PART VI: SUMMARY OF RISK MANAGEMENT PLAN

Summary of risk management plan for Carmustine 100 mg Powder and solvent for concentrate for solution for infusion

This is a summary of the risk management plan (RMP) for Carmustine 100 mg Powder and solvent for concentrate for solution for infusion. The RMP details important risks of Carmustine 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 100 mg Powder and solvent for concentrate for solution for infusion's risks and uncertainties (missing information).

Carmustine 100 mg Powder and solvent for concentrate for solution for infusion's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Carmustine 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 100 mg Powder and solvent for concentrate for solution for infusion's RMP.

I. The medicine and what it is used for

Carmustine 100 mg Powder and solvent for concentrate for solution for infusion is authorised for use as palliative therapy (relieving and preventing the suffering of patients) as a single agent or in established combination therapy with other approved anticancer substances in certain types of cancers, like: Brain tumours- glioblastoma, medulloblastoma, astrocytoma and metastatic brain tumours; Multiple myeloma (malignant tumour developing from bone marrow); Hodgkin's disease (lymphoid tumour); Non-Hodgkin's lymphomas (lymphoid tumour); Tumours of gastrointestinal tract or digestive system tract and Malignant melanoma (skin cancer). Carmustine 100 mg Powder and solvent for concentrate for solution for infusion contains Carmustine as the active substance and it is given by intravenous drip.

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

Important risks of Carmustine 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 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 PL and SmPC addressed to patients and health care 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, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Carmustine 100 mg Powder and solvent for concentrate for solution for infusion is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Carmustine 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 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	• Lung damage (including in children) [Pulmonary toxicity (including in paediatric population)] • Decrease in production of blood cells in bone marrow (Bone marrow toxicity) • Liver damage (Hepatotoxicity) • Kidney damage (Nephrotoxicity) • Harmful effects to the digestive system including nausea and vomiting (Gastrointestinal toxicity including nausea and vomiting) • Skin reactions taking place at the site where injection of medicinal product is given including hazards due to leakage of medicine, from a blood vessel or tube into the tissue around it (Injection site reaction including extravasation hazard) • CNS toxicity
Important potential risks	• Ability to produce other cancers (Secondary malignancies) • Effect on reproduction including harmful effects to unborn baby and impaired fertility (Reproduction toxicity including embryotoxicity, Teratogenicity and impaired fertility)
Missing information	• Use in pregnancy and breast feeding women (Use during pregnancy and lactation)

II.B Summary of important risks

Important identified risks

Lung damage (including in children) [Pulmonary toxicity (including in paediatric population)]	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported to occur within 3 years of therapy and appears to be dose related with cumulative doses of 1200-1500 mg/m^2 being associated with increased likelihood of lung fibrosis. 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. Concomitant use of melphalan with carmustine also leads to increased risk of pulmonary toxicity.
Risk factors and risk groups	Risk group includes: – Paediatric population – Patients taking concomitant melphalan Risk factors include smoking, the presence of a respiratory condition, existing radiographic abnormalities, sequential or concomitant thoracic irradiation and association with other agents that cause lung damage.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.4, 4.5, 4.8 • PIL sections 2, 3, 4 • Recommendations mentioned in SmPC section 4.4: Lung function should be examined and monitored regularly during the carmustine therapy. Baseline pulmonary function studies and chest X-ray should be conducted along with frequent pulmonary function tests during treatment. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Decrease in production of blood cells in bone marrow (Bone marrow toxicity)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, delayed and cumulative bone marrow toxicity is a common and severe toxic

	adverse reaction of carmustine. Myelosuppression is very common side effect reported with the carmustine. 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. 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.
Risk factors and risk groups	Risk group includes: – Individuals who suffer from decreased circulating platelets, leucocytes or erythrocytes either from previous chemotherapy or other causes. – Patients taking combination with other myelosuppressive medicinal products
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 • PIL sections 2, 3, 4 • Recommendations mentioned in SmPC section 4.4: Complete blood count should be monitored frequently for at least six weeks after a dose. 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. In addition to dose-adjustment, the liver, kidney and lung function should be examined and monitored regularly during the carmustine therapy. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Liver damage (Hepatotoxicity)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, hepatotoxicity has been reported with the use of carmustine. The risk of hepatotoxicity also increases due to alcoholic content of this medicine (this medicinal product contains 0.57 vol % ethanol (alcohol), it means 7.68 g per dose equivalent to 11.32 ml of beer

