Pregnancy
Carmustine should not be administered to patients who are pregnant. Safe use in pregnancy has not been established and therefore the benefit must be carefully weighed against the risk of toxicity. Carmustine is embryotoxic in rats and rabbits and teratogenic in rats when given in doses equivalent to the human dose (see section 5.3). If Carmustine medac is used during pregnancy, or if the patient becomes pregnant while taking (receiving) Carmustine medac, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding
It is unknown whether carmustine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Carmustine medac is contraindicated during breast-feeding and up to seven days post-treatment (see section 4.3).

Fertility
Carmustine may impair male fertility. Males should be advised of potential risk of infertility and to seek fertility/family planning counselling prior to therapy with carmustine .

4.7 Effects on ability to drive and use machines

Carmustine medac has no or negligible influence on the ability to drive and use machines. However, the possibility will have to be taken into consideration, that the alcohol quantity in these pharmaceutical medicines can impair the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The table includes adverse reactions that were presented during treatment with this medicinal product but may not necessarily have a causal relationship with the medicinal product. Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed may not reflect the rates observed in clinical practice. Adverse reactions are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse reactions are included if the incidence is ≥ 5% higher in the treatment group.

Tabulated list of adverse reactions

The following table includes adverse reactions of carmustine listed by MedDRA system organ class and frequency convention presented in order of decreasing seriousness:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1 000 to <1/100); Rare (≥1/10 000 to < 1/1 000); Very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Not known	Opportunistic infections (including fatal)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute leukaemia, bone marrow dysplasia – following long-term use.
Blood and lymphatic system disorders		

	Very common	Myelosuppression.
	Common	Anaemia.
Nervous system disorders	Very common	Ataxia, dizziness, headache.
	Common	Encephalopathy (high-dose therapy and dose-limiting).
	Not known	Muscular pain, status epilepticus, seizure, grand mal seizure.
Eye disorders	Very common	Ocular toxicities, transient conjunctival flushing and blurred vision due to retinal haemorrhages.
Cardiac disorders	Very common	Hypotension, due to the alcohol content of the solvent (high-dose therapy).
	Not known	Tachycardia
Vascular disorders	Very common	Phlebitis.
	Rare	Veno-occlusive disease (high-dose therapy).
Respiratory, thoracic and mediastinal disorders	Very common	Pulmonary toxicity, interstitial fibrosis (with prolonged therapy and cumulative dose)* Pneumonitis.
	Rare	Interstitial fibrosis (with lower doses).
Gastrointestinal disorders	Very common	Emetogenic potential. Nausea and vomiting – severe
	Common	Anorexia, constipation, diarrhoea, stomatitis.
Hepatobiliary disorders	Common	Hepatotoxicity, reversible, delayed up to 60 days after administration (high-dose therapy and dose-limiting), manifested by: - bilirubin, reversible increase - alkaline phosphatase, reversible increase - SGOT, reversible increase.
Skin and subcutaneous tissue disorders	Very common	Dermatitis with topical use improves with reduced concentration of compounded product, hyperpigmentation, transient, with accidental skin contact.

	Common	Alopecia, flushing (due to alcohol content of solvent; increased with administration times <1-2 h), injection site reaction.
	Not known	Extravasation hazard: vesicant
Renal and urinary disorders	Rare	Renal toxicity.
Reproductive system and breast disorders	Rare	Gynecomastia.
	Not known	Infertility, teratogenesis.
Metabolism and nutrition disorders	Not known	Electrolyte abnormalities (hypokalemia, hypomagnesemia and hypophosphatemia)

* An increased risk for pulmonary toxicities upon treatment with conditioning regimes and HPCT for females has been reported. So far, this increased risk is described for the treatment itself including conditioning regimes without carmustine (e.g. TBI or busulfan-cyclophosphamide) or with carmustine (BEAM: carmustine, etopside, cytarabine and melphalan or CBV: cyclophosphamide, carmustine and etoposide).

