

Summary of the Risk Management Plan (RMP)

BiCNU[®]

Carmustine 100 mg Powder and solvent for solution for infusion

Product concerned (brand name): BiCNU[®]

Active substance: Carmustine

Strength: 100 mg Powder and solvent for solution for infusion

Pharmaceutical form: Powder and solvent for infusion solution

Version number: 1.0

Date: 20-Nov-2017

Marketing Authorisation Holder: IDEOGEN AG, Freienbach

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as a part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of BiCNU is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of BiCNU in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedinfo.ch) approved and authorized by Swissmedic. IDEOGEN AG, Freienbach is fully responsible for the accuracy and correctness of the content of the published summary RMP of BiCNU.

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LIST OF ABBREVIATIONS

| | |
|------|------------------------------|
| EU: | European Union |
| HIV: | Human Immunodeficiency Virus |
| HL: | Hodgkin's Lymphoma |
| NO: | Nitricoxide |
| NHL: | Non-Hodgkin's lymphoma |
| RMP: | Risk Management Plan |
| UK: | United Kingdom |
| WHO: | World Health Organization |

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Brain tumour

Tumours that begin in brain tissue are known as primary brain tumours. Primary brain tumours are classified by the type of tissue from which they originate. The most common brain tumours are gliomas, which begin in the glial (supportive) tissue. In Europe, about 27,000 new cases of malignant brain tumours are diagnosed every year. As per World Health Organization (WHO) classification, brain tumours are graded from 1 to 4, according to their behavior, such as how fast they grow and how likely they are to grow back after treatment. A malignant (cancerous) brain tumour is either grade III or IV, whereas grade I or II tumours are usually classed as benign (non-cancerous). In 2013, 10,624 new brain tumour cases were registered in the UK; 5,164 (49%) in males and 5,460 (51%) in females, giving a male: female ratio of around 9:10. Brain tumours can affect people of any age, including children, although they tend to be more common in older adults. It has been reported that more than 90% of patients with glioma showed recurrence at the original tumor location and that multiple lesions developed in 5% after treatment.

Non-Hodgkin's lymphoma (NHL)

Non-Hodgkin lymphoma is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout the body. The most common symptom of NHL is a painless swelling in a lymph node, usually in the neck, armpit or groin. NHL occurs in about 17 persons per 100,000 and thus can be considered a rare disease. Non-Hodgkin lymphoma can occur at any age, but chances of developing the condition increase as person gets older, with most cases diagnosed in people over 65. Slightly more men than women are affected.

Hodgkin's lymphoma (HL)

Hodgkin lymphoma is an uncommon cancer that develops in the lymphatic system, which is a network of vessels and glands spread throughout the body. The most common symptom of HL is a painless swelling in a lymph node, usually in the neck, armpit or groin. HL is a rare disease, occurring in about 2-3 persons per 100,000, most of the patients being diagnosed at an age of 20-30. Hodgkin's lymphoma being a rare disease, data on children are scarce. Up to 15% of patients with limited stage disease and 35%–40% of patients with advanced stage disease either do not achieve complete remission (disappearance of all signs of disease) initially or the disease recur within the first few years after initial treatment.

VI.2.2 Summary of treatment benefits

An article published by Wasserman and colleagues discussed clinical studies indicating tumours in which the carmustine has shown activity as below. A complete response is defined as complete disappearance of measurable tumour and a partial response is a greater than 50% reduction in the size of measurable tumour with no concurrent development of new lesions. Out of 142 brain tumour patients, 67 (47%) achieved at least partial response with carmustine, out of 213 patients with Hodgkin's disease, 94 (44%) achieved at least partial response with carmustine and out of 107

patients with Non-Hodgkin's disease 30 (28%) patients achieved at least partial response with carmustine.

VI.2.3 Unknowns relating to treatment benefits

Carmustine is indicated for the treatment of relapsed Grade III and IV Glioma, Hodgkin's disease and Non-Hodgkin's lymphoma.

There is no evidence to suggest that the effectiveness of Carmustine 100 mg Powder and solvent for solution for infusion would be any different in any sub-group within the group of people (target population) intended to use this medicine.

VI.2.4 Summary of safety concerns

Important identified risks

| Risk | What is known | Preventability |
|---|---|---|
| Harmful effects on lungs including children (pulmonary toxicity [including in paediatric population]) | <p>Pulmonary toxicity characterized by scarring and stiffening of the lungs causing breathlessness (pulmonary fibrosis) has been reported in up to 30% of the patients. This may occur within 3 years of therapy. Total doses above 300 mg/m² increases likelihood of lung fibrosis.</p> <p>Carmustine may cause serious (possibly fatal) lung related disorder with breathing problems. The lung problems can occur years after treatment.</p> <p>Risk factors include smoking, presence of a respiratory condition, pre-existing X-ray abnormalities, sequential or concomitant upper- and middle-back radiation and other medications that cause lung damage.</p> <p>Pulmonary toxicity is very common (may affect more than 1 in 10 people) side effect reported with carmustine.</p> <p>Pulmonary fibrosis (including fatalities), Collection of pus, blood or protein in lung tissue (lung infiltration), inflammation</p> | <p>Carmustine should be used with extreme caution in children due to high risk of lung toxicity and should not be used in children below 18 years of age for the treatment of brain tumour.</p> |

| Risk | What is known | Preventability |
|--|---|--|
| | <p>of lung tissue (pneumonitis), collection of excess fluid around the lung (pleural effusion), difficulty in breathing (dyspnoea) are common (may affect up to 1 in 10 people) side effects reported with carmustine.</p> | |
| <p>Decrease in production of blood cells in bone marrow (bone marrow toxicity)</p> | <p>Decrease in the number of blood cells (myelosuppression) particularly decrease in white blood cells and platelets (thrombocytopenia and leukopenia), which can lead to bleeding and severe infections in patients already at risk, is a common and severe toxic effect of carmustine.</p> <p>Myelosuppressive effect of carmustine gets stronger with repeated usage (cumulative).</p> <p>Myelosuppression is very common (may affect more than 1 in 10 people) side effect reported with carmustine.</p> <p>Bleeding, decrease in different types of white blood cells (known as leukopenia, neutropenia, pancytopenia), decrease in platelets (thrombocytopenia) and decrease in red blood cells (anaemia) are common (may affect up to 1 in 10 people) side effects reported with carmustine.</p> | <p>Repeat doses of carmustine should not be administered more frequent than every 6 weeks.</p> <p>The patient should be closely monitored.</p> <p>Patients' blood count should be monitored frequently to avoid toxicity in their bone marrow and doctor would adjust the dose if necessary.</p> |
| <p>Harmful effects to liver (hepatotoxicity)</p> | <p>Yellowing of the skin or whites of the eyes caused by liver or blood problems, increase in bilirubin (a substance found in bile), increase in alkaline phosphates and transaminases (liver enzymes) are very common (may affect more than 1 in 10 people) side effects reported and enlarged liver</p> | <p>Before starting the treatment, patient's liver function should be tested by doctor and should be monitored regularly during the treatment.</p> |

