Public Assessment Report

Decentralised Procedure

BiCNU 100 mg-Powder and solvent for solution for infusion

Procedure No: UK/H/5765/001/DC

UK Licence No: PL 42117/0007

Emcure Pharma UK Limited
BiCNU 100 mg-Powder and solvent for solution for infusion
(carmustine)

This is a summary of the public assessment report (PAR) for BiCNU 100 mg-Powder and solvent for solution for infusion (PL 42117/0007; UK/H/5765/001/DC). BiCNU 100 mg-Powder and solvent for solution for infusion will be referred to as BiCNU throughout this report, for ease of reading. It explains how BiCNU was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use BiCNU.

For practical information about using BiCNU, patients should read the package leaflet or contact their doctor or pharmacist.

What is BiCNU and what is it used for?
BiCNU is a ‘generic medicine’. This means that BiCNU is similar to a ‘reference medicine’ already authorised in the European Union (EU), specifically Austria, called Carmubris – Trockenstechampulle mit Losungmittel, 100 mg (powder and solvent). BiCNU is also similar to another reference medicine, BiCNU 100 mg powder and solvent for solution for infusion, which was authorised in the UK to the Marketing Authorisation Holder Bristol Myers Squibb in 1979 but was withdrawn from the UK market in 2009 for commercial reasons.

BiCNU is used 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 tumors - glioblastoma, medulloblastoma, astrocytoma and metastatic brain tumors
- Multiple myeloma (malignant tumor developing from bone marrow)
- Hodgkin’s disease (lymphoid tumor)
- Non-Hodgkin’s lymphomas (lymphoid tumor)

How does BiCNU work?
BiCNU contains the active substance carmustine, which belongs to a group of anticancer substances known as nitrosourea that act by slowing the growth of cancer cells.

How is BiCNU used?
BiCNU is given into the vein of a patient by a drip, over a one to two hour period (intravenous infusion). BiCNU will always be given to the patient by a healthcare professional with experience in the use of anticancer agents. The dosage will be based on the medical condition and body size of the patient, and their response to the treatment.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

This medicine can only be obtained with a prescription.

How has BiCNU been studied?
No additional studies were needed as BiCNU is a generic medicine that is given by infusion and contains the same active substance as the reference medicine, Carmubris – Trockenstechampulle mit Losungmittel, 100 mg (powder and solvent).
**What are the possible side effects of BiCNU?**
Because BiCNU is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For information about side effects that may occur with using BiCNU, please refer to the package leaflet or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency website.

**Why is BiCNU approved?**
It was concluded that, in accordance with EU requirements, BiCNU has been shown to have comparable quality and to be bioequivalent to Carmubris – Trockenstechampulle mit Losungmittel, 100 mg. The MHRA, therefore, decided that, as for the reference product, Carmubris – Trockenstechampulle mit Losungmittel, 100 mg, the benefits outweigh the identified risks and recommended that this product can be approved for use.

**What measures are being taken to ensure the safe and effective use of BiCNU?**
A Risk Management Plan (RMP) has been developed to ensure that BiCNU is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side-effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about BiCNU**
Spain and the UK agreed to grant a Marketing Authorisation for BiCNU on 24 July 2015. The Marketing Authorisation in the UK was granted to Creative Pharma Solutions s.r.o. on 21 August 2015 (PL 43021/0002). This licence subsequently underwent a change in ownership procedure on 16 October 2015 to the current Marketing Authorisation holder Emcure Pharma UK Limited (PL 42117/0007).

The full PAR for BiCNU follows this summary.

For more information about the use of BiCNU, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2015.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States have granted a Marketing Authorisation (MA) for the medicinal product BiCNU 100 mg-Powder and solvent for solution for infusion (UK/H/5765/001/DC; PL 43021/0002).

This product is a prescription-only medicine (legal status POM) indicated as palliative therapy as a single agent or in established combination therapy with other approved chemotherapeutic agents in the following:

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

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Spain as a Concerned Member State (CMS).

The application was made under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicinal product. The reference medicinal product which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area is BiCNU 100 mg Powder and Solvent for solution for infusion; this reference product was authorised to Bristol-Myers Squibb Holdings Ltd on 06 March 1979 (PL 00125/0108) and was subsequently withdrawn from the UK market in 2009 for commercial reasons. The European reference medicinal product for this application is Carmubris – Trockenstechampulle mit Losungmittel, 100 mg, which was authorised to Emcure Pharma UK Limited, in Austria on 31 July 1996.

BiCNU contains the active ingredient carmustine. Carmustine is an alkylating agent used as an antineoplastic in the treatment of brain tumours, multiple myeloma, Hodgkins disease and Non-Hodgkins lymphoma. It is thought that the antineoplastic and toxic activities of BiCNU may be due to metabolites.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Since BiCNU is intended for generic substitution, its use will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

The Applicant has provided a justification for not submitting new clinical data in accordance with the current *Guideline on the Investigation of Bioequivalence* (CPMP/QWP/EWP/1401/98 Rev.1/Cov**); bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved reference product.
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports issued by the inspection services of the MHRA as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 208) on 24 July 2015. After a subsequent National phase, a licence was granted in the UK on 21 August 2015. This licence subsequently underwent a change in ownership procedure on 16 October 2015 to the current Marketing Authorisation holder Emcure Pharma UK Limited (PL 42117/0007).
II Quality aspects

II.1 Introduction
This application is submitted according to Article 10(1) of Directive 2001/83/EC, as amended, with BiCNU 100 mg powder and solvent for solution for infusion (PL 00125/0108) as the reference product which has been authorised in the EEA for not less than 6/10 years but was subsequently withdrawn from the UK market in 2009 for commercial reasons. The European Reference Product Carmubris – Trockenstechampulle mit Lösungsmittel, 100 mg was authorised in Austria to Bristol Meyers Squibb on 31 July 1996 but subsequently underwent a change in ownership to the current Market Authorisation Holder, Emcure Pharma UK Limited, in 2013.

The product consists of one vial of lyophilised powder and one vial of solvent:

- Each vial of powder contains 100 mg of the active substance carmustine, which is formulated as a yellowish powder for reconstitution. The powder is packed in a Type I amber glass vial (30 ml capacity) sealed with a dark grey bromobutyl lyo rubber stopper and aluminium seal, having a polypropylene cap.

- Each vial of solvent contains 3 ml of dehydrated alcohol, which is a colourless to light yellow solvent solution. The solvent is packed in a Type I glass vial (5 ml capacity) sealed with a grey bromobutyl rubber stopper with an aluminium seal having polypropylene cap.

The carmustine powder is reconstituted with the 3 ml sterile solvent, followed by 27 ml of sterile water for injection. The osmolarity of the solution for infusion that is reconstituted with dehydrated ethanol and sterilized water is 15.6 mOsmol/l. This reconstituted clear colourless solution may be further diluted with sodium chloride for injection or 5% glucose for injection, prior to infusion.

The excipients used in the manufacture of the carmustine powder are dehydrated alcohol and nitrogen. There are no additional excipients used in the manufacture of the solvent.

II.2 Drug Substance
Carmustine
INN: Carmustine
Structure:

Molecular formula: $C_5H_9Cl_2N_3O_2$
Molecular weight: 214.1
Appearance: A yellowish, granular powder
Solubility: Very slightly soluble in water, very soluble in methylene chloride, freely soluble in ethanol.
Carmustine is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

The manufacture and control of the active substance, carmustine, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability. Satisfactory information has been provided on the stability of the active substance and on the packaging materials.

II.3 Medicinal Product

Pharmaceutical development
The pharmaceutical development of BiCNU has been described and is satisfactory.

The Applicant has justified the absence of a bioequivalence study based on the CPMP Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). This is discussed in Section IV.2.

The excipients used in the manufacture of the finished product meet the requirements of the current Ph. Eur.

Satisfactory Certificates of Analysis have been provided for the excipients showing compliance with their proposed specifications.

None of the excipients are sourced from animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the BiCNU powder and solvent, together with an appropriate account of the manufacturing processes. Validation reports for three production-scale batches of the BiCNU powder and solvent have been provided. The process validation data provided is satisfactory.

Product Specifications
The finished product specifications are satisfactory. Satisfactory batch analysis was performed on three production-scale batches of the BiCNU powder and solvent. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the BiCNU powder and solvent, packed in the packaging proposed for marketing. The data from these studies support a shelf life for of 2 years. The storage conditions for the BiCNU powder and solvent are ‘Store in a refrigerator (2 – 8 °C)’ and ‘The original package should be protected from light’.

After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°C - 8°C) in a glass container. The reconstituted solution, further diluted with 500 ml sodium chloride for injection or 5% glucose for injection, in glass or polypropylene containers, results in a solution which should be utilized within 8 hours at room temperature and be protected from light.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended for this application.

III  Non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of carmustine are well-known. As carmustine is a widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The Applicant’s non-clinical overview has been written by an appropriately qualified person. The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate. Section 5.3 of the SmPC is satisfactory.

Since the formulation of BiCNU is intended for generic substitution, it will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

There are no objections to the approval of this application from a non-clinical point of view.

IV  Clinical aspects

IV.1  Introduction
No new clinical data have been submitted and none are required for an application of this type. The Applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2  Pharmacokinetics
The Applicant has provided a justification for not submitting new clinical data. The proposed product BiCNU 100 mg powder and solvent for solution for infusion is intended for intravenous administration. It contains the same active substance in the same quantity and in the same dosage form as the reference product. According to the current Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1/Corr**), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. There are no excipient interactions which might affect the pharmacokinetics of the active substance.

