Summary of risk management plan for Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion (carmustine)

This is a summary of the risk management plan (RMP) for Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion. The RMP details important risks of Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion, how these risks can be minimised, and how more information will be obtained about Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion's risks and uncertainties (missing information).

Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion should be used.

Important new concerns or changes to the current ones will be included in updates of Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion's RMP.

I. The medicine and what it is used for

Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion is authorised for 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.

Obvius Investment B.V. aims to include the following new indication to the existing marketing authorisation for Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion: As conditioning treatment prior to autologous haematopoietic progenitor cell transplantation (HPCT) in malignant haematological diseases (Hodgkin's disease / Non-Hodgkin's lymphoma) (see SmPC for the full indication).

It contains carmustine as the active substance and it is given intravenously after reconstitution and dilution.

Further information about the evaluation of Carmustine Obvius's benefits can be found in Carmustine Obvius's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/carmustine-obvius

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion, together with measures to minimise such risks and the proposed studies for learning more about Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Pulmonary toxicity (including in paediatric population) Bone marrow toxicity Hepatotoxicity Nephrotoxicity
Important potential risks	Embryotoxicity and teratogenicity
Missing information	None

II.B Summary of important risks

Important identified risk 1: Pulmonary toxicity (including in paediatric population)

Evidence for linking the risk to the medicine	Numerous studies in lymphomas, malignant gliomas and breast cancer have established a strong correlation between 1,3-bis[2-chloroethyl]-1-nitrosurea (BCNU) dose and pulmonary toxicity. The incidence of pulmonary toxicity is 10% when cumulative BCNU doses are 800 mg/m^2 as a single agent, but in combination with other cytotoxic drugs, particularly cyclophosphamide, the tolerated dose is lower. Several studies have demonstrated that doses of 600 mg/m^2 or higher are associated with an increased risk of pneumonitis, and for many years 450 mg/m^2 has been considered the upper dose limit for BCNU and is the standard dose used in the CBV regimen (cyclophosphamide, BCNU, etoposide) [Till, 2012]. Pulmonary fibrosis is a severe complication typically developed months or years after repetitive doses of 1,3-bis[2-chloroethyl]-1-nitrosurea (BCNU or carmustine) and the risk is increased when the cumulative dose is greater than 1200 mg/m^2 [Shen, 2004].
Risk factors and risk groups	Some risk factors, such as history of irradiation to lung, cigarette smoking, female gender and high doses of product, are known to be associated with BCNU-related pulmonary injury [Shen, 2004].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.4 of the SmPC includes a warning stating that pulmonary toxicity occurs with a frequency ranging up to 30% in patients receiving carmustine. 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. As a precautionary measure, baseline pulmonary function studies and chest X-ray should be conducted along with frequent pulmonary function tests during treatment. Section 2 of the PL states that before treatment and regularly during treatment the patient's lung function must be tested. This section of the PL also states that since an X-ray of the chest region and lung function test will be conducted before treatment is started. In addition, high-dose treatment with Carmustine Obvius (up to 600 mg/m^2) is only performed in combination with subsequent stem cell transplantation. Such a higher dose can increase frequency or severity of lung, kidney and heart toxicities as well as infections. Legal status: Restricted medical prescription medicine. Additional risk minimisation measures: None.

Important identified risk 2: Bone marrow toxicity	
Evidence for linking the risk to the medicine	Myelotoxicity is one of the most common treatment-related adverse events for patients receiving systemic antineoplastic therapy or radiotherapy to bone marrow–producing regions. Myeloid cytopenias—including neutropenia, thrombocytopenia, and anaemia—are the most frequently seen manifestations of treatment-related myelotoxicity and one of the most common reasons for dose modifications, dose delays, or discontinuation of therapy, potentially limiting therapeutic benefit. Lymphopenia, although less common, presents unique challenges and may place the patient at increased risk for opportunistic and often life-threatening infections [Kurtin, 2012]. A serious and frequent adverse effect associated with systemic administration of carmustine is delayed hematologic toxicity, which is cumulative and usually occurs 4-6 weeks after administration of the drug. Thrombocytopenia is generally the most severe hematologic effect, appearing and subsiding earlier than other hematologic toxicities; however, both leukopenia and thrombocytopenia may be dose-limiting toxicities. Thrombocytopenia usually is evident at approximately 4 weeks and persists for about 1-2 weeks, and leukopenia usually is evident at approximately 5-6 weeks and persists for 1-2 weeks. Following repeated doses of carmustine, however, cumulative myelosuppression manifested as more depressed indices or as more prolonged suppression may occur. Anaemia also occurs, but generally is less frequent and less severe than other hematologic toxicities [McEvoy, 2015].
Risk factors and risk groups	Factors associated with high risk for chemotherapy-induced myelotoxicity include: - Host-related factors: age > 65 years, female gender, Eastern Cooperative Oncology Group (ECOG) Performance Status >1, malnutrition, immunosuppression, comorbidities such as chronic obstructive pulmonary disease, diabetes, renal impairment or liver disease, open wounds or recent surgery, active infection or pre-existing fungal infections and drug-drug interactions. - Disease- and treatment-related factors: high tumour burden /extensive disease, history of chemotherapy or radiation, pre-existing cytopenias, bone marrow involvement with tumour, type of chemotherapy, dose intensity of chemotherapy, elevated lactate dehydrogenase level, hypoalbulinemia, hyperbilirubinemia or haematological malignancy hospitalization [Kurtin, 2012].
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.8. PL section 4. According to section 4.3 of the SmPC, product is contraindicated in case of severe bone marrow depression. In addition, section 4.4 of the SmPC includes a warning stating that bone marrow toxicity is a common and severe toxic adverse reaction in patients receiving carmustine. As a precautionary measure, 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. Repeat doses of Carmustine Obvius should not 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. Section 2 of the PL states that product must not be used in patients suffering from suppression of blood cell formation in the bone marrow. This section of the PL also states that the doctor will monitor blood counts of the patient weekly for at least 6 weeks after a dose and that product would not be given more frequently than every 6 weeks. The dosage will be confirmed with the blood count. Legal status: Restricted medical prescription medicine. Additional risk minimisation measures: None.

