CBG MEB

Public Assessment Report

Scientific discussion

Gemcitabine Fresenius Kabi 38 mg/ml concentrate for solution for infusion

(gemcitabine hydrochloride)

NL/H/2447/002/DC

Date: 23 March 2015

This module reflects the scientific discussion for the approval of Gemcitabine Fresenius Kabi 38 mg/ml concentrate for solution for infusion. The procedure was finalised at 15 October 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 Gemcitabine Fresenius Kabi 38 mg/ml concentrate for solution for infusion, from Fresenius Kabi Oncology Plc.

The product is indicated for:

- the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
- treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
- in combination with cisplatin, as first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
- the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.
- in combination with paclitaxel, for the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Gemzar 200 mg and 1000 mg powder for solution for infusion (NL license RVG 17854) which was registered in the Netherlands by Eli Lilly Nederland BV on 27 March 1995. In addition, reference is made to Gemzar authorisations in the individual member states (reference product). The reference product is no longer registered in the Netherlands since 1 September 2014.
This application concerns a line extension. The MAH already has two products containing gemcitabine: Gemcitabine Fresenius Kabi 40 mg/ml, concentrate for solution for infusion, registered in procedure NL/H/2447/001/DC, and Gemcitabine Fresenius Kabi 38 mg/ml powder for solution for infusion, registered in procedure UK/H/2569/001/DC. Besides the strength, the new product also differs from the already registered concentrate for solution for infusion regarding composition, as it does not contain ethanol.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, hybrid application, as the pharmaceutical form is different from the reference product.

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

II. QUALITY ASPECTS

II.1 Introduction

Gemcitabine Fresenius Kabi is a concentrate for solution for injection and contains as active substance gemcitabine hydrochloride, corresponding to 38 mg of gemcitabine per ml concentrate. The product is a sterile, clear colourless to light straw coloured solution with pH 7.0-9.0.

The concentrate is packed into 6 ml (200 mg/5.26 ml), 30 ml (1000 mg/26.3 ml) or 100 ml (2000 mg/52.6 ml) clear glass vials, closed with a Fluorotec (chlorobutyl) rubber closure and an aluminium flip-off over seal.

The excipients are propylene glycol (30% v/v (310.8 mg/ml)), macrogol 400, water for injections, and sodium hydroxide and concentrated hydrochloric acid for pH adjustment.

The concentrate must be diluted with at least 500 ml of sodium chloride 9 mg/ml to a concentration of between 2 and 5 mg/ml, depending on body surface area and recommended dose.

II.2 Drug Substance

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

The CEP procedure is used for the active substance by both active substance manufacturers. 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
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEPs. Additional requirements for residual solvents, water content, microbial quality, and endotoxins are included. All parameters included in the drug substance specification are considered adequate to guarantee a consistent, sufficient quality. All analytical methods have been described in full detail. Batch analytical data demonstrating compliance with this specifications have been provided for nine batches.

Stability of drug substance
The active substance is stable for three years for one manufacturer and four for the other when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The development studies were aimed at obtaining a product similar to the innovator product (powder for solution for infusion, i.e. not ready-to-use), which is stable at room temperature, ready-to-use (concentrate for solution for infusion), and does not contain ethanol. The concentration and the amount of propylene glycol and Macrogol 400 are justified based on the maximum daily intake of these excipients and their maximum daily intake with proposed drug product. Although the current product has a different composition than the reference product, the product on administration will have the same dosage form (solution for infusion). Comparative studies were performed, showing the similarity with the originator product.
The packaging is usual and suitable for the product at issue. It was shown that the product is compatible with the usual diluent sodium chloride injection (0.9% w/v). On the request of the authorities the method of sterilisation was changed from aseptic filling to terminal sterilisation by moist heat. The sterility and bacterial endotoxins are tested prior to release of every batch of Gemcitabine Fresenius Kabi 38 mg/ml concentrate for solution for infusion. Testing of sterility is part of both the batch release and the shelf-life specifications, thereby ensuring that the drug product complies with pharmacopoeial requirements. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The concentrate for solution for infusion is prepared by weighing the components and dissolving in water for injections. The pH is measured and if necessary adjusted to a final pH of solution between 7.0 - 9.0 with NaOH or HCl. The volume is adjusted to final volume with water for injections. The final

