SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CARMUSTINE OBVIUS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 100 mg carmustine.

Each vial of solvent contains 3 ml ethanol anhydrous (that is equivalent to 2.37 g).

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Powder and solvent for concentrated solution for infusion.

Appearance of powder for reconstitution: white to almost white powder .

Appearance of solvent: colourless clear liquid.

Appearance of reconstituted solution: clear, colorless to light yellow pH: 4.0 to 6.8.

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 as palliative therapy as a single agent or in establishedcombination therapy with other approved agents in the following:

- Brain tumors - glioblastoma, medulloblastoma, astrocytoma and metastaticbrain tumors.
- Multiple myeloma - in combination with glucocorticoid such asprednisone.
- Hodgkin’s disease - as secondary therapy in combination with other approved drugs in patients who relapse while being treated with primarytherapy, or who fail to respond to primary therapy.
- Non-Hodgkin’s lymphomas - as secondary therapy in combination withother

approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

4.2 Posology and method of administration

Adults:

Posology of intravenous administration:
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 asingle dose or divided into two daily injections 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 beadjusted accordingly.

A repeat course of Carmustine should not be given until circulating blood elementshave returned to acceptable levels (platelets above 100,000/ mm^3, leukocytes above4,000/ 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:

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

Children:
Carmustine should be used with extreme caution in children due to the high risk of pulmonary toxicity (see Warnings).

Elderly:
In general, dose selection for an elderly patient should be cautious, usually starting atthe low end of the dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Because elderly patients are more likely to have decreased renal function, care shouldbe taken in dose selection, and renal function should be monitored.

Method of administration:
Following reconstitution (please, see Section 6.6) with sterile diluent (3 ml vial provided) and dilution with water for injection, Carmustine should be administered byintravenous drip

over one to two hour period. The time of infusion should not be less than one hour otherwise it leads to burning and pain at the injected area. The injectedarea should be monitored during the administration.
There are no limits for the period of application of carmustine therapy. In case thetumor remains uncurable or some serious or untolerable side effects appear, the carmustine therapy must be terminated.

4.3 Contraindications

Carmustine should not be given to individuals who:

- have demonstrated a previous hypersensitivity to the active substance (carmustine), to other nitrosoureas or to any of the excipients listed insection 6.1
- suffer from decreased circulating platelets, leucocytes or erythrocyteseither from previous chemotherapy or other causes.

4.4 Special warnings and precautions for use

Carmustine may be administered only by specialists experienced in the field of chemotherapy.

Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur with a frequency ranging up to 30%. This may occur within 3 yearsof therapy and appears to be dose related with cumulative doses of 1200-1500 mg/m^2being 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.

Cases of late pulmonary fibrosis, occurring up to 17 years after treatment have also been reported. In a long-term follow-up of 17 patients who survived childhood brain tumors eight (47%) died of lung fibrosis. Of these eight deaths, two occurred within 3years of treatment and 6 occurred 8-13 years after treatment. Of the patient who died,the median age at treatment was 2.5 years (range 1-12); the median age of the long survivors was 10 years (5-16 years at treatment). All five patients treated under the age of 5 years have died of pulmonary fibrosis. In this study the dose of Carmustine did not influence fatal outcome nor did co-administration of vincristine or spinal irradiation. Of the remaining survivors available for follow up, evidence of lung fibrosis was detected in all patients. The risk and benefit of Carmustine therapy mustbe carefully considered especially in young patients, due to extremely high risk of pulmonary toxicity.

Carmustine is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximately those employed clinically.
Bone marrow toxicity is a common and severe toxic effect of Carmustine. Complete blood count should be monitored frequently for at least six weeks after a dose. In addition to this, the liver, kidney and lung function should be examined and monitoredregularly during the carmustine therapy. Repeat doses of Carmustine 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 dose (see section 4.2).

This medicinal product contains 0.57 vol% ethanol (alcohol), it means 7.68 g perdose. This corresponds to 11.32 ml of beer or 4.72 ml wine per dose.

