24 July 2014
EMA/552423/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Busulfan Fresenius Kabi

International non-proprietary name: Busulfan

Procedure No. EMEA/H/C/002806

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 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Oncology Plc. submitted on 2 August 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Busulfan Fresenius Kabi, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 October 2012.

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 for which a Marketing Authorisation is or has been granted in the Union 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:

Busulfan Fresenius Kabi followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option.

Busulfan Fresenius Kabi followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients.

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.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

The market exclusivity of the chosen reference product expired on 11 July 2003.

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.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Busilvex 6 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Pierre Fabre Médicament
- Date of authorisation: 09-07-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/03/254/001

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

- Product name, strength, pharmaceutical form: Busilvex 6 mg/ml concentrate for solution for infusion
- Marketing authorisation holder: Pierre Fabre Médicament
- Date of authorisation: 09-07-2003
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/03/254/001

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Fresenius Kabi Oncology Plc
Lion Court, Farnham Road
Bordon
Hampshire
GU35 0NF United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 2 August 2013.
- The procedure started on 21 August 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2013.
- During the PRAC meeting on 05 December 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 16-19 December 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 December 2013
- CHMP adopted a report on similarity of Busulfan Fresenius Kabi with Tepadina on 19 December 2013.
- The summary report of the inspection carried out at the following site Fresenius Kabi Oncology Ltd between 14-17 April 2014 was issued on 30 June 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 March 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 April 2014.
- During the PRAC meeting on 08 May 2014, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 19- 22 May 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 June 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 01 July 2014.
- During the PRAC meeting on 10 July 2014, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 21-24 July 2014, 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 Busulfan Fresenius Kabi.

2. Scientific discussion

2.1. Introduction

Busulfan Fresenius Kabi is a generic medicinal product of Busilvex which has been authorised in the EU since 09 July 2003.

The active substance of Busulfan Fresenius Kabi is busulfan an alkyl sulfonate (L01AB01) and a potent cytotoxic agent and a bifunctional alkylating agent. In aqueous media, release of the

methanesulphonate groups produces carbonium ions which can alkylate DNA, thought to be an important biological mechanism for its cytotoxic effect.

The safety and efficacy profile of busulfan has been demonstrated in several clinical trials details of which can be found in the EPAR for Busilvex. In addition, there is extensive post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Busilvex, summary of the clinical data of busulfan is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

Busulfan Fresenius Kabi is administered intravenously and is 100% bioavailable; therefore, a bioequivalence study versus the reference product Busilvex was not required.

The approved indication is:

Busulfan followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option.

Busulfan followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients

The indication proposed for Busulfan Fresenius Kabi is the same as authorized for the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 6 mg/ml of busulfan as active substance.

Other ingredients are: dimethylacetamide and macrogol 400.

The product is available in clear colourless glass vials (type I) with teflon faced rubber stopper and sealed with aluminium flip-off seal.

2.2.2. Active substance

General information

The chemical name of busulfan is Butane-1, 4-diyl di(methanesulfonate); 1,4-Butanediol dimethanesulfonate.

The active substance is described in the Ph Eur as white or almost white crystalline powder which is very slightly soluble in water and in ethanol and freely soluble in acetone and in acetonitrile.

As there is a monograph of busulfan in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for busulfan 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.

Specification

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. Monograph except the specification for solubility

Stability

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The stability data supports the retest period.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The purpose of the development study was to develop a generic essentially similar to the reference product, Busilvex 6 mg/ml concentrate for solution for infusion. No bioequivalence study was performed and the justification given is that the product is to be administered as an intravenous solution, containing the same active substance and excipients in the same concentration as the reference product.

The excipients used in the formulation are qualitatively and quantitatively similar to those used in the reference product. The selected grade of dimethylacetamide complies with the Ph Eur monograph. The selected grade of macrogol (polyethylene glycol) is multicompendial. Busulfan Fresenius Kabi must be diluted with 0.9% sodium chloride injection or 5% glucose injection. Dilution fluid compatibility studies were carried out. Compatibility with both solutions was demonstrated.

The following characteristics of the reference product were studied in order to establish the target profile for the generic product: dosage form, dosage strength, route of administration, container closure, storage conditions, shelf life, dilution fluids, and stability after dilution. It was concluded that the solubility, assay, impurities, residual solvents and water content are considered as critical quality attributes that can be significantly affected by the formulation used and the process design. A risk assessment was conducted on these parameters as part of the pharmaceutical development studies.

Based on the targeted product profile and the risk assessment made, it was concluded that the following studies should be carried out: selection of excipients, effect of water content, effect of headspace gas, light sensitivity, selection of filter and filter compatibility, compatibility with equipment and stainless steel container. Details of the studies performed were provided and found satisfactory.

The manufacturing process comprises of bulk manufacturing, aseptic filtration and filling. The choice of selection of manufacturing temperature, sterilisation method together with other critical process parameters was justified.

The primary packaging proposed for Busulfan Fresenius Kabi is a clear colourless glass vial (type I) with teflon faced rubber stopper and sealed with aluminium flip-off seal. Compatibility with the primary packaging material chosen is shown and a photo stability study has been presented. A stopper compatibility study has been carried out and it was concluded that both the glass vial and the stopper are compatible with the drug product. Container closure integrity testing of the sealed container has

been carried out and the test data sheets. The proposed container closure system is commonly used for parenterals. It is in line with the requirements specified in the Ph Eur.

Manufacture of the product and process controls

The manufacturing process comprises of bulk manufacturing, aseptic filtration process, aseptic filling, stoppering, sealing and washing, optical inspection and washing.

Sterilizing grade filters are used for filtration and sterilization. Integrity testing is performed pre and post filtration by the bubble point test. The filters are discarded after post-filtration integrity testing

Major steps of the manufacturing process have been validated in three commercial scale batches by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for appearance, identification (TLC, HPLC), degradation products, extractable volume (Ph Eur), water (Ph Eur), sterility (Ph Eur), bacterial endotoxins (Ph Eur), impurities (HPLC), particulate contamination (Ph Eur), assay (HPLC), and colour absorbance (UV).

Batch analysis results in three batches of commercial scale confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of 3 production batches of finished product stored under long term conditions for 18 months (1 batch) and 17 months (2 batches) at 5ºC ± 3ºC (upright and inverted) and for up to 6 months under accelerated conditions at 25ºC ± 2ºC / 60% ± 5% RH according to the ICH guidelines were provided. The batches of Busulfan Fresenius Kabi are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the following tests: appearance, water content, degradation products, impurities, assay, colour absorbance, particulate contamination, sterility, bacterial endotoxins and seal integrity.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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. Recommendation(s) for future quality development

N/A

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.

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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Busulfan Fresenius Kabi 6 mg/ml manufactured by Fresenius Kabi is considered unlikely to result in any significant increase in the combined sales volumes for all busulfan containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion and conclusion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of busulfan are well known. No non-clinical data are submitted with this application. Published literature has been reviewed and is considered of suitable quality.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), justification for not providing ERA is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

There were no clinical studies conducted in support of this application.

Exemption

The proposed composition of Busulfan Fresenius Kabi 6 mg/ml concentrate solution for infusion is identical to the reference product. It is for intravenous use, containing the same active substance in the same concentration as the innovator product Busilvex. It is also similar to the reference product in terms of strength, route of administration, dosage form and physico-chemical characteristics. According to the CPMP guideline “Note or Guidance on the Investigation of Bioequivalence” (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), there is no requirement for a bioequivalence study for such products.

2.4.2. Discussion on clinical aspects

The applicant has not conducted any clinical studies for the application. Instead appropriate justification is provided to support the claim that the proposed product is essentially similar to the originator. The qualitative composition is identical with that of the originator and the applicant’s proposed SmPC is compliant with the reference product with no novel claims or dose recommendations.

2.4.3. Conclusions on clinical aspects

The CHMP considers Busulfan Fresenius Kabi 6 mg/ml concentrate solution for infusion approvable from the clinical point of view.

2.4.4. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.5. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

The Applicant identifies the following safety concerns as shown in the table.

Table: Summary of safety concerns

Important Identified Risks	- Myelosuppression (Neutropenia with/without infection, Thrombocytopenia, Anaemia, Pancytopenia) - Venooclusive liver disease - Seizures - Interstitial pulmonary fibrosis - Reproductive toxicity - Lens disorders/cataracts - Second malignancies
Important Potential Risks	- Cardiac tamponade
Missing information	- Use in patients with hepatic impairment - Use in patients with renal impairment - Use in the elderly - Use in obese children and adolescents

Pharmacovigilance plan

The Applicant has provided the following table for the summary of the Pharmacovigilance Plan:

Table: Overview of planned pharmacovigilance actions

Safety Concern	**Proposed Pharmacovigilance Activities (only routine)**
Important Identified Risks	
Myelosuppression (neutropenia with/without infection, thrombocytopenia, anaemia, pancytopenia)	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Venooclusive liver disease	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Seizures	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Interstitial pulmonary fibrosis	- Single AE report analysis

	- Signal detection, Aggregate Reports - Review in PSURs
Reproductive toxicity	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Lens disorders/cataracts	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Second malignancies	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Important Potential Risks	
Cardiac tamponade	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Missing Information	
Use in patients with hepatic impairment	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Use in patients with renal impairment	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Use in elderly	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs
Use in obese children and adolescents	- Single AE report analysis - Signal detection, Aggregate Reports - Review in PSURs

Risk minimisation measures

According to the Applicant, no additional risk minimization activities have been identified for the reference medicinal product. The Applicant has provided the following table for the summary of the Risk Minimisation Measures:

Table: Summary table of Risk Minimisation Measures

Safety Concern	Proposed Risk Minimisation Measures (only routine)
Important Identified Risks	
Myelosuppression (neutropenia with/without infection, thrombocytopenia, anaemia, pancytopenia)	Guidance in SPC Section 4.4 “special warnings and precautions for use” and Section 4.8 “Undesirable effects”
Venooclusive liver disease	Guidance in SPC Section 4.4 “special warnings and precautions for use” and Section 4.8 “Undesirable effects”
Seizures	Guidance in SPC Section 4.4 “special warnings and precautions for use” and Section 4.8 “Undesirable effects”
Interstitial pulmonary fibrosis	Guidance in SPC Section 4.4 “special warnings and precautions for use” and Section 4.8 “Undesirable effects”
Reproductive toxicity	Guidance in SPC Section 4.4 “special warnings and precautions for use”, Section 4.6 “fertility, pregnancy and lactation”, and Section 4.8 “Undesirable effects”
Lens disorders/cataracts	Guidance in SPC Section 4.8 “Undesirable effects”
Second malignancies	Guidance in SPC Section 4.4 “special warnings and precautions for use”.
Important Potential Risks	
Cardiac tamponade	Guidance in SPC Section 4.4 “special warnings and precautions for use”.
Missing Information	
Use in patients with hepatic impairment	Guidance in SPC Section 4.2 “Posology and method of administration”, Section 4.4 “Special warnings and precautions for use” and Section 4.8 “Undesirable effects”
Use in patients with renal impairment	Guidance in SPC Section 4.2 “Posology and method of administration”, Section 4.4 “Special warnings and precautions for use” and Section 4.8 “Undesirable effects”
Use in elderly	Guidance in SPC Section 4.2 “Posology and method of administration”.
Use in obese children and adolescents	Guidance in SPC Section 4.2 "Posology and method of administration"

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

3. Benefit-Risk Balance

This application concerns a generic version of busulfan concentrate for solution for infusion. The reference product Busilvex is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option followed by cyclophosphamide (BuCy2) and as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients followed by cyclophosphamide (BuCy4) or melphalan (BuMel). 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 did not contain new data either on the pharmacokinetics and pharmacodynamics nor on the efficacy and safety of the active substance; the applicant's 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. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Busulfan Fresenius Kabi is not similar to Tepadina within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Busulfan Fresenius Kabi indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option followed by cyclophosphamide (BuCy2) and as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is favourable and 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)

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and 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 of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.