IV.3  Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4  Clinical efficacy
No new clinical efficacy data are required for this application and none have been submitted.

IV.5  Clinical safety
No new clinical safety data are required for this application and none have been submitted.

IV.6  Risk Management Plan (RMP)
The Marketing Authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to BiCNU.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

### Summary table of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Pulmonary toxicity [Including in paediatric population]</th>
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<tbody>
<tr>
<td></td>
<td>Bone marrow toxicity</td>
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<td>Hepatotoxicity</td>
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<td>Nephrotoxicity</td>
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<td>Gastrointestinal toxicity including nausea and vomiting</td>
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<td>Injection site reaction including extravasation hazard</td>
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<tr>
<td>Important potential risks</td>
<td>Secondary malignancies</td>
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<td>Reproduction toxicity including embryotoxicity,</td>
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<td>teratogenicity and impaired fertility</td>
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<tr>
<td>Missing information</td>
<td>Use during pregnancy and lactation</td>
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</table>
## Planned risk minimisation activities

<table>
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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
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<tbody>
<tr>
<td>Important identified risk: Pulmonary toxicity [including in paediatric population]</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern: Section 4.2: BiCNU should be used with extreme caution in children due to high risk of pulmonary toxicity. Section 4.4: 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 years of therapy and appears to be dose related with cumulative doses of 1200-1500 mg/m² 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. Cases of late pulmonary fibrosis, occurring up to 17 years after treatment have also</td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
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<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td>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 3 years of treatment and 6 occurred 8-13 years after treatment. Of the patients 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 BiCNU 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 BiCNU therapy must be carefully considered especially in young patients, due to extremely high risk of pulmonary toxicity. It is recommended that pulmonary function should be monitored. Section 4.5: In combination with melphalan – the concomitant use leads to increased risk of pulmonary toxicity.</td>
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<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td></td>
<td>Section 4.8: Respiratory, thoracic and mediastinal disorders</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern:</td>
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<tr>
<td></td>
<td>pulmonary toxicity (up to 30%), BCNU pneumonitis (20% for doses &gt;450 mg/m²), interstitial fibrosis (&lt;1%, up to 50% for cumulative doses &gt;1,400 mg/m²)</td>
<td>Section 4.2: When BiCNU is used in combination with other myelosuppressive drugs or in patients in whom bone marrow reserve is depleted, the doses should be adjusted accordingly.</td>
</tr>
<tr>
<td>Important identified risk:</td>
<td></td>
<td>A repeat course of BiCNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/µl, leukocytes above 4,000/µl), and this is usually in six weeks. Blood counts should be monitored frequently and repeat courses should not be given before</td>
</tr>
<tr>
<td>Bone marrow toxicity</td>
<td></td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
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</table>
BiCNU 100 mg-Powder and solvent for solution for infusion

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<td>six weeks because of delayed hematologic toxicity. (1)</td>
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<td>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:</td>
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<tr>
<th>Nadir after Prior Dose</th>
<th>Percentage of prior dose to be given</th>
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</thead>
<tbody>
<tr>
<td>Leucocytes/μl</td>
<td>Platelets/μl</td>
</tr>
<tr>
<td>&gt;4000</td>
<td>&gt;100,000</td>
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<tr>
<td>3000 - 3999</td>
<td>75,000 - 99,999</td>
</tr>
<tr>
<td>2000 - 2999</td>
<td>25,000 - 74,999</td>
</tr>
<tr>
<td>&lt;2000</td>
<td>&lt;25,000</td>
</tr>
</tbody>
</table>

Section 4.3:

BiCNU should not be given to individuals who suffer from decreased circulating platelets, leucocytes or erythrocytes either from previous chemotherapy or other causes.

Section 4.4:

