26 April 2018
EMA/CHMP/88371/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Carmustine Obvius

International non-proprietary name: carmustine

Procedure No. EMEA/H/C/004326/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Carmustine Obvius
Applicant:	Obvius Investment B.V De Cuserstraat 93 1081 CN Amsterdam Netherlands
Active substance:	CARMUSTINE
International non-proprietary name:	carmustine
Pharmaco-therapeutic group (ATC Code):	alkylating agents, nitrosoureas (L01AD01)
Therapeutic indication(s):	Carmustine is effective in 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
Pharmaceutical forms:	Powder and solvent for concentrate for solution for infusion
Strength:	100 mg
Route of administration:	Intravenous use
Packaging:	Powder: vial (glass) Solvent: vial (glass)
Package sizes:	1 vial + 1 vial

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List of abbreviations

ASCT	autologous stem cell transplantation
BCNU	carmustine
BEAM	carmustine, etoposide, cytarabine, melphalan
CBV	cyclophosphamide, carmustine, and etoposide
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CR	complete response
DLCL	Diffuse large cell lymphoma
EFS	event-free survival
GBM	glioblastoma multiforme
HDC	high-dose chemotherapy
NHL	Non-Hodgkin's lymphoma
NRM	non-relapse mortality
OS	overall survival
O6BG	O^6-benzylguanine
PD	progressive disease
PFS	progression-free survival
PR	partial response
SD	Stable disease
SmPC	Summary of Product characteristics
TMZ	temozolomide
TTP	time to progression

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Obvius Investment B.V submitted on 6 May 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Carmustine Obvius, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 November 2015. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication.

Carmustine Obvius is 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.

• Hodgkin's disease - as secondary therapy in combination with other approved drugs in patientswho relapse while being treated with primary therapy, or who fail to respond to primarytherapy.

• 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 primarytherapy.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data with the reference medicinal product Carmubris instead of non-clinical and clinical unless justified otherwise

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Carmubris, 100 mg, powder and solvent for solution for infusion
- Marketing authorisation holder: Emcure Pharma UK Ltd.
- Date of authorisation: 31 July 1996
- Marketing authorisation granted by:
  - Member State (EEA) : Austria
    - National procedure
- Marketing authorisation number: 1-21762

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form:
- Carmubris, 100 mg, powder and solvent for solution for infusion
- Marketing authorisation holder: Emcure Pharma UK Ltd.
- Date of authorisation: 31 July 1996
- Marketing authorisation granted by:
  - Member State (EEA): Austria
    - National procedure
- Marketing authorisation number: 1-21762

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Juris Pokrotnieks

- The application was received by the EMA on 6 May 2016.
- The procedure started on 16 June 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 September 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 16 September 2016.
- During the meeting on 13 October 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List ofQuestions to all CHMP members on 27 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.

- During the CHMP meeting on 20 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 18 September 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 September 2017.
- During the CHMP meeting on 12 October 2017, the CHMP agreed on a second list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated second List of Outstanding Issueson 19 January 2018.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 8 February 2018.
- During the CHMP meeting on 22 February 2018, the CHMP agreed on a third list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated second List of Outstanding Issues on 27 March 2018.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second Listof Outstanding Issues to all CHMP members on 11 April 2018.
- The CHMP adopted a report on similarity with Iclusig, Xaluprine, Imbruvica, Revlimid, Torisel , Ledaga, Venclyxto, Adcetris , Gazyvaro, Arzerra, Blincyto and Besponsa on 26th April 2018.
- During the meeting on 26 April 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Carmustine Obvius.

2. Scientific discussion

2.1. Introduction

Carmustine is a cell-cycle phase nonspecific antineoplastic agent belonging to the nitrosourea group of compounds (bischlo-roethyl nitrosourea), which exerts tumour cytotoxicity via multiple mechanisms. As an alkylating agent, it can alkylate reactive sites on nucleoproteins, thus interfering with DNA and RNA synthesis and DNA repair. It is able to form interstrand crosslinks in DNA, which prevents DNA replication and transcription. Carmustine undergoes spontaneous nonenzymatic decomposition under physiological conditions to release reactive intermediates with alkylating and carbamoylating activities, which are thought to be responsible for the antineoplastic and cytotoxic activities of carmustine.

The pharmaceutical form and mode of administration of the proposed product is the same as reference product – powder and solvent for solution for infusion. The active substance of Carmustine Obvius 100 mg, powder and solvent for solution for infusion is the same as for reference product – carmustine.

Carmustine is an alkylating agent used as an antineoplastic agent. It is considered that the antineoplastic and toxic activities of Carmustine Obvius may be due to metabolites.

Carmustine has been used for more than 40 years and has a well-defined place in different oncological treatment protocols, such as in BEAM (carmustine, etoposide, cytarabine, melphalan) and transplantation of haemopoietic stem cells in patients with chemosensitive first relapse of Hodgkin's disease irrespective of length of initial remission (Schmitz et al 2002).

This is an abridged marketing authorisation application for CARMUSTINE 100 mg -Powder and solvent for concentrate for solution for infusion, which are essentially similar to the reference product Carmubris-Trockenstechampull mit Lösungsmittel, 100 mg (Emcure Pharma UK, Ltd., UK) and is therefore filed under Article 10(1) of Directive 2001/83/EC (i.e. a generic application).

Carmustine has been on the European markets since 15 August 1998, but has been on discontinuation in the EU since February 2014 due to a number of reasons mostly related to complexities in the manufacturing of the active substance. The applicant Obvius claimed eligibility to the centralised procedure on the basis that the shortage and impact on patients would be addressed, thus fulfilling patients' needs.

The originator Carmubris is approved in the following indications:

Carmustine is effective in the following malignant neoplasms as a single agent or in combination with other antineoplastic agents and/or other therapeutic measures (radiotherapy, surgery):

- Brain tumors - glioblastoma, Brain-stem gliomas, medulloblastoma, astrocytoma, ependymoblastomas and brain metastases
- Second line treatment for NHL and Hodgkin's disease
- Tumours of the gastrointestinal system
- Malignant melanoma in combination with other effective ani-neoplastic medicinal products
- multiple myeloma (in combination with a glucocorticoid such as prednisone),

The generic product Carmustine Obvius has applied for part of the originator's indications.

Carmustine Obvius is indicated is indicated in adults as part of established combination therapy with other approved chemotherapeutic agents, in the following:

- Brain tumors - glioblastoma, Brain-stem gliomas, medulloblastoma, astrocytoma and Ependymoblastomas
- Second line treatment for NHL and Hodgkin's disease

The strength and pack size (100mg carmustine powder and 3ml solvent, 1 vial each) are consistent with the dosage regimen and duration of use.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder and solvent for concentrate for solution for infusion containing 100 mg of carmustine as the active substance.

There are no other ingredients in the lyophilised powder apart from the active substance. The solvent used for the reconstitution is ethanol anhydrous and does not contain any other ingredients either.

The product is available in a pack containing one vial with the powder (for concentrate for solution for infusion) and one ampoule with solvent. The powder is contained in a 50 ml brown type I hydrolytic glass vial with light grey 20 mm bromobutyl rubber stopper and sealed with a dark red aluminium flip-off cap; the solvent is contained in a 5 ml clear type I glass ampoule, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of carmustine is 1,3-bis(2-chloroethyl)-3-nitrosourea corresponding to the molecular formula $C_5H_9Cl_2N_3O_2$. It has a relative molecular mass 214.05 g/mol and the following structure (Figure 1):

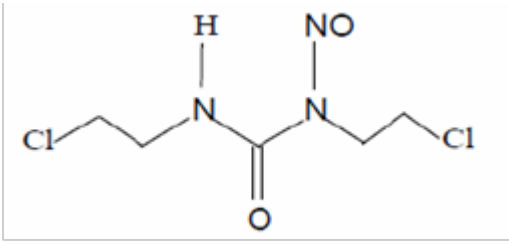


Figure 1. Structure of carmustine

Carmustine appears as a light yellow granular powder. It is very slightly soluble in water and freely soluble in ethanol.

As there is a monograph of Carmustine in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for Carmustine which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The active substance is packaged in double LDPE bags with desiccant placed inside a metal can as described in the CEP.

Specification

The active substance specification shown in Table 1 includes tests for: appearance, identity (IR, HPLC), assay (HPLC, UV), water content (KF), heavy metals (ICP-MS), organic impurities (HPLC), 2-Chloroethylamine (TLC), acetaldehyde and 2-Chloroethanol, ethanol (GC), bacterial endotoxins (Ph. Eur.) and microbiological purity (Ph. Eur.).

Table 1. Carmustine active substance specification

Tests	Specification	Method
Parameter		
Appearance *	Light yellow powder, essentially free of foreign matter	Visual inspection
Identity		
IR*	Spectrum corresponds to the spectrum of reference standard	Ph. Eur. 2.2.24
HPLC*	The retention time of the main peak corresponds to the peak of reference standard	In-house HPLC
Assay		
Carmustine (HPLC)*	98.0 – 102.0% calculated on the anhydrous and solvent-free basis	In-house HPLC
Carmustine (UV)	98.0 – 102.0%	According to Ph. Eur. 1187 monograph and Ph. Eur. 2.2.25
Water content (Karl Fischer)*	≤ 0.5%	According to monograph USP <921> Method Ic
Purity		
Inorganic impurities		
Heavy metals	≤ 20 ppm	USP <231> method II
Organic impurities		
Ether-insoluble substances*	≤ 0.1%	According to monograph USP,
Impurity A (HPLC)*	≤ 0.5%	In-house HPLC
Unspecified impurities (HPLC)*	≤ 0.10%	In-house HPLC
Total sum of impurities (HPLC)*	≤ 1.0%	In-house HPLC
Organic impurities (TLC)		
2-Chloroethylamine	≤ 0.2%	In-house TLC
Organic impurities (GC)		
2-Chloroethanol	≤ 0.1%	In-house GC
Acetaldehyde	≤ 0.1%	In-house GC
Ethanol	≤ 0.5%	In-house GC
Microbiological determinations		
Bacterial endotoxins*	≤ 0.10 EU/mg	Ph. Eur. 2.6.14
TAMC*	≤ 10^3 CFU/g	Ph. Eur. 2.6.12
TYMC*	≤ 10^2 CFU/g	Ph. Eur. 2.6.12

*: Used for re-test

The specification tests and acceptance criteria ensure compliance with the Carmustine Ph. Eur. monograph and the CEP. The CEP includes three additional test methods compared to the monograph: test for 2-Chloroethylamine by TLC, residual acetaldehyde, residual ethanol and 2-chloroethanol by GC.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three commercial batches are provided. The results are within the specifications and consistent from batch to batch.

Stability

The proposed re-test period and packaging material for carmustine are covered by the CEP. The retest period is 2 years stored in double LDPE bags with desiccant inside a metal can at 2-8 ºC.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Powder for concentrate for solution for infusion

Carmustine Obvius 100 mg powder for solution for infusion is a yellowish powder. Before administration powder should be reconstituted in ethanol and water for injection and further diluted with suitable diluents.

Table 2. Complete composition of Carmustine Obvius per vial

Ingredient	Reference	Amount (mg/vial)	Function
Carmustine	Ph. Eur. 1187	100 mg	Active substance
Ethanol, anhydrous	Ph. Eur. 1318	None[1]	Solvent
Water for Injection	Ph. Eur. 0169	None[1]	Solvent

[1] -is a process ingredient, which evaporate during lyophilisation, and is therefore not part of the final product

Carmustine Obvius is a simple formulation containing only the active substance carmustine. Taking into account the fact that it concerns a powder for solution for infusion (parenteral use) no extensive development studies were performed. According to the information obtained from EDQM, water is used in the final step of synthesis of active substance (in final recrystallization). As the active substance is further used for parenteral infusion, the applicant upon the CHMP request demonstrated compliance of the water used in the final steps of the synthesis with the corresponding requirements of CPMP/QWP/158/01 Revision “Note for guidance on quality of water for pharmaceutical use”.

Excipients used as processing solvents in the manufacture of carmustine 100 mg powder for solution for infusion are ethanol and water for injection, which are evaporated during freeze-drying step and are not present in the finished product. The quality of excipients used during manufacturing process is confirmed to comply with Ph.Eur. monographs 1318 (Ethanol, anhydrous) and 0169 (Water for injections) and are commonly used in the pharmaceutical industry.

The reference product Carmubris (from EU market) has been characterised with respect to a chemical-pharmaceutical properties; i.e. appearance, pH, density, osmolality, reconstitution time, assay, impurities profile, water content and container closure characterization.

From a pharmaceutical point of view, Carmustine Obvius and the reference products have the same active substance, the same pharmaceutical form and the same route of administration. Comparative studies between the generic product and two batches of the reference product Carmubris have been performed and show essential similarity with respect to major physicochemical parameters (appearance, appearance of the reconstituted solution, pH value, density, assay, osmolality, reconstitution time, water content, impurity A, any unspecified impurity and total impurities). The impurity profiles between the test and reference products are comparable; the only minor difference being the presence of an unknown impurity in the reference product. Osmotic values were compared between generic product and reference product and can also be considered as comparable. The reference product shows slightly higher water content.

In conclusion, Carmustine Obviuscan be considered as essentially similar to the reference product as it contains the same qualitative and quantitative composition in active ingredient and is presented in the same pharmaceutical form.

The pharmaceutical development studies focused mainly on development of a stable bulk solution with appropriate concentration of the active and compounding temperature to assure bulk solution stability and development and optimisation of the lyophilisation process resulting in a stable product with pharmaceutically acceptable physico-chemical properties. The development of the manufacturing process (compounding, filtration, filling and freeze drying process) for the drug product Carmustine Obvius has been performed at Oncotec Pharma Produktion GmbH. Because carmustine is very slightly soluble in water and freely soluble in ethanol, the active substance is dissolved in ethanol and water is added subsequently to form the bulk solution. The active substance is very reactive and rapidly degrades through formation of Impurity A and multiple other impurities when exposed to heat (room temperature), oxidation, acid/alkali treatment and light. The degradation is significantly increased when the active substance is in solution. The solubility of the active substance and the stability of bulk solution were tested at different concentrations and temperatures. The data showed a temperature effect on the stability of the bulk solution and that a low concentration (3 mg/ml) at a low temperature (12.5 ± 2.5°C) leads to a stable bulk solution of carmustine in a 12.5 vol% ethanol solution without precipitation and crystal formation. Therefore the above values for these three parameters have been set for use in the routine manufacture. Results indicated that the temperature of the bulk solution was critical for the stability of the bulk solution, thus the temperature was set as critical process parameter to be monitored during the compounding process. Nitrogen is used during routine compounding, filling and freeze drying to minimise the amount of oxidative reactions during manufacture. Its quality complies with the Ph.Eur. monograph for Nitrogen. The active substance is also sensitive to light, therefore light protective conditions (equipment closed with aluminium lids and filling at the red light) are considered during manufacturing process. Moreover, the time from addition of active substance to freeze drying is important as the active substance degrades in solution. Development studies with bulk solution were

performed and a holding/processing time was defined. The time from addition of active substance to the end sterile filtration is defined to 4 hours to ensure enough time for filling and loading of the freeze dryer within a total of 8 hours from compounding.

The freeze drying program was tested with the pilot scale freeze dryer to confirm the designed freeze drying program.

Lyophilisation parameters were evaluated and optimised according to target of final water content, amount of impurities, assay and optimal lyophilisation cycle total length by changing filling volume, concentration of active substance in ethanol solution, drying temperatures and time and overfilling. The main focus in the lyophilisation cycle development was related to cake appearance, water content, assay and content of the related substances. Based on the critical temperatures and several trial runs, in which temperatures and times of the separate steps were varied, the lyophilisation cycle parameters were established as shown in Table 3:

Table 3. Carmustine lyophilisation cycle parameters

Compounding process				
Temperature	12.5 ± 2.5 °C			
Concentration of DS in the bulk	3.0 mg / ml			
Filling process				
overfilling	5.0 %			
Upper filling limit	35.4 g			
Lower filling limit	33.4 g			
Filling quantity desired	34.4 g			
Freeze drying Program				
	Shelf temperature [°C]	Pressure [µbar]	Time[min]	N_2
1. Loading	5	-	-	no
2. Freezing (ramp)	- 5	-	30	yes
3. Freezing (hold)	- 5	-	60	yes
4. Freezing (ramp)	- 45	-	30	yes
5. Freezing (hold)	- 45	-	240	yes
6. Primary drying (hold)	- 45	500	30	yes
7. Primary drying (ramp)	15	500	300	yes
8. Primary drying (hold)	15	500	2790	yes
9. Secondary drying (hold)	15	500	1020	yes
10. Preventilation	5	800 mbar	-	yes
11. Stoppering	5	800 mbar	-	yes
12. Final ventilation	5	-	-	yes
13. End	-	-	-	-

The duration of the freeze drying cycle was increased during cycle optimization studies due to the reduction of the concentration of Carmustine in bulk solution and leads to a homogenous result of the finished product after the freeze drying.

It is proposed to use 5 % overfill of bulk solution in the vials prior to freeze drying during filling process thus ensuring acceptable content of carmustine in the final freeze dried product. According to the applicant, an overfilling of 5 % is required for the routine production to achieve an assay of 100 % due to small molecule weight, the fluffy cake structure and the high filling limit might have caused a sublimation effect/micro blow out (molecules can be pulled out of the vial by the sublimation force).

It has been demonstrated that dry heat sterilization and radiation sterilization lead to significant degradation of the finished product since carmustine is a thermolabile substance, therefore sterilisation by aseptic processing and filtration, was considered the most appropriate method. The choice of sterilisation method is considered satisfactorily justified according to *the "Decision trees for the selection of sterilisation methods" (CPMP/QWP/054/98).* Taking also into account the known sensitivity of the active substance to elevated temperature (melting range ~30 °C), the bulk solution processing temperature was set accordingly and the manufacturing process includes use of nitrogen to avoid oxidation. Satisfactory information regarding the impact of the employed filter (PVDF) used for sterilization on assay and impurity profile has been provided including acceptable validation reports.

The active substance is known to be light sensitive. Therefore brown glass vials are used as primary packaging. Additional warning to keep drug product in outer packaging and protect from light also during clinical use are stated in the product information. The vials are stoppered with light grey 20 mm bromobutyl stoppers and sealed with a dark red aluminium flip-off cap. The proposed container closure system is common for freeze dried powders and suitable for the current finished product. The size of vial (50 ml) was chosen to cover the filling amount and reconstitution amount. As the finished product is a dry powder, according to chapter 3.2.1 of the European Pharmacopoeia, it is justified to use a glass quality conforming to type I glass. The rubber stoppers are made of bromobutyl rubber, which are recommended by Ph. Eur. 3.2.9 to be used in manufacture of parenteral dosage forms.

Solvent

The solvent is used for the reconstitution of lyophilised carmustine and consists of anhydrous ethanol; there are no other components (Table 4).

Table 4. Complete composition of solvent per vial (3.3 ml)

Ingredient	Reference	Quantity	Function
Ethanol, anhydrous	Ph.Eur. 1318	3.3 ml	Solvent

Nitrogen is used in the manufacturing process, but is not present in the finished product. Anhydrous ethanol is a colourless to light yellow, clear liquid and complies with Ph.Eur. 1318 monograph requirements. The

nitrogen gas used in the manufacture of the ethanol solvent complies with Ph. Eur. monograph for Nitrogen. No formulation development has been performed.

The manufacturing process is a simple process of filling ethanol in vials. The most critical issue is the sterility of the diluent as it is intended for intravenous use. A manufacturer for the diluent who has prior experience with both sterile products as well as working with ethanol was selected in this regard. The diluent is sterilised by a combination of aseptic filtration and aseptic processing. The sterilisation method has been justified in according to the "Decision trees for the selection of sterilisation methods" (CPMP/QWP/054/98) taking into account the physicochemical properties of the solvent (ethanol) e.g. boiling point.

A risk analysis investigation the different manufacturing steps of the production process for *Ethanol in vials* has been performed for all steps of the process. The possible risks connected to each step and the content of preventive controls have been summarised and presented. It has been concluded that the critical steps are: preparation of the bulk solution, sterile filtration, filling/crimping of the vials.

The overall strategy of the steps taken to ensure the sterility of the ethanol solvent was provided. The overview of the performed media fill runs was presented in the dossier.

It has been clarified that an overfill of 0.3 ml is applied and, therefore, 3.3 ml of solvent is filled in the ampoule in order to ensure that the health care professionals can withdraw at least 3.0 ml required for the powder reconstitution.

The initial container closure system for the diluent was glass Type I vials sealed with stoppers and a combined flip off cap. During the final manufacturing runs of three commercial scale batches, high values of Residue on Evaporation and Absorbance were obtained. During development of the manufacturing process several issues arose as the filling line as well as the intended stopper resulted in OOS results on absorbance as well as Residue on Evaporation. Root cause analysis and re-development work has been described in detail. In order to avoid the risk of introducing impurities from the stoppers, it was decided to use glass ampoules as the primary container for the ethanol solvent, as the absorbance and residue on evaporation is not expected to be affected by the container closure system when using glass ampoules. A different manufacturer of the ethanol solvent was also introduced.

The proposed container closure system consists of a 5 mL, Form B, OPC Type I Clear glass ampoule. The glass ampoules are tested in accordance with Ph. Eur. 3.2.1.

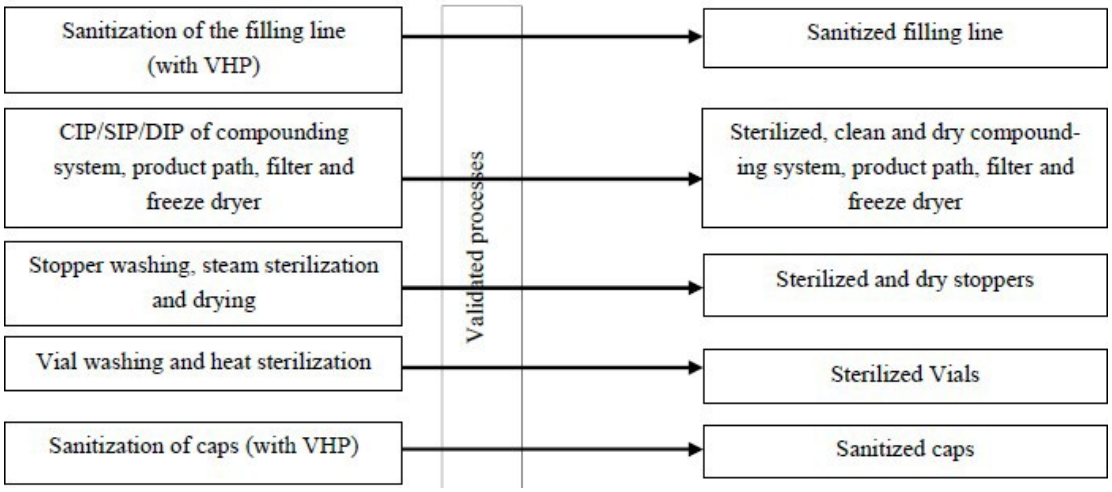
Manufacture of the product and process controls

Powder for concentrate for solution for infusion

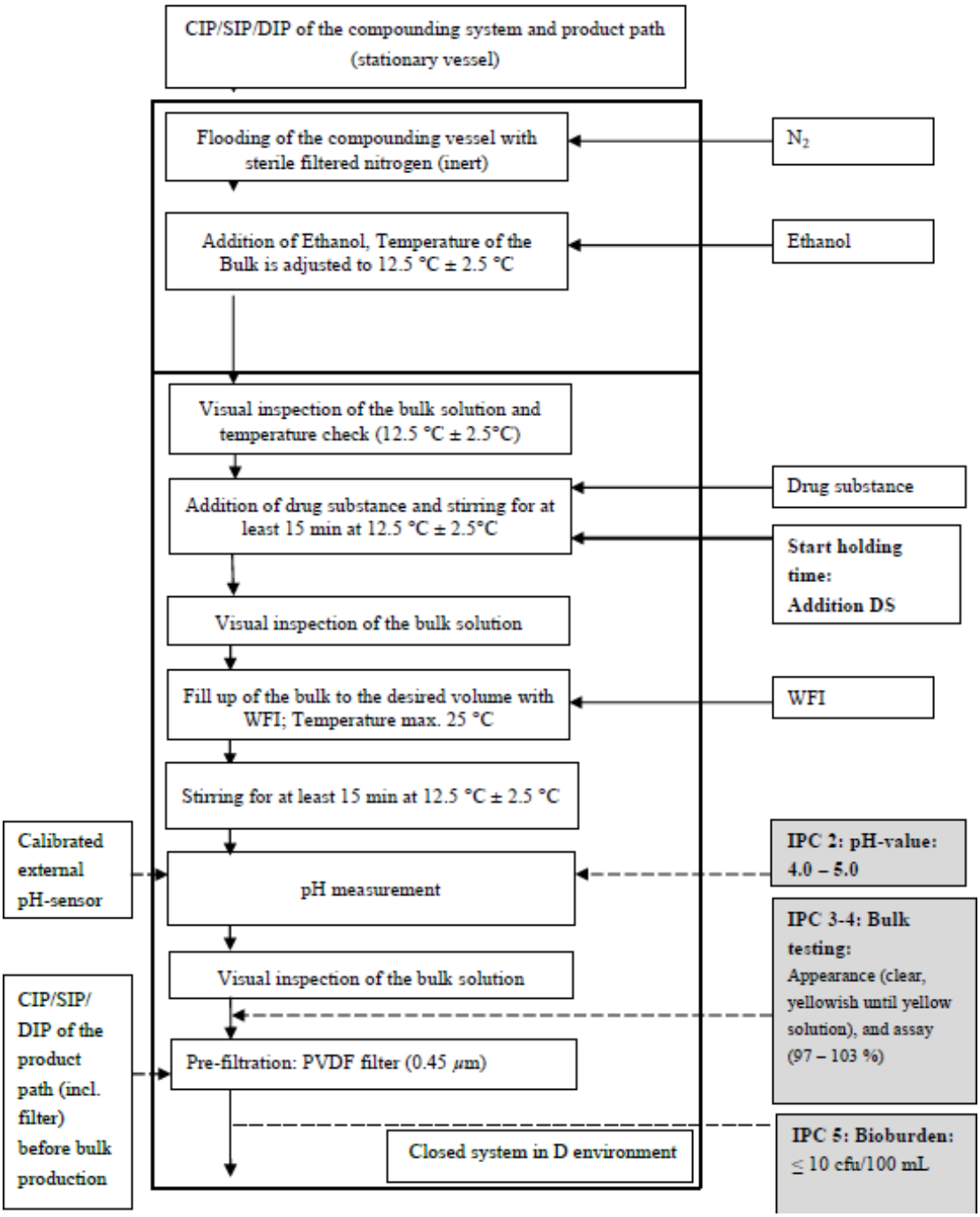
The main steps of the manufacturing process are the preparation of primary packaging materials, preparation of the solution, pre-, sterile filtration, filling into vials, lyophilisation and closing of the vials, labelling and packaging. A production flow chart, identifying the in-process controls, is presented in Figure 2.

Step 1 - Preparation

a) Preparation of equipment and primary packaging



Step 2 & 3 - Compounding of the bulk solution & Sterile filtration of the bulk



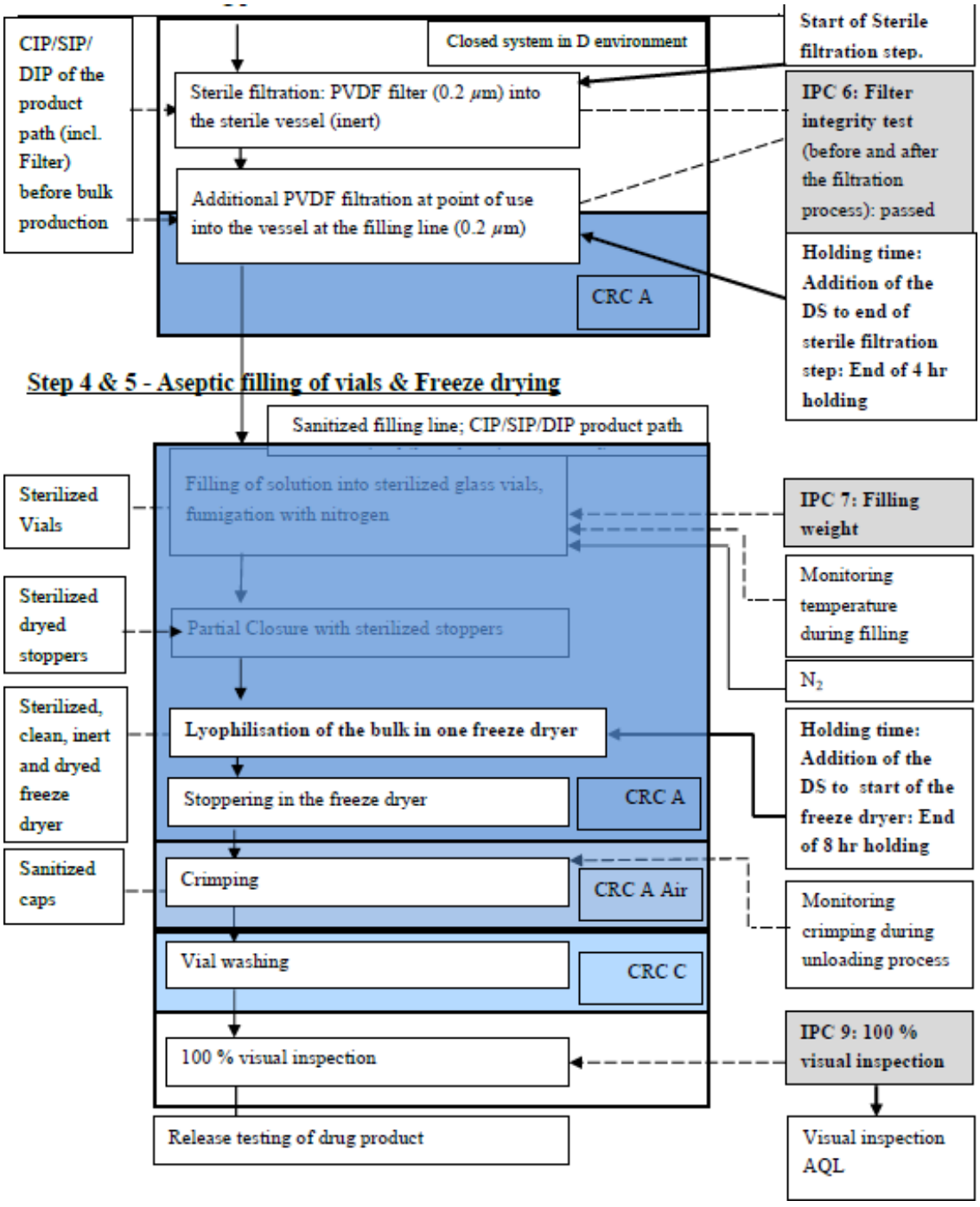


Figure 2. Carmustine Obvius powder for solution for infusion manufacturing process flow chart

No holding time on the bulk solution has been defined and therefore no intermediates have been defined. However, due to the rapid degradation of the active substance when in a solution maximum processing times during routine manufacturing process have been defined during development studies and confirmed by validation studies. The material of container at which these studies have been performed was stated. Nitrogen is used during routine compounding, filling and freeze drying steps to minimize the amount of oxidative reactions during manufacture.

Time and temperature is stated for primary packaging sterilisation cycles.

The primary container closure system (50 mL glass vial) is sterilised by dry heat in accordance with Ph. Eur. 5.1.1. The sterilisation process is performed according to a validated procedure and undergoes a regular revalidation using a worst-case concept. The validation package for the heat sterilization process was provided. The latest report on the routine revalidation of the process using the worst-case vial size of 100 mL is also included. The validation reports confirm the proposed sterilisation process efficacy.

The steam sterilisation of the rubber stoppers is performed at standard Ph.Eur. conditions of at least 121°C for at least 15 minutes, therefore no further information was requested.

Filter validation data (reports) has been provided with regards to bacterial retention capacity, solution compatibility and extractable/leachable.

Sterile filtration, filling of vials and lyophilisation are defined as critical steps. Filtration step is controlled by the bioburden limit prior to sterile filtration and filter integrity testing before and after filtration. Filling step is controlled by testing of fill weight. Continuous control of time, pressure and temperature is performed by computer monitoring throughout the lyophilisation process step. The control strategy of critical steps is satisfactory to ensure consistent manufacturing process and quality of finished product.

The aseptic manufacturing process by sterile filtration in combination with a lyophilisation process, is considered a non-standard manufacturing process in accordance with Annex II of the Guideline on process validation for finished products, therefore validation has been performed on three consecutive commercial scale batches manufactured in accordance with the commercial process. Information regarding media fill runs at the proposed manufacturing site has also been included in the dossier. The results obtained during the validation of the manufacturing process in general confirm that all the parameters tested of all the batches are in line with the required specifications and could be considered as validated.

Solvent

Anhydrous ethanol is pre-filtered and sterile filtered, and aseptically filled in ampoules. The main steps of the manufacturing process are the preparation of primary packaging materials, preparation of bulk ethanol volume, sterile filtration, aseptic filling into vials, closing and inspection. A production flow chart, identifying the in-process controls, is presented in Figure 3.

Ingredient	Manufacturing step	In-process control
Step 1 - Preparation		
	hot steam sterilisation of bulk preparation equip-ment	T ≥ 121°C, t ≥ 15 min
	Hot air sterilisation of empty ampoules	T ≥ 275 °C, t ≥ 3 min with endotoxin reduction level ≥ 10^3 IU
Step 2 - Weighing of bulk		
Ethanol	Preparation of bulk solution	Volume: 45 L ethanol
Step 3 - Sterile filtration		
	Two times sterile filtration of the bulk solution	N2-pressure: 1.5 – 2.5 bar Bioburden: TAMC: < 10 CFU/100 ml TYMC: < 10 CFU/100 ml Particle monitoring: 0.5 µm particles: ≤ 3520 / m³ 5.0 µm particles: ≤ 20 / m³
	Integrity test of sterile filters after filtration	Forward flow test: ≤ 3.0 mL/min
Step 4 – Aseptic Filling		
	Filling the ampoules	Filling volume every 60 min: Action limits: 3.20 – 3.40 mL target: 3.3 mL
	Environmental monitoring	Microbial and particle monitoring
Step 5 – Closing and inspection		
	Closing of ampoules	
	Environmental monitoring	Microbial and particle monitoring
	optical inspection	Inspection of ampoules

Figure 3. Ethanol solvent manufacturing process flow chart.

Critical steps have been defined as preparation of bulk solution, sterile filtration, filling of ampoules, closing. The IPCs for each step were described and are adequate. The bioburden is controlled before sterile filtration with acceptable limit; filter integrity is controlled after filtration.

The holding time during routine manufacture from addition of ethanol to end of filtration is not more than 24 hours and has been justified by filter validation data as well as process validation data.

Both the sterile filtration and filling steps are performed in the presence of nitrogen. The reason for using nitrogen gas is to create positive pressure for solution transfer during filtration and filling. The presence of nitrogen also reduces the risk of oxidation of the ethanol, and of ignition of the flammable ethanol. The nitrogen is removed during manufacture and is not present in the final product.

The manufacturing process is considered to be a non-standard process. A process validation of the manufacturing process of the ethanol solvent has been performed on three consecutive commercial scale validation batches. The conclusion is that the process is validated and suitable for the intended use. Satisfactory filter validation data was provided with respect to extractables from filter, bacterial retention capacity and solution compatibility. The overview of the performed media fill runs was also presented. The bracketing approach applied is acceptable.

Product specification

Powder for concentrate for solution for infusion

The release and shelf-life specifications for the Powder for solution for infusion, reproduced in Table 5, include appropriate tests and limits for appearance of powder (visual), clarity and colour of reconstituted solution (Ph. Eur.), pH of reconstituted solution (Ph. Eur.), osmolality (Ph. Eur.), reconstitution time, visible and sub-visible particles (Ph. Eur.), identity (HPLC, IR), assay (HPLC), related impurities (HPLC), water content (Ph. Eur.), residual solvent (Ph. Eur.), uniformity of dosage units by weight variation (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and container closure integrity (Ph. Eur.).

Table 5. Carmustine Obvius powder for solution for infusion release and shelf-life specifications

Test parameter	Acceptance criteria	Method
Appearance		
Appearance of Powder (lyophilisate)	White to almost white lyophilisate or powder	Visual examination
Clarity of the reconstituted solutions	Clear solution (< ref solution I)	Ph. Eur. 2.2.1
Colour of reconstituted solution	Colourless to light yellow solution (< GY4 ref. solution)	Ph. Eur. 2.2.2
pH of the reconstituted solution	4.0 – 5.0	Ph. Eur. 2.2.3
Osmolality	≤ 2200 mOsm/kg	Ph. Eur. 2.2.35
Reconstitution time	≤ 1 min	In-house
Particles		
Visible particles	The solid is solved completely / Practically free of visible particles	Ph. Eur. 2.9.20 USP <1>
Sub-visible particles	≥ 10 µm: ≤ 6.000/vial ≥ 25 µm: ≤ 600/vial	Ph. Eur. 2.9.19 method 1 USP <788>
Identity		
Identity by IR[b]	Complies with the reference spectrum	Ph. Eur. 2.2.24 USP <197F>
Identity Retention time by HPLC[b]	Retention time of main peak corresponds to the peak of the reference standard	HPLC
Assay		
Carmustine content by HPLC	95.0 - 105.0%	HPLC
Related impurities by HPLC Impurity A[a] Any single unspecified impurity Total sum of impurities	 ≤ 1.0% ≤ 0.1% ≤ 1.0%	HPLC
Water content by Karl Fischer	≤ 1.0%	Ph. Eur. 2.5.12 USP <921> method A
Residual solvent Ethanol[b]	 ≤ 5000 ppm[b]	Ph.Eur.2.4.24 USP <621>
Uniformity of Dosage Unit		
Uniformity of Dosage Unit by weight	10 units: AV: ≤ L1 % (15.0)	Ph. Eur. 2.9.40

variation	30 units: AV: ≤ L1 % (15.0) No unit is less than (1 – L2 * 0.01)*M nor more than (1 + L2 * 0.01)*M where L1 = 15.0; L2 = 25.0	
Microbial quality		
Sterility	Sterile	Ph. Eur. 2.6.1 USP <71>
Bacterial endotoxins	≤ 0.70 EU/mg	Ph. Eur. 2.6.14; method C USP <85>
Other		
Container Closure Integrity test[b]	CCI confirmed	Ph. Eur. 3.2.9 USP <1207>

a: Chemcial name is 1,3-Bis(2-chloroethyl)urea, BCU

b: only tested at release.

The specifications for the drug product in general is prepared in line with requirements given in ICH guideline Q6A as well as with the requirements set in the current Ph. Eur. for parenteral preparations. The applied endotoxin limit has been calculated as requested and is considered acceptable considering adult only patient population.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data from three production scale has been presented. All data is within specification. The results show that the finished product can be manufactured with consistent quality and meet its specifications.

Solvent

The release and shelf-life specifications for the Solvent, reproduced in Table 6, include appropriate tests and limits for appearance (visual), identity (relative density, IR), extractable volume (Ph. Eur.), acidity or alkalinity (Ph. Eur.), residue on evaporation (Ph. Eur.), assay (Ph. Eur.), absorbance (Ph. Eur.), volatile impurities (Ph. Eur.), visible and sub-visible particles (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

Table 6. Solvent release and shelf-life specifications.

Release and end of shelf life specification

Test	Acceptance criteria	Method
Appearance	Clear glass ampoules with colourless liquid	Visual inspection
Identity relative density	0.790 to 0.793	Ph. Eur. 2.2.5
Identity IR	Complies with the reference spectrum	Ph. Eur. 2.2.24
Extractable volume	Not less than 3.0 ml	Ph. Eur. 2.9.32
Appearance of content	Complies	Ph. Eur. 2.2.1, Ph. Eur. 2.2.2, II
Acidity or alkalinity	Complies	Ph. Eur. 1318
Residue on evaporation	≤ 25 ppm (m/V)	Ph. Eur. 1318
Assay	≥ 99.5 % (V/V) resp. 99.2 % (m/m)	Ph. Eur. 1318
Absorbance	≤ 0.40 at 240 nm	Ph. Eur. 2.2.25
	≤ 0.30 from 250 to 260 nm	
	≤ 0.10 from 270 to 340 nm	
	The spectrum shows a steadily descending curve with no observable peaks or shoulders	
Volatile impurities*	Methanol ≤ 200 ppm V/V	Ph. Eur. 2.2.28
	Acetaldehyde + acetal ≤ 10 ppm V/V	
	Benzene ≤ 2 ppm	
	Total of other impurities ≤ 300 ppm	
Visible particles	Practically free of visible particles	Ph. Eur. 2.9.20
Sub-visible particles	≥ 10 µm: ≤ 6.000/ampoule	Ph. Eur. 2.9.19 1B
	≥ 25 µm: ≤ 6.00/ampoule	
Sterility	Sterile	Ph. Eur. 2.6.1
Bacterial endotoxins	<8.0 I.U./ml	Ph. Eur. 2.6.14; method C

*) only tested for release of batch

The specification for the Solvent contains all the tests described in the Ph. Eur. monograph 1318 for ethanol anhydrous. Since the route of administration is i.v. the Ph. Eur. tests for visible and sub-visible particles as well as sterility and endotoxin are also included in the specification. The specification limit for bacterial endotoxins is calculated in accordance with Ph.Eur. 5.1.10.

In addition, a Ph. Eur. Test for extractable volume ensures that the amount in each vial is acceptable. Filling volume is ensured through in-process controls by weighing thus ensuring the uniformity of content in the diluent vials.

All the analytical procedures tests are performed according to Ph. Eur. Only exception is the appearance which is a very simple test. Method validation reports for sterility test method and bacterial endotoxin test method have been provided. Satisfactory information regarding the reference standards used for testing has been presented.

Batch results for three commercial scale batches demonstrated compliance with the proposed specifications.

Stability of the product

Powder for concentrate for solution for infusion

Stability data from three production scale batches stored in the proposed packaging both in upright and inverted position under long term conditions for up to 18 months (2°C -8°C) and under accelerated conditions 25°C / 60 % RH for 6 months according to the ICH guidelines was provided.

All tests in the specification were performed at the 18 month time point (including endotoxin and sterility), including the new tests in the updated specification. Both HPLC methods were demonstrated to be stability indicating. No trend is observed for up to 18 month storage at 2-8°C. All data are within the updated specification limits for all three batches for both upright and inverted positions of the vials. Results from the accelerated conditions show a time dependent degradation, where carmustine content is OOS after 6 months and the content of impurity A is OOS after 6 months. The water content increased however stayed within the specification limits. Additional data with the recently implemented method for testing unknown impurities were also provided and support the original data.

An elevated temperature stability study was performed on three commercial scale batches stored at elevated temperature at 25°C/60% RH for 24 hours and 7 days, followed by 6 month storage at long term conditions (2-8°C). Vials were stored both upright and inverted position. All data are within the specification. The generated data supports temperature excursions, i.e. such as those likely during transport of the product.

In addition, a stress stability study was conducted to demonstrate the stability indicating capability of the analytical methods. Samples were exposed to heat, light, acid, alkali and oxidative treatments. Based on these data it is concluded that the finished product in solution is much less stable as compared to in a lyophilisate. It is known that the active substance is light sensitive. The stress study confirmed as expected that the drug product when exposed to daylight, especially in solution, showed very significant degradation and heavy formation of unspecified impurities and should therefore be protected from light.

An in-use/compatibility stability study has been performed upon request of the CHMP during the procedure. The study was performed on two commercial scale batches mimicking the clinical use of the product. The purpose of the in-use/compatibility study was to support an in-use shelf-life. The stability commitments in this regard are also noted and are acceptable.

The previously proposed pre-cooling step (precooling of the 5% glucose and with 0.9% sodium chloride solutions to be used for reconstitution and dilution) has been excluded from description of handling procedures for healthcare professionals, as is not justified from clinical point of view.

The two commercial scale batches of Carmustine Obvius have been tested and compared with one batch of the reference product Carmubris. The study was conducted in glass containers with PVC free PE infusion sets, stored at inverted position at room temperature, protected from light and tested after 0, 1, 2, 3 and 4 hours to demonstrate quality of Carmustine Obvius within proposed period of use (infusion 1-2 hours) and compatibility with proposed container and solvents solutions listed in the SmPC.

The parameters investigated were clarity and color of solution, pH, osmolality/density, assay of carmustine, impurity A, unknown impurities and total impurities, visual particles/sub-visual particles. The acceptance criteria for clarity, color of solution, pH, osmolality/density are the same as for release/shelf-life specification. The results for reconstituted/diluted carmustine solution were found within proposed limits

and are acceptable. The acceptance criteria for impurity A, unknown impurities and total impurities are the same as for release/shelf-life specification and are considered qualified and justified in accordance with the Ph. Eur. monograph on Carmustine (1187) and guideline CPMP/ICH/2738/99 Impurities in new Drug Products.

Out of specification results for ready for use infusion solution were observed for assay. During storage assay decreases more than 5 % at testing time point 4 hour.

The comparison of the stability of the reconstituted/diluted Carmustine Obvius with the stability of the reference product it has been shown that the in-use assay content and degradation profile of the generic product and reference product Carmubris shows similar degradation tendencies with approximate 4-5 % decrease in assay from initial value at testing time point 3 h. At testing time point 4 h decrease in assay is more than 5 % i.e. 6-7%. It is known that active substance is susceptible for degradation in solution, however it should be noted that severe mass imbalances (e.g. assay decrease without increase of impurity level) were observed during in-use stability studies, and were not explained by the applicant. However considering the similar degradation profile between the test and reference product and the observed assay/impurity imbalance, the acceptance criteria for assay in the in-use specification (Table 7) 87.2 % - 106 % and the administration of the infusion solution must be completed within 3 hours after preparation of solution (SmPC 6.3 and 6.6).

Table 7. In use shelf-life specifications.

Test parameter	Acceptance criteria, In-use shelf-life	Method
Appearance and Chemical		
Clarity of solution	Clear solution (< ref solution I)	Ph. Eur. 2.2.1
Color of solution	Colorless to light yellow (< GY4)	Ph. Eur. 2.2.2
pH of the solution	4.0 – 5.0 in 5% Glucose 4.0 – 6.8 in 0.9% NaCl	Ph. Eur. 2.2.3
Osmolality	≤ 450 mOsm/kg	Ph. Eur. 2.2.35
Assay		
Carmustine content by HPLC	0.1645 – 0.2000 mg/mL (87.2 - 106.0%)	HPLC
Impurities		
Related impurities by HPLC		
Impurity A	≤ 1.0%	HPLC
Any unspecified	≤ 0.1%	HPLC
Specified at RRT 0.23	≤ 0.2%	HPLC
Total sum of impurities	≤ 1.0%	HPLC
Visible particles	The solid is dissolved completely / Practically free of visible particles	Ph. Eur. 2.9.20 USP <1>
Sub-visible particles	≥ 10 µm: ≤ 25 per mL	Ph. Eur. 2.9.19 method 1 USP <788>
	≥ 25 µm: ≤ 3 per mL	

Out of specification results for ready for use infusion solution were also observed for particulate contamination. During storage tests results for visual and sub-visual particle doesn't fulfill Ph. Eur. requirements for parenteral preparations. However the CHMP noted that in accordance with Ph.Eur. all parenteral preparations have to be tested for visible/subvisible particles and in-use specification should include test for particles in accordance with guidelines *CPMP/ICH/367/96 Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, where it is

stated that both chemical and physical parameters should be monitored. The CHMP also noted that the manufacturer should be able to control quality of the product during lifecycle, and therefore the test for visible/sub-visible particles should be included in the in-use specification. Analytical results demonstrating compliance with Ph.Eur requirements for parenterals regarding visible/sub-visible particles were provided.

Based on the provided stability data, a shelf life of 24 months for the powder vials has been demonstrated. The product must be stored and transported refrigerated (2°C – 8°C), and kept in the vial and ampoule in the outer carton, in order to protect from light. The in-use shelf-life claim of 3 hours at room temperature for the reconstituted and diluted with 5% glucose or 0.9% NaCl solution as stated in the SmPC (section 6.6) is also acceptable. The reconstituted and diluted solutions must be administered over 1-2 hours and administration must be finalised within 3 hours after reconstitution of the product (section 6.3).

Solvent

Stability data was provided from three production scale batches and one at 50% the full scale batch size stored in the proposed packaging both in upright and inverted position under long term conditions (2°C-8°C and 25°C/60% RH) for up to 6 months and under accelerated conditions (40°C/75% RH) for 6 months according to the ICH guidelines.

All tests in the specification were performed. All the results are within the updated specification limits for all three batches for both upright and inverted positions of the vials.

In addition 18 months supportive stability data performed on 3 batches of Dehydrated Alcohol Injection, USP in glass vials with a coated rubber stopper, at 25°C/60% RH have been presented. Samples in this study were tested according to USP specification which is very much similar to Ph. Eur. The results from this study comply with the acceptance criteria for up to 18 months and demonstrate that ethanol is stable for at least 18 months when stored in glass vials with coated rubber stoppers.

Extrapolation of the pivotal stability data is applied and 12 months shelf-life is proposed. Considering the nature of the solvent (ethanol anhydrous) and primary packaging (glass ampoule), the proposed extrapolation of the shelf life to 12 months is accepted. According to the stability data (25°C long-term condition and 40°C accelerated condition), no special storage conditions are necessary. Additionally, the stability of ethanol ampoules in 2-8°C is shown as the ethanol solvent ampoules will be packed together with the carmustine powder which is to be stored at 2-8°C.

Powder and solvent for concentrate for solution for infusion

Due to fact that ethanol solvent ampoules will be packed together with the carmustine powder, the accepted shelf-life for powder for concentrate for solution for infusion and solvent package is limited to the accepted shelf life of the solvent which is shorter than the powder.

In conclusion, the proposed shelf life of 12 months and the storage conditions for the finished product (powder vial and solvent ampoule) as stated in the SmPC (sections 6.3 and 6.4) are acceptable. The product must be stored and transported refrigerated (2°C - 8°C), and kept in the vial and ampoule in the outer carton, in order to protect from light.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Issues related to the stability of the, prone to degradation, active substance, the finished product, and the reconstituted and diluted product ready for administration have been satisfactorily addressed and appropriate instructions are included in the SmPC regarding reconstitution, dilution, handling and administration. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

The Applicant following a request from the CHMP has submitted phase I (pre-screening) evaluation. Using the equation of Du Bois* (Du Bois & Du Bois, 1916) the body surface area in a human weighing 70kg with a height of 185cm can be calculated to 1.85m^2. According to the proposed SmPC the maximum dose of Carmustine Obvius 100mg powder and solvent for concentrate for solution for infusion is 200mg/m^2 which thereby equal a maximum dose per inhabitant of 370mg. $PEC_{surface\ water}$ can then be calculated as –

$PEC_{surface\ water}$ = 370 x 0.01/200 x 10 = 0.00185mg/liter equals 1.85µg/liter. The Applicant stated that the emission of active substance is larger than the action limit of < 1µg/liter.

Refinement of the $PEC_{surface\ water}$ was made. The calculation was based on the fact that the medicine is used once every 6 weeks so the value was divided with 42. $PEC_{surface\ water}$ value resulted 0.044µg/liter. The $logK_{OW}$ value is 1.53. A revised ERA was submitted in which a refinement of Fpen according to the "Guideline on the

environmental risk assessment of medicinal products for human use" has been performed. Fpen was calculated based on published prevalence data for the sought indications. The calculated value for PECsurface water using the refined Fpen values for all individual indications fell below the action limit of 0.01 µg/L, as did the summed PECsurface water of all indications combined. This value was calculated as 0.0057 µg/L.

Based on this calculation, and since no other environmental concerns for the active substance carmustine became apparent (especially since the octanol-water partition coefficient of 1.53 was well below the action limit of 4.5), it is concluded that Carmustine Obvius is unlikely to represent a risk for the environment and that ERA studies should be waived.

2.3.3. Discussion on non-clinical aspects

Carmustine is a cell-cycle phase nonspecific antineoplastic agent of nitrosourea type, which exerts tumour cytotoxicity via multiple mechanisms. As an alkylating agent, it can alkylate reactive sites on nucleoproteins, thus interfering with DNA and RNA synthesis and DNA repair. It is able to form interstrand crosslinks in DNA, which prevents DNA replication and transcription. Carmustine undergoes spontaneous nonenzymatic decomposition under physiological conditions to release reactive intermediates with alkylating and carbamoylating activities, which are thought to be responsible for the antineoplastic and toxic activities of carmustine.

The non-clinical overview provides detailed information on *in vitro* and *in vivo* activity, efficacy and pharmacodynamic drug interaction studies in animal models and human tumour cell cultures from the published literature. The safety pharmacology of carmustine has not been demonstrated due to the lack of published data.

Formal non-clinical pharmacokinetic studies have not been conducted and it is considered acceptable for generic application. The non-clinical overview provides comprehensive overview of published information on pharmacokinetics of carmustine, including parameters in different animal species.

The biological half-life of carmustine is short. Intravenously administered BCNU is rapidly degraded to reactive intermediates with a half-life of approximately 15 min in humans. In studies on dogs, using radiolabeled BCNU, approximately 28–30% of the total radioactivity administered was excreted in the urine in 6 h. Pharmacokinetic study in the dog demonstrates a rapid decline of carmustine in the plasma following intravenous injection.

Systemically administered carmustine is distributed to most tissues, including the brain. Carmustine crosses the blood-brain barrier readily, which has been observed in both dogs and monkeys. Carmustine is unstable in aqueous solution and undergoes spontaneous decomposition to release reactive intermediates.

Carmustine is inactivated through enzymatic biotransformation. Excretion is primarily in the urine: most rapid in mice and less rapid in dogs and monkeys.

The range of non-clinical data presented in the dossier is typical for a generic application. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

The CHMP considers that no further non-clinical studies are required.

Following the submission of a revised ERA it is concluded that Carmustine Obvius is unlikely to represent a risk for the environment and that ERA studies should be waived.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Carmustine Obvius and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

Carmustine Obvius 100mg powder and solvent for concentrate for solution for infusion is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Carmustine Obvius containing 100 mg powder and solvent for solution for infusion containing carmustine, the same active substance in the same quantity and in the same dosage form as the reference product.

It is intended for intravenous administration. 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.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of carmustine based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

GCP

N/A

The use of carmustine is well established. The Applicant has provided a justification for not submitting new clinical data (pharmacokinetic/pharmacodynamics studies).

The updated overview included following additional scientific publications on efficacy of carmustine in proposed indications:

Author	Study	Diagnosis	Treatment	Endpoints/outcome
Rao et al. (2005)	North Central Cancer	newly diagnosed Grade 3	carmustine (40 mg/m2/d) on Days 1–3, oral etoposide (50 mg/d) on Days 1–21 and 29–49, and cisplatin	Primary: 23 months survival

	Treatment Group trial 98-72-51 – phase II, single arm, open label	anaplastic astrocytoma (n=29)	(20 mg/m2/d i.v.) on Days 1–3 and 29–31. The regimen was repeated every 8 weeks for three cycles, with conventionally fractionated RT (5000 cGy with a 1000-cGy boost) delivered concurrently with the third cycle	No results provided in Clinical overview, except abstract conclusion - pre-RT chemotherapy with this regimen is insufficiently active in patients with anaplastic astrocytoma
Gill et al. (2008)	Retrospective study	Recurrent embryonal central nervous system (CNS) tumours (medulloblastoma, cerebral neuroblastoma, pineoblastoma, and primitive neuroectodermal tumours) in adults (n=23)	**Conventional dose chemotherapy** (n=13) cisplatin-containing regimens cisplatin (20 mg/m2 on Days 1–5), etoposide (60 mg/ m2 on Days 1–3), and cyclophosphamide (500 mg/m2 on Day 1, every 4–5 weeks); cisplatin (45 mg/m2 on Days 2 and 3) and etoposide (100mg/m2 on Days 1–3, every 4 weeks); single agent cisplatin (60 mg/m2 administered on Day 1, every 3–4 weeks). nitrosourea-containing regimens: lomustine (120 mg/m2 on Day 1), procarbazine (60 mg/m2 on Days 7–20), and vincristine (1.4 mg/m2 on Days 7 and 28, every 6 weeks); and lomustine (120 mg/m2 on Day 1) and procarbazine (60 mg/m2 on Days 7–20, every 6 weeks) **HDC with ASCT** (n=10) Cycle 1 - Thiotepa (200 mg/m2 on Days 25, 24, and 23) and carmustine (100 mg/m2 on Days 25, 24, and 23). ASCT on Day 0 + granulocyte-macrophage–colony-stimulating	Conventional dose chemotherapy: TTP = median 0.58 years OS= median 2.00 years HDC with ASCT TTP = median 1.25 years OS = median 3.47 years Conclusion: When compared with conventional cisplatin-based and/or nitrosourea-

			factor (GM-CSF) at a dose of 5 µg/kg daily beginning on Day 6 Cycle 2 - thiotepa (200 mg/m2 on Days 25, 24, and 23) and carboplatin (400 mg/m2 on Days 25, 24, and 23). ASCT on Day 0 + GMCSF at a dose of 5 µg/kg s.c daily beginning on Day 6 and continued until the ANC was ≥500/µL	based chemotherapy regimens, which have previously been shown to be active in this setting, HDC with ASCT results in prolonged TTP and median survival, with acceptable toxicity.
Gill et al. (2008)	Retrospective study	Recurrent embryonal central nervous system (CNS) tumours (medulloblastoma, cerebral neuroblastoma, pineoblastoma, and primitive neuroectodermal tumours) in adults (n=23)	**Conventional dose chemotherapy** (n=13) cisplatin-containing regimens cisplatin (20 mg/m2 on Days 1–5), etoposide (60 mg/ m2 on Days 1–3), and cyclophosphamide (500 mg/m2 on Day 1, every 4–5 weeks); cisplatin (45 mg/m2 on Days 2 and 3) and etoposide (100mg/m2 on Days 1–3, every 4 weeks); single agent cisplatin (60 mg/m2 administered on Day 1, every 3–4 weeks). nitrosourea-containing regimens: lomustine (120 mg/m2 on Day 1), procarbazine (60 mg/m2 on Days 7–20), and vincristine (1.4 mg/m2 on Days 7 and 28, every 6 weeks); and lomustine (120 mg/m2 on Day 1) and procarbazine (60 mg/m2 on Days 7–20, every 6 weeks) **HDC with ASCT** (n=10) Cycle 1 - Thiotepa (200 mg/m2 on Days 25, 24, and 23) and carmustine (100 mg/m2 on Days 25, 24, and 23). ASCT on Day 0 + granulocyte-	Conventional dose chemotherapy: TTP = median 0.58 years OS= median 2.00 years HDC with ASCT TTP = median 1.25 years OS = median 3.47 years Conclusion: When compared with conventional cisplatin-based and/or

			macrophage–colony-stimulating factor (GM-CSF) at a dose of 5 µg/kg daily beginning on Day 6 Cycle 2 - thiotepa (200 mg/m2 on Days 25, 24, and 23) and carboplatin (400 mg/m2 on Days 25, 24, and 23). ASCT on Day 0 + GMCSF at a dose of 5 µg/kg s.c daily beginning on Day 6 and continued until the ANC was ≥500/µL	nitrosourea-based chemotherapy regimens, which have previously been shown to be active in this setting, HDC with ASCT results in prolonged TTP and median survival, with acceptable toxicity.
Van den Bent et al. (2009)	EORTC Brain Tumour Group Study 26034 - a randomized, controlled, phase II trial	Reccurent glioblastomas after prior radiotherapy (n=110)	**Erlotinib** 150 mg/daily, (n=54) <u>Control arm</u> **TMZ** (n=27) - 200 mg/m2 on days 1 to 5 every 4 weeks in chemotherapy-naïve patients or at 150 mg/m2 on days 1 to 5 every 4 weeks after prior adjuvant chemotherapy, with dose escalation to 200 mg/m2 in the absence of significant toxicity **Or** **BCNU (carmustine)** (n=29) 80mg/m2 on days 1 to 3 every 8 weeks for max 5 cycles. Due to carmustine induced myelosuppression dose was reduced to 60 mg/m2 on days 1 to 3 every 8 weeks	<u>Primary endpoint</u> **6 months PFS**: Erlotinib - 11.4% (95% CI, 4.6% - 21.5%) (median 1.8 months) TMZ/BCNU - 24.1% (median 2.4 months) <u>Secondary endpoints</u>: Partial response Erlotinib – 3.7% (n=2) TMZ/BCNU – 9.6% (n=5) Stable disease: Erlotinib 16.7% (n=9) TMZ/BCNU – 34.6% (n=18)

				6 months OS Erlotinib 57.6% TMZ/BCNU – 58.5 Median OS Erlotinib – 7.7 mo TMZ/BCNU – 7.3
Kong et al. (2010)	Retrospective study to investigate efficacy of adjuvant chemotherapy	Gliomatosis cerebri (=37)	**Chemotherapy (n=19) – TMZ** 200 mg/m2 × consecutive 5 days per month, 3-9 cycles; n=10 **nitrosurea based (BCNU (n=4), PCV**[(procarbazine/lomustine/vincristine] n=5) **Control -Radiotherapy alone (n=18)**	**OS** – Chemotherapy – median 24,2 months (95%CI: 23.4-24.9 months); Control – median 13.1 months (95%CI 10.4-15.9 months) Between patients treated with TMZ and those with nitrosourea-based chemotreatment, there was no significant difference of survival (p > 0.05 by log-rank test) **PFS** Chemotherapy – median 16.0 months (95% CI: 11.7-20.2 months) Control – median 6.0 months (95% CI: 4.9-7.1

				months)
Venur et al. (2015)	Review	Newly diagnosed and recurrent glioblastoma	Cytotoxic chemotherapy with TMZ, TMZ +RT Carmustine polymer wafers Bevacizumab Cilengitide Cytotoxic chemotherapy with TMZ, BCNU, PVC regimen Bevacizumab, lomustine Cediranib Enzastaurin	Recurrent glioblastoma: BCNU following surgery and standard radiotherapy – median TTP =13.3 weeks PFS at 6 months – 17.5%
Blumenthal et al. (2015)	Southwest Oncology Group (SWOG) Study S0001 - Phase III open-label	Newly diagnosed glioblastoma and gliosarcoma (histologically confirmed astrocytoma) (n=183)	**Arm 1** - O6BG + BCNU (reduced dose) plus radiation therapy (RT) (n=90) 40mg/m2 BCNU 6 hours after the administration of 120mg/m2 O6BG intravenously over 1 hour every 6 weeks **Arm 2** - BCNU (standard dose)plus radiation therapy (n=89) BCNU 200 mg/m2 intravenously over 1 hour every 6 weeks. A maximum of seven cycles were allowed Radiation therapy - once per day, 5 days per week	Median OS : O6BG + BCNU = 11 months (95%CI 8 – 13 months) BCNU +RT= 10 months (95%CI 8 – 12 months) PFS: O6BG + BCNU = 4 months (95%CI 4 – 5 months) BCNU +RT= 4 months (95%CI 4 – 5 months) Conclusion: The addition of O6-BG to the standard regimen of radiation and BCNU for treatment of

				newly-diagnosed glioblastoma and gliosarcoma did not offer added benefit and caused additional toxicity. Hypothesis that extrinsic depletion of MGMT renders GBM more sensitive to alkylating therapy with BCNU is not supported

Hodgkin's disease

Author	Study	Diagnosis	Treatment	Endpoints/outcome
Akhtar et al. (2007)	Retrospective, observational cohort study	Primary refractory Hodgkin's lymphoma (n=66)	<u>Salvage chemotherapy</u> -ESHAP (etoposide 40mg/m 2 i.v. over 1–3 h daily for 4 days, solumedrol 500mg i.v. daily for 4 days, cisplatin 25 mg/m2/day i.v. as a continuous infusion over 24 h daily for 4 days and ara-C 2000 mg/m2 i.v. over 2–3 h, following completion of cisplatin on day 5 <u>HDC and ASCT</u> BEAM-BCNU 300 mg/m2 i.v. day -6, etoposide 200 mg/m2 i.v. daily for 4 days on days -5, -4, -3 and -2. Ara-C 200 mg/m2 i.v. q	<u>Post-HDC ASCT Response</u> 76% CR = 53% (n=35) PR =21% (n=14) NR/SD -5% (n=3) PD -15% (n=10) <u>OS</u> -64%, median 57 months EFS – 36% 33% died due to disease <u>Conclusion:</u> HDC ASCT is considered standard option

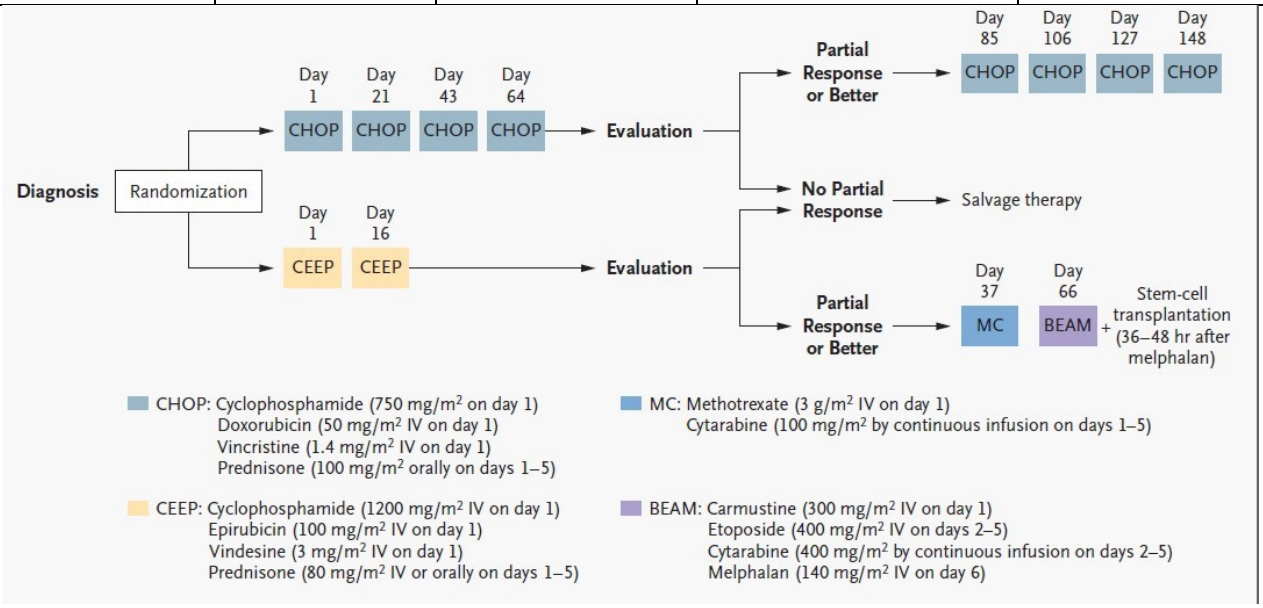
			12 h (twice a day) daily for 4 days -5, -4, -3 and -2. Melphalan 140mg/m 2 i.v. on day -1). Stem cell reinfusion was performed on day 0 and G-CSF 300 mg s.c. twice a day was started from day +1 until engraftment	
William et al. (2013)	Retrospective cohort study	Hodgkin's lymphoma (n=225)	<u>Conditioning regimen</u> prior ASCT: CBV (cyclophosphamide, carmustine, and etoposide) OR BEAM (carmustine, etoposide, cytarabine, and melphalan)	At a median follow-up of 8 (range, 2-26) years, 225 patients were alive and disease-free 2 years after ASCT **At 5 years**: <u>PFS</u> BEAM =92% CBV =73% <u>OS</u> BEAM = 95% CBV =87% **At 10 years**: <u>PFS</u> BEAM =79% CBV =59% <u>OS</u> BEAM = 84% CBV =66% Conclusion: BEAM is associated with lower risk of progression and longer survival
Czyz et al.	Retrospective	Refractory or relapsed	Salvage chemotherapy	10 year OS = 76%

(2013)	cohort study	Hodgkin's lymphoma (n=132; Refractory n=89; relapsed n=43) Median follow-up 68 months	The high-dose modified BEAM regimen: carmustine (total dose 300 mg/m2), etoposide (total dose 800 mg/m2), cytarabine (total dose 6,000 mg/m2), melphalan (total dose 140 mg/m2) and dexamethasone (total dose 168 mg/m2)	PFS=66% Conclusion: Patients with relapsed or refractory HL without adverse prognostic factors may be cured with HDT and ASCT
Sobol et al. (2014)	Prospective study	Refractory or relapsed Hodgkin's lymphoma (n=31) Median follow-up 7 years	Attenuated dose BEAM conditioning: BCNU (300 mg/m 2 IV once) on day -6, etoposide (100 mg/m 2 IV daily) and cytarabine (100 mg/m 2 IV BID) on days -5 through -2 and melphalan (140 mg/m2 IV once) on day -1.	Response: CR=81% (n=25) PR= 3 patients (subsequently died) RD = 2 patients At 7 years PFS= 36% (95%CI 19 – 54%) OS = 42% (95%CI 23 – 59%) NRM =18% (95%CI 8 – 37%).

Non-Hodgkin's lymphomas

Author	Study	Diagnosis	Treatment	Endpoints/outcome
Salar et al. (2001)	Retrospective study – 35 Spanish hospitals	Clinically aggressive NHL (diffuse large cell lymphoma- DLCL) (n=395) Median follow-up 28 months	Radiochemotherapy: cyclophosphamide (CY) (60 mg/kg for 2 consecutive days) and TBI (9–12 Gy in 1-4 fractions) (n=47) Only chemotherapy:	At 8 years: OS Overall – 51% (95% CI 46–56%) BEAM or BEAC =58% (95% CI 50–66%)

			BEAM (n=164), BEAC (n=145) CBV (n=39). Colony-stimulating factors (n=273) (69%)	CBV =40% (95%CI 24–56%) CY-TBI =31% (95% CI 18–44%) <u>DFS</u> Overall - 43% (95% CI 38–48%) <u>Conclusion:</u> Preparative regimens (HDC) consisting of chemotherapy-only seem more efficacious than CY-TBI as conditioning for DLCL, as indicated by improved OS, DFS and RFS.
Milpied et al. (2004)	Multicenter randomized trial	Previously untreated, histologically proved aggressive lymphoma (n=n=197) Median follow-up 4 years	HDC+ASTC (n=98): CEEP; MC; BEAM CHOP (n=99) (see below)	<u>Event free survival rate</u> median: HDC =55% CHOP =37% <u>5 year survival rate</u>: HDC =74% CHOP= 44% Overall response rate (RR); CR: HDC= 91%; 81% CHOP= 81%; 62% <u>Conclusion</u>: High-dose chemotherapy with autologous stem-cell support is superior to CHOP in adults with disseminated

				aggressive lymphoma
				
Sharma et al. (2013)	Retrospective study	Relapsed or refractory NHL or HL (N=51) Median follow-up =36.6 months	BEAM (n=34) (NHL=26) LEAM (n=17)	2 year OS: BEAM = 61.7% LEAM = 62.7% EFS: BEAM =44.6% LEAM =41.1% <u>Conclusion</u>: Two regimens, BEAM and LEAM are equivalent for early peritransplant outcomes and survival
Auger_Quittet et al. (2014)	Non-comparative meta -analysis	relapsed/refractory diffuse large B-cell lymphoma	Z-BEAM =BEAM + radioimmunotherapy with ^{90}Y-ibritumomab tiuxetan (Zevalin)	2 years OS 84.5% (n=325) 2 years PFS 67.2% (n=285)
Kirshey et al. (2014)	prospective, open-label, single-arm	Aggressive NHL (aNHL): diffuse large B-cell	Salvage/mobilization regimen consisted of R-Dexa-BEAM: rituximab	Primary – PFS: aNHL = median –

	multicentre phase II study	lymphoma 55, mantle cell lymphoma 7, follicular lymphoma (FL) grade 3: 5, indolent Lymphoma (iNHL): FL grade 1–2: 29, marginal zone lymphoma 6, Immunocytoma 1 (n=103)	375 mg/m² day 1, dexamethasone 24 mg t.i.d p.o., days 1–10; carmustine 60 mg/m² i.v., day 2; etoposide 75 mg/m² i.v., days 4–7; cytarabine 200 mg/m² b.i.d i.v., days 4–7 in 2 doses; melphalan 20 mg/m² i.v., day 3. For high dose radio/chemotherapy, two different conditioning regimens were defined in the protocol: chemo-radiotherapy R-TBI/Cy consisted of rituximab 375 mg/m² i.v. days -7, -2, fractionated total body irradiation with 12 Gy, days -6 to -4; and cyclophosphamide 60 mg/kg bodyweight 9bw0 i.v., days -3 to -2. The chemotherapy protocol used for conditioning was R-BEAM (Caballero et al, 1997): rituximab 375 mg/m² i.v. days -8, -2, carmustine 300 mg/m² i.v., day -7; cytarabine 400 mg/m² b.i.d. i.v., days -6 to -3; etoposide 200 mg/m² i.v. b.i.d., days -6 to -3; melphalan 140 mg/m² i.v., day -2	0.83 years iNHL =median 3.7 years overall response rate after salvage therapy was 62% for aNHL and 78% for iNHL patients. <u>Conclusion</u>: R-DexaBEAM followed by HDT can be considered a valid salvage option for NHL.
Caimi et al. (2015)	Retrospective study	Median follow-up 39.4 months	HDC+autologous HCT: BEAM (carmustine, 300 mg/m2, etoposide,	<u>4-year OS rates</u> BEP =80.4%

			cytarabine, and melphalan) (n=64) BEP (carmustine 600 mg/m2, etoposide, and cisplatin) (n=65)	BEAM = 72.3%, No statistically significant differences in the OS and PFS of non-Hodgkin's lymphoma or Hodgkin lymphoma. <u>Conclusion:</u> BEP is a valid alternative to BEAM in autologous HCT. Although associated with more renal and electrolytic toxicities, BEP results in similar disease control and long-term survival as BEAM
Truelove (2015)	Retrospective study	Aggressive Non-Hodgkin Lymphoma (n=46)	BEAM-Campath - conditioned allogeneic SCT	<u>1 year</u> PFS = 41% OS =54% <u>5 year</u> PFS = 36% OS = 42%

Exemption

Bioequivalence testing with the reference product is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1) which states that "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".

The pharmaceutical form and mode of administration as well as the qualitative and quantitative composition of Carmustine Obvius 100 mg powder and solvent for solution for infusion is the same as of the reference product Carmubris 100 mg, powder and solvent for solution for infusion (Carmubris-Trockenstechampulle mit Lösungsmittel, 100 mg (Emcure Pharma UK, Ltd., UK)).

The use of carmustine is well established. The Applicant has provided a justification for not submitting new clinical data.

2.4.2. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

Carmustine is a well-known active substance. As the product is administered as an aqueous i.v. solution the Applicant is not required to submit a bioequivalence study or to provide the results of clinical trials.

Clinical overview on the clinical pharmacology is adequate. The PK of carmustine is well known and satisfactory described by the Applicant. Overview based on literature review is appropriate and acceptable. Section 5.2 of SmPC is acceptable and in line with the originator's.

According to the ESMO guidelines current standard of care for patients with Glioblastoma Multiforme up to age 70 or fit elderly patients older than 70 years is a concomitant and adjuvant temozolomide in addition to radiotherapy. The Applicant has updated Clinical overview and included 8 publications covering period 2004-2015 regarding efficacy of carmustine in brain tumours.

The Applicant updated the Clinical overview with 4 publications covering period 2007-2014 regarding efficacy of carmustine in Hodgkin's disease. Referred publication by William et al (Clin Lymphoma Myeloma Leuk 13 (4), 417-423. 2013 Jun 15) regarding impact of conditioning regimen on outcome of 2-year Disease-Free Survivors of autologous stem cell transplantation for Hodgkin lymphoma was submitted to discuss the use of the product in this context. The Applicant also updated Clinical overview and included 10 publications covering period 2001-2015 regarding efficacy of carmustine in Non-Hodgkin's lymphomas.

The indications with reference to Hodgkin's and non-Hodgkin's lymphomas are very broad considering the current clinical use of the product, i.e. as part of a conditioning regimen for haematopoietic stem cell transplantation (high dose chemotherapy/mini-BEAM) which is a standard treatment option for relapsed/refractory disease.

Pulmonary toxicity has been observed in up to 30% of patients. In cases where pulmonary toxicity started early (within 3 years of treatment), pulmonary infiltrates and/or pulmonary fibrosis occurred, some of which were fatal. The patients were between 22 months and 72 years old. Risk factors include smoking, respiratory disease, existing radiographic abnormalities, sequential or concomitant thoracic radiation, as well as combination with other active substances that can cause lung damage. The incidence of adverse reactions is probably dose-related; cumulative doses of 1200-1500 mg/m^2have been associated with an increased likelihood of pulmonary fibrosis. During treatment, lung function tests (FVC, DLCO) should be performed regularly. Patients showing a baseline value of <70% of expected forced vital capacity or carbon monoxide diffusion capacity in these tests are at particular risk.

Based on the conclusions of the results from the published pilot study of a French Society of Pediatric Oncology (SFOP) (Chastanger et al. 2007) in view of the high risk of pulmonary toxicity Carmustine Obvius should not be used in children and adolescents due to the high risk of pulmonary toxicity (See SmPC section 4.4, 4.8. and 4.3).

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. Long-term follow-up observation of 17 patients who survived brain tumours in childhood showed that 8 of them succumbed to pulmonary fibrosis. Two of these 8 fatalities occurred within the first 3 years of treatment and 6 of them occurred 8-13 years after treatment. The median age of patients who died on treatment was 2.5 years (1-12 years), the

median age of long-term survivors on treatment was 10 years (5-16 years). All patients younger than 5 years of age at the time of treatment died from pulmonary fibrosis; neither the carmustine dose nor an additional vincristine dose or spinal radiation had any influence on the fatal outcome. All remaining survivors available for follow-up were diagnosed with pulmonary fibrosis. Pulmonary toxicity also manifested in the post-marketing phase as pneumonitis and interstitial lung disease.

The European Medicines Agency has completed a review of carmustine containing medical products pursuant to Article 107b of Directive 2001/83/EC (PSUSA/00010349/201504). The Agency's Coordination Group of Mutual Recognition and Decentralised Procedures for Human use (CHDh) on December 16, 2015 has adopted a position on the PSUR for carmustine (powder and solvent for solution for infusion) - EMA/CMDh/819842/2015 – requesting update of product information to update Section 4.8 of the SmPC and Section 4 of the PL with information on pulmonary toxicity. There have been also publications regarding follow-up data for the patients up to 25 years from the date of carmustine treatment from a long-term follow-up study. (O'Driscoll et al. Chest, Volume107, Issue 5, May 1995, Pages 1355–1357 and Lohani et al. *Chest.* 2004;126(3):1007.)

Further, it is recommended that –although not generally requested for generics- periodic safety updates for Carmustine Obvius will be submitted as per the frequencies in the EURD list.

2.4.4. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Carmustine Obvius and as the active substance does not differ in properties with regards to safety and efficacy of the reference product was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	- Pulmonary toxicity (Including in paediatric population) - Bone marrow toxicity - Hepatotoxicity - Nephrotoxicity - Gastrointestinal toxicity including nausea and vomiting - Injection site reaction including extravasation hazard - CNS toxicity
Important potential risks	- Secondary malignancies - Embryotoxicity and teratogenicity - Impaired fertility
Missing information	- Use during lactation

Pharmacovigilance plan

There are no additional pharmacovigilance activities for this medicinal product.

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product, which is in line with the reference medicinal product.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks:		
Pulmonary toxicity (including in paediatric population)	SmPC sections: 4.2, 4.4, 4.5, 4.8, 4.9, 5.1 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Bone marrow toxicity	SmPC sections: 4.2, 4.3, 4.4, 4.8, 4.9 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Hepatotoxicity	SmPC sections: 4.4, 4.8, 4.9 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Nephrotoxicity	SmPC sections: 4.2, 4.3, 4.4, 4.8 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Gastrointestinal toxicity including nausea and vomiting	SmPC section: 4.8 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Injection site reaction including extravasation hazard	SmPC sections: 4.2, 4.8, 6.6 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
: CNS toxicity	SmPC section: 4.8 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Important potential risks		
Secondary malignancies	SmPC section: 4.4 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Embryotoxicity and teratogenicity	SmPC sections: 4.6, 4.8, 5.3 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.
Impaired fertility	SmPC section: 4.6, 4.8, 5.3 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.

Missing information		
Use during lactation	SmPC section: 4.3, 4.6 The legal status of the product is: prescription only.	Currently available data does not support the need for additional risk minimisation activities.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.4 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Carmustine BiCNU (Carmubris). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of carmustine [100 mg, powder and solvent for solution for infusion]. The reference product Carmubris (carmustine) is indicated for Brain tumors - glioblastoma, Brain-stem gliomas, medulloblastoma, astrocytoma and Ependymoblastomas; Second line treatment for NHL and Hodgkin's disease; Tumours of the gastrointestinal system; Malignant melanoma in combination with other effective anti-neoplastic medicinal products; Multiple myeloma (in combination with a glucocorticoid such as prednisone).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the provided clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Carmustine Obvius is not similar to Iclusig, Xaluprine , Imbruvica, Revlimid, Torisel , Ledaga, Venclyxto, Adcetris , Gazyvaro, Arzerra, Blincyto and Besponsa within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 (see Appendix 1).

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Carmustine Obvius is favourable in the following indications:

Carmustine is effective in 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- Please note this constitutes a deviation from the MA of the originator product (medical prescription).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result ofan important (pharmacovigilance or risk minimisation) milestone being reached.

References

DGHO: Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. Pressemittelung. Weltweit nur ein Hersteller und jetzt dramatische Preissteigerung bei Krebsmedikament. Berlin, 30. Januar 2015. http://www.dgho.de/informationen/presse/pressemitteilungen/weltweit-nur-ein-hersteller-und-jetzt-dramatische-preissteigerung-bei-krebsmedikament

Guittard P. Lettre d'information destinée aux pharmaciens hospitaliers et prescripteurs Concernés. Cournon d'Auvergne, le 24 novembre 2014.

Guittard P. Lettre d'information destinée aux pharmaciens hospitaliers. Objet: rupture de stock en BICNU® (carmustine). Cournon d'Auvergne, le jeudi 27 août 2015.

NHS (Surrey, West Sussex and Hampshire Cancer Network): Taylor S, Tucker C, Laurie A. Mini-BEAM. Version 4. Review date: May 2015.

Schmitz N, Pfistner B, Sextro M, et al; German Hodgkin's Lymphoma Study Group; Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. 2002 Jun 15;359(9323):2065-71.

Tirelli U, Berretta M, Spina M, Michieli M, Lazzarini R. Oncologic drug shortages also in Italy. Eur Rev Med Pharmacol Sci. 2012 Jan;16(1):138-9