ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Carmustine Obvius 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: white to almost white powder or lyophilisate.

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 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

4.2 Posology and method of administration

Carmustine Obvius 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 Obvius 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 Obvius 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 Obvius 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 dosage 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.

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 Obvius should be reduced if the glomerular filtration rate is reduced.

Method of administration
Carmustine Obvius 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.

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

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

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 Obvius should not to be given more frequently than every six weeks. The bone marrow toxicity of carmustine is cumulative and therefore the dosage 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.

This medicinal product contains 0.57 vol% ethanol (alcohol), i.e. up to 7.62 g per dose, equivalent to 11.2 ml beer or 4.65 ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines, and may impair your ability to drive or use machines.

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. If Carmustine Obvius is used during pregnancy, or if the patient becomes pregnant while taking (receiving) Carmustine Obvius, 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 Obvius 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 Obvius 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 (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**
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).
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.

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 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 Obvius 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

1 year.

After reconstitution and dilution
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 (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 20-22°C as Carmustine degrades faster at higher temperatures.

Infusion of Carmustine Obvius 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.

7. MARKETING AUTHORISATION HOLDER

Obvius Investment B.V.
De Cuserstraat 93
1081 CN Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1278/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

<{DD/MM/YYYY}>

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

European Pharma Hub Ltd
7000/9 hrsz, warehouse 15 and 16
Gyál, 2360
HUNGARY

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 agreeed 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 Obvius 100 mg powder and solvent for concentrate for solution for infusion
carmustine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 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

Obvius Investment B.V.
De Cuserstraat 93
1081 CN Amsterdam
The Netherlands

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 Obvius 100 mg powder for concentrate for solution for infusion
carmustine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 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

Obvius Investment B.V.
De Cuserstraat 93
1081 CN Amsterdam
The Netherlands

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 Obvius
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 Obvius 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 Obvius is and what it is used for
2. What you need to know before Carmustine Obvius is given to you
3. How to use Carmustine Obvius
4. Possible side effects
5. How to store Carmustine Obvius
6. Contents of the pack and other information

1. What Carmustine Obvius is and what it is used for

Carmustine Obvius 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 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

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

Do not use Carmustine Obvius:
- 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 Obvius.

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 Obvius 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 Obvius 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").

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 Obvius must not be used in children and adolescents aged <18 years.

Other medicines and Carmustine Obvius
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 Obvius 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 Obvius 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 Obvius 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 Obvius 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 Obvius contains ethanol (alcohol)
This medicine contains 0.57 vol% ethanol (alcohol), which means 7.62 g per dose. This corresponds to 11.2 ml of beer or 4.65 ml wine, per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

3. How to use Carmustine Obvius

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

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

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 Obvius 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 Obvius 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 Obvius 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 oesophgus, yellow-coulouring 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

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 Obvius

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 Obvius is stable for 3 hours, stored in a glass container and protected from light.

After reconstitution and dilutionthe 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 Obvius 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 Obvius looks like and contents of the pack
Carmustine Obvius is a powder and solvent for concentrate for solution for infusion.

The powder is white to almost white powder supplied in a brown glass vial.
The solvent is a colourless clear liquid supplied in a clear glass ampule.

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

Marketing Authorisation Holder
Obvius Investment B.V.
De Cuserstraat 93
1081 CN Amsterdam
The Netherlands

Manufacturer
European Pharma Hub Ltd.
2360 Gyál, 7000/9 hrsz.
Hungary

This leaflet was last revised in

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 Obvius 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.

Reconstitution and dilution of the powder for concentrate for solution for infusion:
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.

The 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 Obvius 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 Obvius 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 Obvius 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 Obvius 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 dosage 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.

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 Obvius 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.