These amounts arise from a calculated example with 320 mg of carmustine (200 mg/m^2 for 1.6 m^2) dissolved in 9.6 ml (sterile dehydrated ethanol) and a volume of1686 ml (see section 6.6).

For patients addicted to alcohol, this quantity can be harmful to health.

This must be considered in pregnant and breast-feeding women as well as in high-risk groups (patients with liver disease or epilepsy).

The alcohol content in this medicinal product may alter the effects of other drugs.

The alcohol content in this medicinal product may impair the ability to drive and the ability to use machines.

4.5 Interaction with other medicinal products and other forms of interaction

In combination with:

- phenytoin – reduced activity of antiepileptic medicinal products must be reckoned in the concomitant use with chemotherapeutic medicinal products
- cimetidine – the concomitant use leads to delayed, major, suspected, increased carmustine toxic effect (due to the inhibition of carmustine metabolism)
- digoxin – the concomitant use leads to delayed, moderate, suspected, decreasedeffect of digoxin (due to the decreased digoxin absorption)
- melphalan – the concomitant use leads to increased risk of pulmonary toxicity

4.6 Fertility, Pregnancy and lactation

Carmustine should not normally be administered to patients who are pregnant or mothers who are breast-feeding. Male patients should be advised to use adequate contraceptive measures during the treatment with carmustine for at least 6 months.

Pregnancy

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 andteratogenic in rats when given in doses equivalent to the human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women ofchildbearing potential should be advised to avoid becoming pregnant.

Breast-feeding
It is not known whether carmustine or its metabolites excrete in the mother´s milk. Breast-feeding should not be permitted during the treatment.

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 willhave to be taken into consideration, that the alcohol quantity in these pharmaceuticalmedicines can impair the competency to drive and the ability to operate machines.

4.8 Undesirable effects

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 areavailable, adverse events are included if the incidence is ≥ 5% higher in the treatmentgroup.

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

The following table includes adverse effects of Carmustine divided by groups according to MedDRA terminology with frequency of occurrence: 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):

MedDRA system organ class	**Frequency**	**Adverse effects**
		Clinically important side effects are in *italics*
Infections and Infestations	not known	Opportunistic infections (including fatal outcome)
Neoplasms benign, malignant and unspecified (includingcysts and polyps)	common	Acute leukemias, bone marrow dysplasias; following long-term use.
Blood and lymphatic systemdisorders	common	Anaemia.
	very common	*Myelosuppression; onset 7-14 days, nadir 21-35 days, recovery 42-56 days; cumulative,*
		dose related, delayed and often biphasic.
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; retinal haemorrhages.

MedDRA system organ class	Frequency	Adverse effects
		Clinically important side effects are in *italics*
Cardiac disorders	very common	Hypotension, due to alcohol content of diluent (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	*Interstitial fibrosis (with lower doses).*
Gastrointestinal disorders	very common	*emetogenic potential: >250 mg/m^2 high; ≤ 250 mg/m^2 high-moderate*
	very common	*Nausea and vomiting, severe; begins within 2-4 h of administration and lasts for 4-6 h.*
	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	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 (due to alcohol content of diluent; increased with administration times <1-2 h), injection site reaction.
Renal and urinary disorders	rare	*Renal toxicity (for cumulative doses <1,000 mg/m^2).*
Reproductive system and breast disorders	rare	Gynecomastia.
	not known	Infertility, teratogenesis.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

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

Liver necrosis, interstitial pneumonitis, encephalomyelitis.A specialized antidote is not available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antineoplastic medicine, alkylating agent, nitrosourea
ATC-Code: L01AD01

Carmustine alkylates DNA and RNA, has also been shown to inhibit several enzymesby carbamoylation of amino acids in proteins. It is thought that the antineoplastic andtoxic activities of Carmustine may be due to metabolites.