Description of selected adverse reactions

Myelosuppression
Myelosuppression is very common and begins 7-14 days of administration with recovery 42-56 days of administration. The myelosuppression is dose and cumulative dose related, and often biphasic.

Respiratory, thoracic and mediastinal disorders

Pulmonary fibrosis (with fatal outcome), pulmonary infiltration

Pulmonary toxicity has been observed in up to 30% of patients. In cases where pulmonary toxicity started early (within 3 years of treatment), pulmonary infiltrates and/or pulmonary fibrosis occurred, some of which were fatal. The patients were between 22 months and 72 years old. Risk factors include smoking, respiratory disease, existing radiographic abnormalities, sequential or concomitant thoracic radiation, as well as combination with other active substances that can cause lung damage. The incidence of adverse reactions is probably dose-related; cumulative doses of 1200-1500 mg/m^2 have been associated with an increased likelihood of pulmonary fibrosis. During treatment, lung function tests (FVC, DLCO) should be performed regularly. Patients showing a baseline value of <70% of expected forced vital capacity or carbon monoxide diffusion capacity in these tests are at particular risk.
In patients having received carmustine in childhood or adolescence, cases of extremely delayed-onset pulmonary fibrosis (up to 17 years after treatment) have been described.
Long-term follow-up observation of 17 patients who survived brain tumours in childhood showed that 8 of them succumbed to pulmonary fibrosis. Two of these 8 fatalities occurred within the first 3 years of treatment and 6 of them occurred 8-13 years after treatment. The median age of patients who died on treatment was 2.5 years (1-12 years), the median age of long-term survivors on treatment was 10 years (5-16 years). All patients younger than 5 years of age at the time of treatment died from pulmonary fibrosis; neither the carmustine dose nor an additional vincristine dose or spinal radiation had any influence on the fatal outcome.
All remaining survivors available for follow-up were diagnosed with pulmonary fibrosis. Use of carmustine in children and adolescents < 18 years is contraindicated, see section 4.3.

Pulmonary toxicity also manifested in the post-marketing phase as pneumonitis and interstitial lung disease. Pneumonitis is seen for doses >450 mg/m^2 and interstitial lung disease is seen with prolonged therapy and cumulative dose > 1,400 mg/m^2.

Emetogenic potential
The emetogenic potential is high at doses >250 mg/m^2 and high to moderate in doses ≤250 mg/m^2. Nausea and vomiting are severe and begins within 2-4 h of administration and lasts for 4-6 h.

Renal toxicity
Renal toxicity is rare, but occurs for cumulative doses < 1,000 mg/m^2.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The main symptom of intoxication is myelosuppression. In addition, the following serious adverse reactions may occur: liver necrosis, interstitial pneumonitis, encephalomyelitis. A specialized antidote is not available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, nitrosoureas,
ATC code: L01AD01

Mechanism of action
Carmustine is a cell-cycle phase nonspecific antineoplastic agent of the nitrosourea type, which exerts tumor cytotoxicity via multiple mechanisms. As an alkylating agent, it can alkylate reactive sites on nucleoproteins, thus interfering with DNA and RNA synthesis and DNA repair. It is able to form interstrand crosslinks in DNA, which prevents DNA replication and transcription. In addition, carmustine is known to carbamoylate lysine residues on proteins causing irreversible inactivation of enzymes including glutathione reductase. The carbamoylating activity of carmustine is generally considered less significant than the alkylating activity in its action on tumors, but carbamoylation may serve to inhibit DNA repair.

Pharmacodynamic effects
The antineoplastic and toxic activities of carmustine may be due to its metabolites. Carmustine and related nitrosoureas are unstable in aqueous solutions and degrade spontaneously to reactive intermediates that are capable of alkylation and carbamoylation. The alkylating intermediates are believed to be responsible for the antitumor effect of carmustine. However, opinion is divided over the role of the carbamoylating intermediates as mediators of the biological effects of the nitrosoureas. On one hand, their carbamoylating activity was reported to contribute to the cytotoxic properties of their parent medicinal products by inhibiting DNA repair enzymes. On the other hand, it has been speculated that the carbamoylating species may mediate some of toxic effects of carmustine.