Important identified risk 3: Hepatotoxicity	
Evidence for linking the risk to the medicine	Several studies have been conducted with the different concentrations of carmustine used on rats as well as humans resulting in hepatotoxic effects like lipoperoxidation, fluctuations in level of bilirubin, cholestasis, veno-occlusive liver diseases and hepatocytes cell-cycle alterations. In several types of cancers like leukaemia or glioblastoma, carmustine either singly or with some other agents is given to patients which may resulting to hepatic dysfunction [Singh, 2018].
Risk factors and risk groups	Pre-existing medical problems, tumour, immunosuppression, hepatitis viruses and other infections, and nutritional deficiencies or total parenteral nutrition all may affect a host's susceptibility to liver injury [King, 2001].
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.8. PL section 4. Section 4.4 of the SmPC includes a warning stating that hepatic function should be checked prior to treatment and regularly monitored with carmustine therapy. Section 2 of the PL states that before treatment and regularly during treatment the patient's liver function must be tested. Legal status: Restricted medical prescription medicine. Additional risk minimisation measures: None.

Important identified risk 4: Nephrotoxicity	
Evidence for linking the risk to the medicine	Nitrosureas are less likely than other chemotherapeutic drugs to cause acute kidney injury, but they lead to progressive chronic kidney disease over a period of months to years because of chronic tubulointerstitial nephritis. Nitrosureas are generally associated with dose-dependent nephrotoxicity that is clinically characterized by slowly progressive chronic kidney disease. Biopsy studies demonstrate chronic changes including tubular atrophy, interstitial fibrosis and glomerulosclerosis [Shirali, 2014].
Risk factors and risk groups	Patient-related risk factors common to all nephrotoxins and include age older than 60 years, underlying renal insufficiency (e.g., GFR of less than 60 mL per minute per 1.73 m^2), intravascular volume depletion, exposure to multiple nephrotoxins, diabetes, heart failure, and sepsis [Naughton, 2008]. Multiple factors may contribute to the kidney dysfunction associated with chemotherapy in patients with malignant diseases: • Patient-Specific Factors o Female gender o Age > 65 years o Nephrotic syndrome/hypoalbuminemia o Obstructive jaundice o Acute/chronic kidney disease ▪ Cancer-related kidney disease ▪ Other causes of kidney disease o True or effective volume depletion ▪ Decreased glomerular filtration rate ▪ Decline in urine flow rates o Metabolic perturbations ▪ Urine pH o Immune response genes o Pharmacogenetics favouring drug toxicity

	▪ Polymorphisms in hepatic and kidney CYP450 system, kidney transporters • Kidney-Specific Factors o High rate of blood delivery (20-25% of cardiac output) o Biotransformation of substances to reactive oxygen species o High metabolic rate of tubular cells o Proximal tubular uptake of toxins ▪ Apical uptake via endocytosis/pinocytosis ▪ Basolateral transport via organic anion transporter and organic cation transporter • Drug-Specific Factors o Prolonged drug exposure o Direct drug or metabolite cytotoxicity of the drug or metabolite o Drug (or other nephrotoxin) combination that enhances nephrotoxicity o Insoluble parent drug or metabolite with intratubular crystal precipitation [Shirali, 2014].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. According to section 4.3 of the SmPC, product is contraindicated in case of severe (end-stage) renal impairment. In addition, section 4.4 of the SmPC includes a warning stating that upon high-dose therapy with carmustine, the risk and severity for renal toxicity rises. Renal function should be checked prior to treatment and regularly monitored with carmustine therapy. Section 2 of the PL states that product must not be used in patients suffering from higher-grade kidney dysfunction. This section of the PL also states that before treatment and regularly during treatment the patient's renal function must be tested. In addition, high-dose treatment with Carmustine Obvius (up to 600 mg/m^2) is only performed in combination with subsequent stem cell transplantation. Such a higher dose can increase frequency or severity of kidney toxicity. Legal status: Restricted medical prescription medicine. Additional risk minimisation measures: None.

Important potential risk 1: Embryotoxicity and teratogenicity	
Evidence for linking the risk to the medicine	Carmustine was embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose.
Risk factors and risk groups	Pregnant patients. Women of childbearing potential not using contraception.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Section 4.6 of the SmPC includes a warning stating that carmustine is embryotoxic in rats and rabbits and teratogenic in rats when given in doses equivalent to the human dose. Therefore, carmustine should not be administered to patients who are pregnant. As a precautionary measure, 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. 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. Section 2 of the PL states that Carmustine Obvius should not be used during pregnancy because it may harm the unborn baby. Therefore, this medicine should not normally be administered to pregnant women. If used during pregnancy, the patient must be aware of the potential risk to the unborn baby. Women of childbearing potential are advised to use effective contraception to avoid becoming pregnant whilst being treated with this medicine and for at least 6 months after treatment. Male patients should use adequate contraceptive measures while on treatment with Carmustine Obvius and for at least 6 months after treatment to prevent their partners becoming pregnant. Legal status: Restricted medical prescription medicine. Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Carmustine Obvius 100 mg powder and solvent for concentrate for solution for infusion.