solution is filtered twice and then filled into vials to a controlled weight. The vials are stoppered, sealed, washed, sterilized by moist heat, external decontamination, visually inspected, labelled and packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. Tests are included for appearance, color absorbence, identity, extractable volume, pH, assays, related substances, particulate contamination, bacterial endotoxins, seal integrity and sterility. The release and shelf-life limits are not identical, wider limits for impurities are set at end of shelf-life. The proposed limits are acceptable.
Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for three batches for all fill volumes from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three full scale aseptically processed batches stored upright and inverted at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). Furthermore, stability data has been provided for three full scale batches of terminally sterilised batches stored at 25°C/60% RH (3 months) and 40°C/75% RH (3 months).
The conditions used in the stability studies are in accordance with the ICH stability Guideline regarding finished products packaged in impermeable containers. All batches comply with the proposed set of specifications, at all temperatures tested. The stability profile of the aseptically processed batches and the terminally sterilised batches is similar. Photostability studies demonstrated that there is no effect of light on the product stability. The control tests and specifications for the drug product are adequately drawn up. Based on the stability data submitted, the following proposed shelf-life and storage conditions are approved: two years. Store below 25°C. Do not refrigerate or freeze.

Prior to use the Gemcitabine 38 mg/ml concentrate for solution for infusion must be diluted by injection into an infusion bag containing 0.9% sodium chloride solution to obtain the final solution for infusion. It was shown that the diluted solutions are stable at 2°C to 8°C or at 25°C for 7 days. However, from a microbiological point of view, the product should be used immediately.

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 Gemcitabine Fresenius Kabi 38 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 Gemcitabine Fresenius Kabi 38 mg/ml concentrate for solution for infusion 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 hybrid formulation of Gemzar which is available on the European market. Reference is made to 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

Gemcitabine 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

As the product is to be administered after dilution as an aqueous intravenous solution, no difference in absorption rate or bioavailability between Gemcitabine 38 mg/ml concentrate for solution for infusion and the reference product is expected. The 38 mg/ml concentrate for solution for infusion and the reference product Gemzar 200 mg/1000 mg powder for solution for infusion are pharmaceutically equivalent. Therefore the product fulfils the exemption mentioned in the Note for Guidance on bioequivalence '5.1.6 parenteral solutions', a bioequivalence study is not required.
The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Gemcitabine Fresenius Kabi 38 mg/ml, concentrate for solution for infusion.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Myelosuppression - Capillary leak syndrome - Haemolytic uremic syndrome - Severe skin reactions (TEN/SJS) - Radiosensitisation - Pulmonary toxicity - Hypersensitivity - Posterior reversible encephalopathy syndrome
Important potential risks	- Reproductive and development toxicity - Mutagenicity
Missing information	- Experience with gemcitabine with paediatric population - Information on clear dosage recommendation in patients with hepatic and renal impairment

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Gemzar 200 mg/1000 mg powder for solution for infusion. No new clinical studies were conducted. The product can be considered essentially similar to the reference product based on chemical-pharmaceutical properties. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. PRODUCT INFORMATION/USER CONSULTATION

Potential medication errors
The ready-to-use gemcitabine products currently on the market differ with respect to concentration and composition and hence pH, osmolality and storage conditions. This means that the standard working procedures may or should differentiate between the different products, e.g. depending on the final osmolality there may be a need for administration into a central vein or not.
As required by the MEB, information on osmolality and pH of the reconstituted product at relevant clinical concentrations was added to the SmPC, to avoid medication errors.

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Gemcitabine Fresenius Kabi 40 mg/ml concentrate for solution for infusion, NL/H/2447/001/DC. The bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gemcitabine Fresenius Kabi 38 mg/ml concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Gemzar 200 mg and 1000 mg powder for solution for infusion. Gemzar is a well-known medicinal product with an established favourable efficacy and safety profile

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 Gemcitabine Fresenius Kabi 38 mg/ml concentrate for solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 October 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