Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carmustine 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 (see section 6.6), one mL of solution contains 33.3 mg carmustine.

Excipient with known effect
Each vial of solvent contains 3 mL propylene glycol (equivalent to 3.1125 g).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion.

Powder: Pale yellow powder with small quantities of dried flakes or as a dry rigid mass.
Solvent: Clear, colourless, viscous liquid.

The pH and osmolarity of ready-to-use solutions for infusion are:
pH: 4.0 to 6.8 whether diluted with physiological saline or with 5 % dextrose solution
Osmolarity: 320 to 390 mOsmol/l (if diluted in dextrose 50 mg/mL [5 %] solution for injection) or in sodium chloride 9 mg/mL [0.9 %] solution for injection)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Carmustine is indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following:

- Brain tumours - glioblastoma, medulloblastoma, astrocytoma and metastatic brain tumours.
- Multiple myeloma - in combination with glucocorticoid such as prednisone.
- Hodgkin's disease - as secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.
- Non-Hodgkin's lymphomas - as secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.
- Tumours of the GI tract
- Malignant melanoma when used in combination with other antineoplastic drugs.
- Conditioning prior to autologous hematopoietic stem cell transplantation (SCT) in malignant haematological diseases (Hodgkin's/Non-Hodgkin's lymphoma)

4.2 Posology and method of administration

Carmustine 100 mg powder and solvent for concentrate for solution for infusion 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 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 regimen prior to SCT
Carmustine is administered in combination with other chemotherapeutic agents in patients with haematologic malignancies prior to SCT at an intravenous dose of 300 – 600 mg/m^2.

Special populations

Patients with impaired renal function
In patients with impaired 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 take into consideration 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).

Method of administration:
For Intravenous use after recostitution and dilution.

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 or myelosuppression

- Severe (end-stage) renal impairment
- Children and adolescents
- Breastfeeding (refer to section 4.6)

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. The adverse reaction frequency appears to be dose related with cumulative doses of 1200-1500 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.

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.

Use of carmustine in children and adolescents < 18 years is contraindicated, see section 4.3.

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

An increased risk of pulmonary toxicities has been reported with conditioning regimens and SCT in women. To date, this increased risk has been described for the treatment itself, including the conditioning regimen 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.

<u>High-dose therapy</u>
High-dose therapy with carmustine increases the risk and severity of infections, cardiac, hepatic, gastrointestinal, and renal toxicity, as well as nervous system disorders and electrolyte disturbances (hypokalemia, hypomagnesemia, and hypophosphatemia).

<u>Comorbidities and poor disease status</u>
Patients with comorbidities and poorer disease status are at higher risk for adverse events. This is especially important for elderly patients

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

<u>Bone marrow toxicity</u>
Delayed and cumulative 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. In addition to this, the liver, kidney and lung function should be examined and monitored regularly during the carmustine therapy *(see section 4.8).* Repeat doses of Carmustine should not to be given more frequently than every six weeks.

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. Thrombocytopenia is generally more pronounced than leukopenia, but both are dose-limiting adverse effects. Anaemia is common but is usually less pronounced.

The bone marrow toxicity of Carmustine is cumulative and therefore the dosage adjustment must be considered based on nadir blood counts from prior dose (see section 4.2).

<u>Women of childbearing potential/contraception in males and females</u>
Women of childbearing potential 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 during the treatment with carmustine and for at least 6 months after treatment (see section 4.6).

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.

Parenteral administration
The intra-arterial compatibility has not been tested. Severe tissue damage can be expected in case of inadvertent intra-arterial administration.

Experimental direct injection of Carmustine to the carotid artery has been associated with ocular toxicity.

During administration of carmustine, administration site reactions may occur (see section 4.8). Given the possibility of extravasation, close monitoring of the infusion site is recommended for possible infiltration during administration. A special method for handling extravasation is currently unknown.

Accidental contact of the reconstituted infusion solution with the skin has resulted in burns and excessive pigmentation in the affected areas.

Local soft tissue toxicity resulting from extravasation of carmustine has been reported. Infiltration of carmustine may cause swelling, pain, erythema, burning, and skin necrosis.

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 leads to delayed, major, suspected, increased carmustine toxic effect (due to the inhibition of carmustine metabolism) or increased myelotoxicity (e.g. leukopenia and neutropenia)

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

Melphalan
Concomitant use leads to increased risk of pulmonary toxicity
Thrombopenia and leukopenia can be expected when combined with other myelosuppressive drugs, e.g. methotrexate, cyclophosphamide, procarbazine, chlormethine (nitrogen mustard), fluorouracil, vinblastine, actinomycin (dactinomycin), bleomycin, doxorubicin (adriamycin) - or in patients whose bone marrow reserve is depleted due to the disease itself or previous therapy
There is a possibility of cross-resistance with other alkylating substances, e.g. chloromethine and cyclophosphamide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
Women of childbearing potential 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 during the 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 to risk of toxicity must be carefully weighed. Carmustine is embryotoxic in rats and rabbits and teratogenic in rats when given in doses equivalent to the human dose. If carmustine is used during pregnancy, or if the patient becomes pregnant while taking (receiving) carmustine, the patient should be apprised of the potential hazard to the fetus.