Carmustine crosses the blood-brain barrier readily because of its lipophilic nature.

Paediatric population
Carmustine medac should not be used in children and adolescents due to high risk of pulmonary toxicity.

5.2 Pharmacokinetic properties

Distribution
Intravenously administered carmustine is rapidly degraded, with no substance intact detectable after 15 minutes. Because of the good lipid solubility and the lack of ionisation at the physiological pH, carmustine is very well transferred through the blood-brain barrier. Levels of radioactivity in the cerebrospinal fluid are at least 50% higher than those measured concurrently in plasma. The kinetic of carmustine in humans is characterised by a two-chamber model. After the intravenous infusion over 1 hour, the carmustine-plasma level drops in a biphasic manner. The half-life α is 1-4 minutes and the half-life β is 18-69 minutes.

Biotransformation
It is presumed that the metabolites of carmustine cause its antineoplastic and toxic activity.

Elimination
Approximately 60-70% of a total dose is excreted in the urine in 96 hours and about 10% as respiratory CO2. The fate of the remainder is undetermined.

5.3 Preclinical safety data

Carmustine was embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. Carmustine affected the fertility of male rats at doses higher than the human dose. Carmustine, at clinically relevant dose levels, was carcinogenic in rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
No excipients.

Solvent
Ethanol, anhydrous.

6.2 Incompatibilities

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.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years.

After reconstitution and dilution
The solution should be administered within 3 hours after reconstitution and dilution of the product. The solution should be protected from light until end of administration.

6.4 Special precautions for storage

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

Keep the vial and ampoule in the outer carton in order to protect from light.

For storage conditions after reconstitution and further dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder
Brown type I hydrolytic glass vial (50 ml) with light grey 20 mm bromobutyl rubber stopper and sealed with a dark red aluminium flip-off cap.

Solvent
Clear type I glass ampoule (5 ml).

One pack contains one vial with 100 mg of powder for concentrate for solution for infusion and one ampoule with 3 ml of solvent.

6.6 Special precautions for disposal and other handling

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.

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 more heavy and lumpy 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 and every 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 the carmustine vial (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.
Then aseptically add 27 ml of sterile water for injection to the alcohol solution. The 30 ml stock solution needs to be mixed thoroughly. Reconstitution, as recommended, results in a clear, colourless to light yellow stock solution.

The 30 ml stock solution is to be diluted immediately by adding the 30 ml stock solution to either 500 ml 5% glucose or 500 ml sodium chloride 9 mg/ml (0.9%) solution for injection in glass containers. The 530 ml 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 and administration should be finalised within 3 hours from reconstitution of the product.

Administration of the infusion should be performed using a PVC free PE infusion set.
During administration of the medicinal product, the container shall be of suitable glass ware. Further, the ready-to-use solution 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°C-22°C as Carmustine degrades faster at higher temperatures.

Infusion of Carmustine medac in less than one hour may produce intense pain and burning at the site of injection (see section 4.2).

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany
Tel.: +49 4103 8006-0
Fax.: +49 4103 8006-100
E-mail: contact@medac.de

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1278/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2018
Date of latest renewal: 5 May 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Carmustine medac 100 mg powder and solvent for concentrate for solution for infusion
carmustine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder for concentrate for solution for infusion contains 100 mg carmustine.
After reconstitution and dilution, one ml of solution contains contains 3.3 mg carmustine.

3. LIST OF EXCIPIENTS

Ethanol. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for concentrate for solution for infusion

1 vial of 100 mg powder
1 ampoule of 3 ml solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.

Read the package leaflet before use.

Intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution. Avoid skin contact with concentrate for solution for infusion.
May cause birth defects.