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 theblood-brain barrier. Levels of radioactivity in the CSF are at least 50% higher thanthose measured concurrently in plasma.
The kinetic of carmustine in humans is characterized by a two-chamber model. Afterthe intravenous infusion over 1 hour, the carmustine-plasma level drops in a biphasicmanner. The half life α accounts to 1-4 minutes and the half life β accounts to 18-69 minutes.

Metabolism
It is presumed that the metabolites of carmustine causes its antineoplastic and toxicactivity.

Elimination

Approximately 60-70% of a total dose is excreted in the urine in 96 hours and about10% as respiratory CO_2. The fate of remainder is undetermined.

5.3 Preclinical safety data

Carmustine was embryotoxic and teratogenic in rats and embryotoxic in rabbits atdose levels equivalent to the human dose. Carmustine affected the fertlility of malerats 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

Compatibility/ Incompatibility with Containers

The intravenous solution is unstable in polyvinyl chloride container. The carmustine solution can be administered from the glass bottles or polypropylene container only.

The pharmaceutical medicine should be used based on the instructions in Section 6.6 and not mixed up with other pharmaceutical medicines.

6.3 Shelf life

The expiry date of the product is indicated on the packaging material.

After reconstitution and dilution
The solution should be administered within 3 hours after reconstitution and dilution of the product, at temperatures below 20-22°C.
The solution should be protected from light until end of administration.

6.4 Special precautions for storage

Store in a refrigerator (2^0C–8^0C).
The original package should be protected from light.

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.

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: Type I glass ampule (5 ml).

6.6 Special precautions for disposal

IMPORTANT NOTE: The lyophilized dosage formulation contains no preservativeand is not intended as multiple dose vial. Reconstitution and further dilutions should be carried out under aseptic conditions.

Preparation of intravenous solution:
Dissolve 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. Each ml of resulting solution will contain 3.3 mg of Carmustine

Reconstitution as recommended results in a clear colourless to light yellow stock solution which has to be further diluted to 500 ml sodium chloride 9 mg/ml (0.9%) for injection, or 5% glucose 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 must be given intravenously and should be administered by I.V. drip over 1-2 hour period and administration should be finalised within 3 hours from reconstitution of the product. Injection of Carmustine over shorter periods of time may produce intense pain and burning at the site of injection.

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.

NOTE: Reconstituted vials stored under refrigeration should be examined for crystal formation prior to use. If crystals are observed, they may be redissolved by warmingthe vial to room temperature with agitation.

Carmustine has a low melting point (approximately 30.5-32.0ºC or 86.9-89.6ºF). Exposure of this drug to this temperature or above will cause the drug to liquefy andappear as an oil film in the bottom of the vials. This is a sign of decomposition and vials should be discarded.
Guidelines for the safe handling of the antineoplastic agents:

1. Trained personnel should reconstitute the drug.
2. This should be performed in a designated area.
3. Adequate protective gloves should be worn.
4. Precautions should be taken to avoid the drug accidentally coming into contact with eyes. In the event of contact with the eyes, flush with copiousamount of

water and/or saline.

5. The cytotoxic preparation should not be handled by pregnant staff.
6. Adequate care and precaution should be taken in the disposal of items (syringes, needles etc.) used to reconstitute cytotoxic drugs. Excess material and body waste may be disposed of by placing in double sealed polythene bags and incinerating at a temperature of 1,000^{o}C. Liquid wastemay be flushed with copious amounts of water.
7. The work surface should be covered with disposable plastic-backedabsorbent paper.
8. Use Luer-Lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols.The latter may also be reduce by the use of a venting needle.
9. Any unused product or waste material should be disposed of in accordancewith local requirements for biohazardous waste.

7 MARKETING AUTHORISATION HOLDER

K.S.KIM INTERNATIONAL (SK-PHARMA) LTD,
94 Yigal Alon Str., Tel-Aviv-Yafo, 6789139.

8 MARKETING AUTHORISATION NUMBER(S)

167-65-36628-99

9 MANUFACTURER:

OBVIUS INVESTMENT B.V.,
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Revised in February 2022 according to MOHs guidelines.

KS_CARM_PI_02/22_V01