Breastfeeding
It is unknown whether carmustine/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

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

No studies have been undertaken on the consequences the medicine on the competency to drive and the ability to operate machines.

However, the possibility will have to be taken into consideration that dizziness is an adverse reaction reported with this medicine which may impair the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The table includes adverse events that were presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events 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 events are included if the incidence is ≥5 % higher in the treatment group.

High dose is defined as >200 mg/m^2

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 (frequency 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**
Clinically important side effects are in *italics*		
Infections and infestations	Not known	Opportunistic infections (including fatal outcome)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	common	Acute leukemias, bone marrow dysplasias; following long-term use.
	Not known	Secondary malignancies
Blood and lymphatic system disorders	common	Anaemia.

	very common	*Myelosuppression*
Immune system disorders	not known	Allergic reaction
Metabolism and nutrition disorders	Not known	Electrolyte disorders (hypokalaemia, hypomagnesaemia, and hypophosphataemia)
Nervous system disorders	very common	Ataxia, dizziness, headache.
	common	Encephalopathy (high-dose therapy and dose-limiting).
	not known	Muscule pain, status epilepticus, seizure, tonic clonic seizure (grand mal seizure).
Eye disorders	very common	Ocular toxicities, transient conjunctival flushing and blurred vision; retinal haemorrhages.
	Rare	Neuroretinitis
Cardiac disorders	very common	Hypotension (high-dose therapy)
	not known	Tachycardia, chest pain
Vascular disorders	very common	Phlebitis
	rare	Veno-occlusive disease (high-dose therapy).
Respiratory, thoracic and mediastinal disorders	very common	*Pulmonary toxicity[1],interstitial fibrosis (with prolonged therapy and cumulative dose* > 1400 mg/m^2) Pneumonitis (for doses > 450mg/m^2).*
	rare	*IInterstitial fibrosis (with lower doses).*
Gastrointestinal disorders	very common	*Nausea and vomiting, severe; emetogenic potential> 250 mg/m^2 medium-high; starts within 2-4 hours after administration and lasts for 4-6 hours*
	common	Anorexia,constipation, diarrhoea, stomatitis.
	Rare	Gastrointestinal bleeding
	Not known	Neutropenic enterocolitis
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	not known	*extravasation hazard: vesicant*
	very common	Dermatitis with topical use improves with reduced concentration of compounded product, hyperpigmentation, transient, with accidental skin contact.
	common	Alopecia, flushing (increased with administration times <1-2 h), injection site reaction.
Renal and urinary disorders	not known	Renal failure, azotemia, decrease in kidney volume
	Rare	*Renal toxicity*
Reproductive system and breast disorders	Rare	Gynecomastia.
	not known	Infertility, teratogenesis.
General disorders and administration site conditions	common	Burning sensation at injection site
	Very rare	Thrombophlebitis

[1]Pulmonary toxicity is also manifested as pneumonitis and interstitial lung disease in post-marketing experience

* 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. Thrombocytopenia is generally more pronounced than leukopenia, but both are dose-limiting adverse effects. Anaemia is common but is usually less pronounced.

Eye disorders
Rapid intravenous infusion may cause conjunctival bleeding within 2 hours, lasting approximately 4 hours.

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/m2 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 4-6h.

Renal toxicity
Renal toxicity is rare, but occurs for cumulative doses < 1,000 mg/m^2. Renal changes with decreased kidney volume, progressive azotemia, and renal failure have been reported after high cumulative doses and after long term therapy with carmustine and related nitrosoureas. Renal impairment was also occasionally observed after low total doses.

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

HPRA Pharmacovigilance
Earlsfort Terrace

IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

The main symptom of intoxication is myelosuppression. In addition, the following serious side effects may occur:

Liver necrosis, interstitial pneumonitis, encephalomyelitis.

A specialized antidote is not available. There are no known myelo-protective substances. Bone marrow transplantation could be an effective measure.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Carmustine (1,3-bis (2-chloroethyl) -1-nitrosourea) is a cell-cycle phase nonspecific antineoplastic agent of the nitrosourea type, which exerts tumour 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 tumours, 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 drugs 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 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 drug intact detectable after 15 minutes. Because of the good lipid solubility and the lack of ionization at the physiological pH, Carmustine is very well transferred through the blood-brain barrier. Levels of radioactivity in the CSF are at least 50 % higher than those measured concurrently in plasma.

The kinetic of carmustine in humans is characterized 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 accounts to 1-4 minutes and the half life β accounts to 18-69 minutes.

Biotransformation

It is presumed that the metabolites of carmustine causes 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 CO_2. The fate of the remainder 20-30 % 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 slightly higher than the human dose. Carmustine, at clinically relevant dose levels, was carcinogenic in rats and mice with a marked increase in the incidence of tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
No excipients

Solvent
Propylene glycol

6.2 Incompatibilities

The solution for infusion is unstable in polyvinyl chloride (PVC) containers. The carmustine solution can be administered from glass bottles or polypropylene container only, using PVC-free infusion set.

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

After reconstitution as recommended, Carmustine for injection is stable for 480 hours under refrigeration (2°-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.

The reconstituted solution further diluted to 500 ml with 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°C-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.

6.4 Special precautions for storage

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

Keep the vials 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
Type I amber glass vial (30 mL) with a dark grey bromobutyl rubber stopper and sealed with a polypropylene cap.

Solvent
Type I clear glass vial (5 mL) with a grey bromobutyl rubber stopper and sealed with a polypropylene cap.

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

6.6 Special precautions for disposal and other handling

The medicinal product contains no preservative and is not intended as multiple dose vial. Reconstitution and further dilutions should be carried out under aseptic conditions.

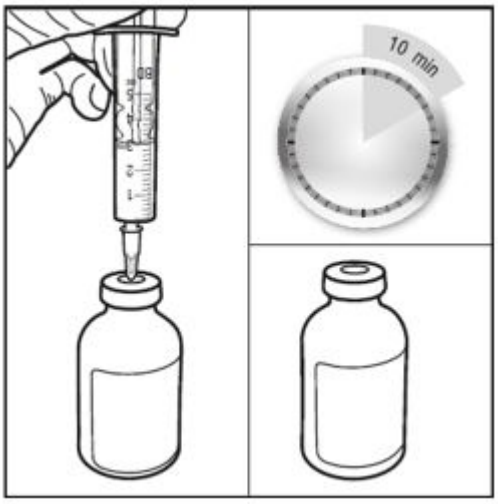
The storage of carmustine at 27°C or higher temperature can lead to liquefaction of the substance, since carmustine has a low melting point (ca. 30.5°C to 32.0°C). An indication of the decomposition is the appearance of an oil film at the bottom of the vial, visible when the vial is held in bright light. This medicine should not be used any further. There can be physical appearances of sharp flakes in the unopened vial as far as rigid mass, however without any decomposition of carmustine.

Reconstitution and dilution for each vial of the powder for concentrate for solution for infusion
Dissolve carmustine (100 mg powder) with 3 ml of the supplied sterile diluent (Propylene Glycol injection) until clear solution is achieved. 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. A step-by-step guide for reconstitution is provided below.

Step 1: Take out both vials from the carton and allow to achieve room temperature. ***(Min. 10 minutes)*.**

Step 2: Aseptically ***withdraw 3 mL sterile diluent*** from the diluent vial with the help of sterile syringe. Ensure complete withdrawal (3 mL) of sterile diluent into the syringe.

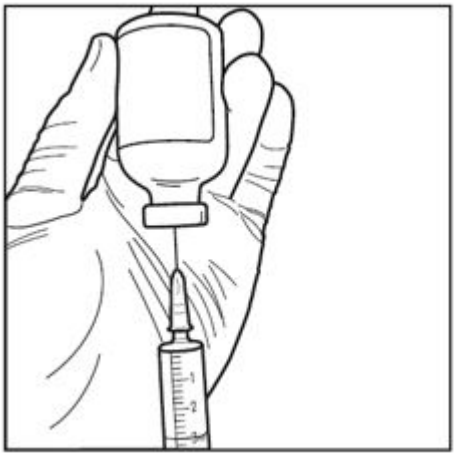
Step 3: Inject the sterile diluent into vial containing 100mg Carmustine and ***allow to wet the product for minimum 10 minutes.***



Step 4: Swirl the vial (move in a circular motion) for ***at least 60 seconds without any stoppage*** to get the clear solution.

Step 5: Keep *the reconstituted vial in inverted position for 5 minutes.*

Step 6: ***Aseptically withdraw the reconstituted solution in inverted position only and prepare solution for infusion after further dilution***



Each ml of the reconstituted 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.

The ready-to-use solution should be administered over 1-2 hours, protected from light. Administration should be finalised within 3 hours from reconstitution/dilution of the medicinal product.

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

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.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Mittelstrasse 5/5a
Schonefeld
12529
Germany

8 MARKETING AUTHORISATION NUMBER

PA22720/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th January 2020
Date of last renewal: 17th April 2024

10 DATE OF REVISION OF THE TEXT

May 2025