8. EXPIRY DATE

EXP

After reconstitution/dilution: See package leaflet for the shelf life of the reconstituted medicine.

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.
Keep the vial and ampoule in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1278/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT

Carmustine medac 100 mg powder for concentrate for solution for infusion

carmustine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder for concentrate for solution for infusion contains 100 mg carmustine.
After reconstitution and dilution, one mL of solution contains contains 3.3 mg carmustine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
100 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.

Read the package leaflet before use.

Intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: Handle with caution. Avoid skin contact with concentrate for solution for infusion.
May cause birth defects.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1278/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT AMPOULE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Carmustine medac
ethanol anhydrous
IV

2. METHOD OF ADMINISTRATION

For dissolving purposes only

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Carmustine medac 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 medac is and what it is used for

Carmustine medac 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 medac

Do not use Carmustine medac:
- 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 medac.

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 medac 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 medac 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 medac (up to 600 mg/m^2) is only performed in combination with subsequent stem cell transplanation. 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 medac must not be used in children and adolescents aged <18 years.

Other medicines and Carmustine medac
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 medac 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 medac 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 pregancy, 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 medac 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 medac 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 medac contains ethanol (alcohol)
This medicine contains 2.4 g of alcohol (ethanol) per vial, which isequivalent to 25.92 g per maximal dose (10vol%). The amount in maximal dose (600 mg/m^2 in 70 kg patient) of this medicine is equivalent to 648 ml beer or 259 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, 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 medac

Carmustine medac 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 medac 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 medac is given with other anti-cancer medicines.

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

The recommended dose of Carmustine medac 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 medac 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 medac 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 medac 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 the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Carmustine medac

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 vial and ampoule in the outer carton in order to protect from light.

After reconstitution and dilution
After reconstitution Carmustine medac is stable for 3 hours, stored in a glass container and protected from light.

The solution should be administered within 3 hours after reconstitution and dilution of the product. 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 medac 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 medac looks like and contents of the pack
Carmustine medac is a powder and solvent for concentrate for solution for infusion.

The powder is an almost white to light yellow powder supplied in a brown glass vial.

The solvent is a colourless clear liquid supplied in a clear glass ampule.

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

Marketing Authorisation Holder and Manufacturer
medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany
Tel.: +49 4103 8006-0
Fax.: +49 4103 8006-100
E-mail: contact@medac.de

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/ema/.

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 medac 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 fine powder, however handling can cause it to appear as a more heavy and lumpy 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 and every vial in the carton. For verification, hold the vial in bright light.

<u>Reconstitution and dilution of the powder for concentrate for solution for infusion</u>
Dissolve the 100 mg Carmustine powder for concentrate for solution for infusion 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. 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 yellow stock solution.
The 30 ml stock solution is to be diluted immediately by adding the 30 ml stock solution to either 500 ml glucose 50 mg/ml (5%) solution for injection or 500 ml sodium chloride 9 mg/ml (0.9%)

solution for injection in glass containers. The 530 ml diluted solution (i.e. the ready-to-use solution) should be mixed for at least 10 seconds before administration.

pH and osmolarity of ready-to-use solutions for infusion
pH 4.0 to 5.0 and 385-397 mOsm/l (if diluted in glucose 50 mg/ml [5%] solution for injection) and pH 4.0 to 6.8 and 370-378 mOsm/l (if diluted in sodium chloride 9 mg/ml [0.9%] solution for injection).

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 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.
During administration of the medicinal product, the container shall be of suitable glass ware. Further, the ready-to-use solutions 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 20-22°C as carmustine degrades faster at higher temperatures.
Administration of the infusion should be performed using a PVC free PE infusion set.

Infusion of Carmustine medac 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 medac 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 medac 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 medac 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 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 dose adjustment:

Nadir after prior dose		*Percentage of prior dose to be given*
Leucocytes/mm^3	*Platelets/mm^3*	
>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/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 medac 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.