Bone marrow toxicity is a common and
<table>
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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<tbody>
<tr>
<td></td>
<td>Severe toxic effect of BiCNU. Complete blood count should be monitored frequently for at least six weeks after a dose. Repeat doses of BiCNU should not to be given more frequently than every six weeks. The bone marrow toxicity is cumulative and therefore the dosage adjustment must be considered on the basis of nadir blood counts from prior dose. Section 4.8: Haematological: Blood and lymphatic system disorders. Anaemia, myelosuppression; onset 7-14 days, nadir 21-35 days, recovery 42-56 days; cumulative, dose related, delayed and often biphasic Section 4.9: The main symptom of intoxication is myelosuppression. A specialized antidote is not available.</td>
<td></td>
</tr>
<tr>
<td>Important identified risk:</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern: Section 4.4:</td>
<td>Currently available data does not support the need for additional risk minimization</td>
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<tr>
<td>Hepatotoxicity</td>
<td></td>
<td></td>
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<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td></td>
<td>It is recommended that liver function should be examined and monitored regularly during the carmustine therapy. Section 4.8: Hepatobiliary disorders Hepatotoxicity, reversible, delayed up to 60 days after administration (&lt;1%, high-dose therapy and dose-limiting) Bilirubin, reversible increase alkaline phosphatase, reversible increase SGOT, reversible increase Section 4.9: Following serious side effects may occur: Liver necrosis.</td>
<td>activities.</td>
</tr>
<tr>
<td>Important identified risk: Nephrotoxicity</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern: Section 4.4: It is recommended that kidney function should be examined and monitored regularly during the carmustine therapy. Section 4.8:</td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>renal toxicity (&lt;1% for cumulative doses &lt;1,000 mg/m²)</td>
<td></td>
</tr>
<tr>
<td>Important identified risk: Gastrointestinal toxicity including nausea and vomiting</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern: Section 4.8: Gastrointestinal disorders: emetogenic potential: &gt;250 mg/m² high; &lt;250 mg/m² high-moderate, anorexia, constipation, diarrhoea, nausea and vomiting, severe; begins within 2-4 h of administration and lasts for 4-6 h, stomatitis</td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
</tr>
<tr>
<td>Important identified risk: Injection site reaction / Local toxicity including extravasation hazard</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern: Section 4.4: BiCNU may be administered only by specialists experienced in the field of chemotherapy. Section 4.8:</td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Extravasation hazard: vesicant dermatitis with topical use improves with reduced concentration of compounded product flushing (due to alcohol content of diluent; increased with administration times &lt; 1-2 h) hyper pigmentation, transient, with accidental skin contact injection site reaction Section 6.6: Reconstituted solution must be given intravenously and should be administered by i.v. drip over one to two hour period. Injection of BiCNU over shorter periods may produce intense pain and burning at the site of injection. Precautions to be taken to avoid accidental contact with eyes or skin.</td>
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<tr>
<td>Important potential risk: Secondary malignancies</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern: Section 4.4: BiCNU is carcinogenic in rats and mice, producing marked increase in tumor</td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
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<tr>
<td>Safety concern</td>
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<td>rabbits at dose levels equivalent to the human dose. Carmustine affected the fertility of male rats at doses higher than the human dose.</td>
<td></td>
<td>Currently available data does not support the need for additional risk minimization activities.</td>
</tr>
<tr>
<td>Missing information: Use during pregnancy and lactation</td>
<td>Creative Pharma Solutions’ proposed SmPC (meant for prescribing physicians) of carmustine will have the following information on this safety concern: Section 4.6: BiCNU 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. BiCNU is embryotoxic in rats and rabbits and teratogenic 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 of</td>
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<td>Safety concern</td>
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|                | childbearing 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.  
Section 5.3:  
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. | |

**V.7 Discussion on the clinical aspects**

The grant of a Marketing Authorisation is recommended for this application.
V User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of BiCNU is acceptable and no new non-clinical or clinical safety concerns have been identified. The Applicant gives an adequate justification for waiving a bioequivalence study. The overall benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labels are listed below:
BiCNU 100 mg-Powder and solvent for solution for infusion

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING CARTON AND LABEL ON VIALS WITH CARMUSTINE

1. NAME OF THE MEDICINAL PRODUCT

BiCNU 100 mg-Powder and solvent for solution for infusion carmustine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of powder contains 100 mg carmustine.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion.

Each vial of powder contains 100 mg carmustine.
Each vial of solvent contains 3 ml dehydrated alcohol (that is equivalent to 2.37 g).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Read the package leaflet before use.

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

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C–8°C).
The original package should be protected from light.
After reconstitution as recommended, BiCNU is stable for 24 hours under refrigeration (2°C - 8°C) in glass container.
10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Guidelines for the safe handling of the antineoplastic agents must be followed.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Creative Pharma Solutions, s.r.o.
Italska 17
120 00 Prague 2
Czech Republic

12. **MARKETING AUTHORISATION NUMBER(S)**

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

UK only: POM in a box

15. **INSTRUCTION ON USE**

For single use only.
Use only clear, colourless to light yellow solution.

UK only: Use as directed by a doctor

16. **INFORMATION IN BRAILLE**
**BiCNU 100 mg-Powder and solvent for solution for infusion**

**UK/H/5765/001/DC**

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<td>LABELS ON VIALS WITH DILUENT</td>
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1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

   Diluent for BiCNU  
   Anhydrous Ethanol  
   For intravenous use.

2. **METHOD OF ADMINISTRATION**

   For single use only.

3. **EXPIRY DATE**

   EXP:

4. **BATCH NUMBER**

   Lot:

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

   3 ml

6. **OTHER**

   Logo
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

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