	or 4.72 ml wine per dose).
Risk factors and risk groups	Risk group includes: – Patients addicted to alcohol – Patients with liver disease
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.8 • PIL section 2, 4 • Recommendations mentioned in SmPC section 4.4: Liver function should be examined and monitored regularly during the carmustine therapy. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Kidney damage (Nephrotoxicity)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, renal toxicity is a rare side effect reported with the carmustine. 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. The risk also increases in elderly patients due to their decreased renal function.
Risk factors and risk groups	Risk group includes elderly patients.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.2, 4.3, 4.4, 4.8 • PIL sections 2, 3, 4 • Recommendations mentioned in SmPC section 4.4: Kidney function should be examined and monitored regularly during the carmustine therapy especially in elderly patients. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Harmful effects to the digestive system including nausea and vomiting (Gastrointestinal toxicity including nausea and vomiting)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that carmustine has been associated with gastrointestinal toxicity including nausea and vomiting. Gastrointestinal bleeding has also been reported side-effect with the use of Carmustine.
Risk factors and risk groups	Incidence and severity of CINV are affected by patient specific and treatment specific factors. Characteristics associated with a higher risk include: – Female sex – Age greater than 3 years – Anxiety – Motion sickness – Poor control with previous chemotherapy Treatment related risk factors include: – Emetic potential – Schedule – Dose – Route – Rate of drug administration
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.8 • PIL section 4 • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Skin reactions taking place at the site where injection of medicinal product is given including hazards due to leakage of medicine, from a blood vessel or tube into the tissue around it (Injection site reaction including extravasation hazard)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, during administration of carmustine, administration site reactions may occur. Infusion of carmustine over shorter periods of time may produce intense pain and burning at the site of injection.
Risk factors and risk groups	Risk factor includes shorter duration of infusion.
Risk minimisation measures	**Routine risk minimisation measures:**

	• SmPC sections 4.2, 4.4, 4.8, 6.6 • PIL sections 3, 4 • Recommendations mentioned in SmPC section 4.4: Given the possibility of extravasation, close monitoring of the infusion site is recommended for possible infiltration during administration. • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

CNS toxicity	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, encephalopathy, ataxia, dizziness, headache, muscular pain, status epilepticus, seizure, grand mal seizure are known to occur with the use of carmustine.
Risk factors and risk groups	The occurrence of nervous system toxicity depends on a variety of factors including the dose of treatment delivered, route of administration, interactions with other agents, the presence of underlying structural nervous system disease, and individual patient vulnerability, most of which are poorly understood.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.8 • PIL sections 4 • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Important potential risks

Ability to produce other cancers (Secondary malignancies)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, carmustine is carcinogenic in rats and mice, producing a marked increase in tumour incidence in doses approximately those employed clinically.
Risk factors and risk groups	The risk factors for secondary malignancies are as follows: • Shared Environmental Risk Factors: Lifestyle factors, such as smoking, alcohol, exercise, sun exposure, and

	diet, human papilloma virus infection. • Genetic Risk Factors: e.g. Retinoblastoma, mutations in the genes BRCA1 and BRCA2. • Therapy-Related Secondary Cancers: Radiation therapy and chemotherapy used to treat a primary cancer
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.8, 5.3 • PIL section 4 • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Effect on reproduction including harmful effects to unborn baby and impaired fertility (Reproduction toxicity including embryotoxicity, Teratogenicity and impaired fertility)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, carmustine may impair male fertility. 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.
Risk factors and risk groups	Risk group includes: – Pregnant woman – Men and women of reproductive age.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.6, 4.8, 5.3 • PIL sections 2, 4 • Prescription only medicine **Additional risk minimisation measures:** • No risk minimisation measures

Missing information

Use in pregnancy and breast feeding women (Use during pregnancy and lactation)	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.4, 4.6, 5.3, 6.6 • PIL section 2 and 4Prescription only medicine

	Additional risk minimisation measures: • No risk minimisation measures

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 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 100 mg Powder and solvent for concentrate for solution for infusion.