| Risk | What is known | Preventability |
|--|--|---|
| | (hepatomegaly), liver failure, veno occlusive liver disease (a disease in which small veins in the liver are obstructed) are uncommon (may affect up to 1 in 100 people) side effects reported with use of carmustine. | |
| Harmful effects to kidney (nephrotoxicity) | Kidney failure is common (may affect up to 1 in 10 people) and abnormal kidney function and accumulation of specific metabolites in the blood (azotaemia) are uncommon (may affect more than 1 in 100 people) side effects reported with use of carmustine. | Before starting the treatment, patient's kidney function should be tested by doctor and should be monitored regularly during the treatment. |
| Harmful effects to the digestive system including nausea and vomiting (gastrointestinal toxicity including nausea and vomiting) | <p>Carmustine have high capacity to induce vomiting (emesis).</p> <p>Nausea and emesis are dose-related and it occurs usually within 2 hours after infusion and usually subside after 4-6 hours.</p> <p>Nausea, vomiting, diarrhoea, inflammation inside the mouth, painful inflammation and ulceration of the mucous membranes (mucositis), tingling sensation in mouth are common (may affect up to 1 in 10 people) side effects and bleeding in stomach or gut and other stomach or gut disorders are uncommon (may affect more than 1 in 100 people) side effects reported with use of carmustine.</p> | Prior to administration of carmustine, antiemetics (medicines for prevention of vomiting) should be given as it is effective in diminishing and preventing this side effect. |
| 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) | <p>Administration of carmustine over shorter periods of time may lead to intense pain and burning at the site of injection.</p> <p>Leakage of carmustine into the surrounding tissue (infiltration) may result in swelling, pain, redness, burning sensation and skin necrosis (death of tissue or</p> | <p>Carmustine should be administered by a doctor, who is experienced in anticancer therapy.</p> <p>After reconstitution, carmustine should be administered by intravenous drip over a one to two hour period.</p> |

| Risk | What is known | Preventability |
|------|---|--|
| | <p>skin). Local soft tissue toxicity has been reported following extravasation (leakage of medicine).</p> <p>Infusion site reactions, Infusion site pain, fever (pyrexia), weakness (asthenia), chills, burning sensation, and extravasation are common (may affect up to 1 in 10 people) side effects reported with use of carmustine.</p> | <p>The injection site should be monitored during the administration.</p> <p>The duration of the treatment is determined by the doctor and may vary for each patient.</p> |

Important potential risks

| Risk | What is known |
|--|--|
| Secondary malignancy | <p>A secondary malignancy is a new cancer that occurs in an individual as a result of previous treatment with radiation or chemotherapy (treatment of disease by the use of chemical substances). Carmustine may lead to secondary tumours including acute leukaemia (cancer of white blood cells) and bone marrow dysplasia (abnormal development of the bone marrow) due to its carcinogenic potential.</p> <p>Secondary malignancies, acute leukaemia, bone marrow dysplasia are common (may affect up to 1 in 10 people) side effects reported with use of carmustine.</p> |
| Effect on reproduction including harmful effects to unborn baby and impaired fertility (reproduction toxicity including embryotoxicity, teratogenicity and impaired fertility) | <p>In animal studies it was shown that carmustine affects fertility in male rats. Carmustine has shown harmful effects to unborn baby in animal studies.</p> |

Missing information

| Risk | What is known |
|--|--|
| Use in pregnant and breast feeding women (use during | <p>Carmustine should not be used during pregnancy because it may harm an unborn baby. Therefore, carmustine should not normally be administered to pregnant women. If used during pregnancy, the</p> |

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| pregnancy and lactation) | <p>patient must be aware of the potential risk to the foetus. Women of childbearing potential are advised to avoid becoming pregnant and to use adequate contraceptive measures during and for at least 6 months after the treatment.</p> <p>Male patients should use adequate contraceptives measures during treatment with carmustine for at least 6 months.</p> <p>It is not known whether carmustine or its metabolites are excreted in human milk. Breast-feeding is not allowed while taking this medicine.</p> |
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VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a product information ("Arzneimittelinformation/ Information sur le médicament") which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The product information ("Arzneimittelinformation/ Information sur le médicament") and the information for patients (Patienteninformation / Information destinée aux patients") for BiCNU can be found on www.swissmedicinfo.ch.

VI.2.6 Planned post-authorisation development plan

There is no planned post authorisation development plan for carmustine 100 mg Powder and solvent for solution for infusion by IDEOGEN AG, Freienbach.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable