Public Assessment Report

Scientific discussion

Etoposide Fresenius Kabi 20 mg/ml, concentrate for solution for infusion

(etoposide)

NL/H/2469/001/DC

Date: 16 September 2014

This module reflects the scientific discussion for the approval of Etoposide Fresenius Kabi 20 mg/ml. The procedure was finalised on 13 March 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Etoposide Fresenius Kabi 20 mg/ml, concentrate for solution for infusion from Fresenius Kabi Oncology Plc.

The product is indicated in adults for the management of:

- resistant non-seminomatous testicular tumours in combination with other chemotherapeutic agents
- small cell lung cancer, in combination with other chemotherapeutic agents
- acute monoblastic leukaemia (AML M5) and acute myelomonoblastic leukaemia (AML M4) when standard induction therapy has failed (in combination with other chemotherapeutic agents).

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the historical innovator product Vepesid 20 mg/ml, concentrate for solution for infusion (NL License RVG 08542), which was registered in the Netherlands by Bristol Myers Squibb in 1981. This MAH chose to withdraw the authorisation in 2008.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Etoposide Fresenius Kabi 20 mg/ml is a clear, light yellow to pale yellow solution with no particulate matter with pH between 3.0 and 4.0.

The concentrate is packed in type I, clear, moulded glass vials of 5 ml, 10 ml, 30 ml and 50 ml closed with a 20 mm bromobutyl rubber closure sealed with a 20 mm flip-off Aluminium overseal (green, blue, red and yellow respectively).

The excipients are: macrogol 300, polysorbate 80 (E433), benzyl alcohol (E1519), ethanol, anhydrous citric acid (E 330).

II.2 Drug Substance

The active substance is etoposide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder, which is practically insoluble in water, sparingly soluble in methanol, slightly soluble in alcohol and in dichloromethane.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The MAH applies the specifications from the Ph. Eur. monograph with the additional CEP requirements. Batch analytical data demonstrating compliance with this specification have been provided for 2 batches.

Stability of drug substance
At least 8 batches have been stored for 5 years, and stability testing is currently continued on more batches. The MAH applies a re-test period of 12 months, which is justified based on the provided data.

II.3 Medicinal Product

Pharmaceutical development
The development is strongly based on the reference medicinal product Vepesid 20 mg/ml, concentrate for solution for infusion of Bristol-Myers Squibb, which is no longer on the market in the EU. The generic formulation is an injectable dosage form having the same pharmaceutical form as Vepesid 20 mg/ml. It also has the same qualitative and quantitative composition in terms of the active substance. It has been demonstrated that terminal sterilization by heat is not possible due to and considering that the solution is a non-aqueous solution. The double sterilizing filtration procedure of the bulk solution is performed according to GMP state of art.

Polysorbate 80 is used as an excipient in Etoposide Fresenius Kabi. Polysorbate 80 can be used for parenteral products comprising a drug substance that is insoluble in water or has a very low solubility, to create a formulation based on formation of micelles, *i.e.* very small spheres consisting of a drug substance core and a bipolar polysorbate 80 outer layer. Micelle formation occurs in the finished drug product and could potentially have an impact on pharmacokinetics and bioavailability of etoposide. However, based on critical micellar concentration (CMC) studies conducted by the MAH and the available literature data, it was concluded that polysorbate 80, at the concentration used in the proposed formulation, does not affect the pharmacokinetics of solubilised etoposide, *i.e.* that micelles do not play a role after infusion and dilution into the bloodstream. Therefore, also considering that the method of administration is the same, the qualitative composition is similar compared to the reference product and the administered dose is identical, no bioequivalence study is required.

Manufacturing process
A common bulk solution for Etoposide Fresenius Kabi 20 mg/ml concentrate for solution for infusion is prepared which is then split into individual fill volumes of 100 mg/5 ml, 200 mg/10 ml, 500 mg/25 ml, and 1000 mg/50 ml presentation. Usual manufacturing steps of sanitation and sterilization of equipment, sterilization/ depyrogenation of primary packaging materials, preparation of bulk solution of etoposide, filtration of bulk solution, aseptic filling, closing and sealing of vials, cleaning of the sealed vials, visual inspection of the sealed vials, visual inspection of the sealed vials, and final packaging and labelling of drug product, are adequately described in detail.
A prospective process validation has been performed on three bulk batches, and each bulk batch was used to fill four different vial sizes i.e. 5 ml, 10 ml, 25 ml in 30 ml and 50 ml vials.
On the basis of the validation results, it is concluded that the solution content is uniform for top, middle and bottom layers for all process validation batches.

Control of excipients
All excipients including the protective gas nitrogen comply with the respective Ph. Eur. monographs.
Also all test procedures are according to these monographs, obviating the need of validation.

Quality control of drug product
Drug product specifications are applied on appearance, identification, extractable volume, pH, alcohol content, benzyl alcohol content, assay, related compounds, benzaldehyde, bacterial endotoxins, sterility, sub-visible particles, colour and seal integrity test. Related compounds (and other parameters) requirements are based either on the BP 2011 monograph on Sterile Etoposide Concentrate or the USP monograph on Etoposide Injection, which is acceptable.
Batch analysis results are provided for the validation batches: 3 bulk batches filled out into four different vial sizes.

Stability of drug product
For the unopened vials 6 months accelerated and 24 months long-term stability data are available, with stability results meeting the set requirements, both at upright and inverted positions. Herewith a shelf life of 24 months can be granted. The finished product was found stable under light exposure.
However, the statement of the reference medicinal product has been adopted: “Do not freeze. Store in the original package, in order to protect from light."

Etoposide should not be used without diluting. For the diluted solutions all stability results at 0-8-24-48 hours for the dilutions with 0.9% NaCl intra-venous infusion or 5% glucose intravenous infusion, both with 0.2 mg/ml and 0.4 mg/ml etoposide, met the set requirements. In-use stability of the diluted solution is stated in the SmPC as up to 24 hours at 15°C to 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Etoposide Fresenius Kabi 20 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Etoposide Fresenius Kabi 20 mg/ml is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Vepesid 20 mg/ml. Reference is made tot the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Etoposide is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

No bioequivalence study has been submitted for this parental application. Etoposide Fresenius Kabi 20 mg/ml, as well as the innovator formulation contains polysorbate 80 at equal amounts (80 mg/ml). According to the Guideline on the investigation of Bioequivalence (CPMP/QWP/EWP/1401/98/Rev 1), a micellar formulation may still be eligible for biowaiver if rapid disassembly of the micelle on dilution occurs, the method and rate of administration is the same as the originator and the excipients do not affect the disposition of the drug substance. This has been sufficiently demonstrated. For Etoposide Fresenius Kabi, the method of administration is the same and the qualitative composition is similar compared to the reference product and the administered dose is identical. No bioequivalence study is required.

IV.3 Risk Management Plan

The MAH has not submitted a risk management plan, as this was not required at the time of application. The MAH proposed that routine pharmacovigilance activities are sufficient and that no additional risk minimisation activities are required. This is considered acceptable.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Vepesid 20 mg/ml. No new clinical studies were conducted. Based on in-vitro and literature data, the MAH sufficiently justified that the pharmacokinetic profile of the product will be similar to the pharmacokinetic profile of this reference product. The pharmacovigilance system is acceptable. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A combination of bridging to a previously user tested package leaflet (PL) for Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion and a focus test was performed to demonstrate the readability for Etoposide Fresenius Kabi 20 mg/ml concentrate for solution for infusion.

The focus test was conducted to address those aspects of the Etoposide 20 mg/ml PL which were not addressed in the bridging report.
The MAH concluded that that the package leaflet for Etoposide 20 mg/ml concentrate for solution for infusion meets the necessary guidance for readability/focus testing as outlined by European Council and MHRA guidance.

Although this is not a straightforward approach, as the texts of parent and daughter PLs are quite different and they concern different types of oncolytics (oxaliplatin belonging to the group of platinum compounds and etoposide to podophyllotoxin derivatives, and both used for different types of cancer), the impression that overall readability is good, was accepted. The bridging report and focus test submitted by the MAH have been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Etoposide Fresenius Kabi 20 mg/ml has a proven chemical-pharmaceutical quality and is a generic form of Vepesid 20 mg/m concentrate for solution for infusion. Vepesid is a well-known medicinal product with an established favourable efficacy and safety profile

No bioequivalence study was deemed necessary, as all conditions for granting a biowaiver have been fulfilled.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Etoposide Fresenius Kabi 20 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 March 2014.

Etoposide Fresenius Kabi 20 mg/ml concentrate for solution for infusion was authorised in the Netherlands on 12 June 2014.

There were no post-approval commitments made during the procedure.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached