CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Gemcitabine Fresenius Kabi 40 mg/ml, concentrate for solution for infusion Fresenius Kabi Oncology Plc, United Kingdom

gemcitabine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2447/001/DC
Registration number in the Netherlands: RVG 110700

3 June 2013

Pharmacotherapeutic group:	antineoplastic and immunomodulating agents, pyrimidine analogues
ATC code:	L01BC05
Route of administration:	intravenous
Therapeutic indication:	bladder cancer, pancreatic cancer, non-small cell lung cancer, breast cancer, ovarian cancer
Prescription status:	prescription only
Date of authorisation in NL:	22 May 2013
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

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 40 mg/ml, concentrate for solution for infusion from Fresenius Kabi Oncology Plc. The date of authorisation was on 22 May 2013 in the Netherlands.

The product is indicated for:

- treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
- treatment of patients with locally advanced or metastatic adenocarcinoma of the pancreas.
- first line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) in combination with cisplatin. Gemcitabine monotherapy can be considered in elderly patients or those with performance status 2.
- 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.
- combination treatment with paclitaxel in 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 SPC.

Gemcitabine (dFdC), which is a pyrimidine antimetabolite, is metabolised intracellularly by nucleoside kinase to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is due to inhibition of DNA synthesis by two mechanisms of action by dFdCDP and dFdCTP. First, dFdCDP inhibits ribonucleotide reductase, which is uniquely responsible for catalysing the reactions that produce deoxynucleoside triphosphates (dCTP) for DNA synthesis. Inhibition of this enzyme by dFdCDP reduces the concentration of deoxynucleosides in general and, in particular, dCTP. Second, dFdCTP competes with dCTP for incorporation into DNA (self-potentiation).

This decentralised procedure concerns a hybrid application with a change in pharmaceutical form (change to solution) and strength (quantitative change to the active substance) compared to the innovator product Gemzar, powder for solution for infusion 200 mg and 1000 mg (NL License RVG 17854), which has been registered in the Netherlands by Eli Lilly Nederland BV since 27 March 1995. In addition, reference is made to Gemzar authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic or hybrid products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Gemcitabine Fresenius Kabi 40 mg/ml, concentrate for solution for infusion is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98).
The concentrations for the innovator and generic differ: 38 mg/ml vs. 40 mg/ml respectively. Other 40 mg/ml generics have been approved previously and are available on the market. The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a hybrid application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is gemcitabine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance 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 both suppliers of 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 drug substance specification was included. The specifications are in line with the Ph.Eur. with additional tests for residual solvents, microbial contamination and water content (by KF). All tests and limits are in line with the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specifications have been provided for three batches.

Stability of drug substance
The claimed retest period is 48 months for one manufacturer and 36 months for the second supplier. The re-test periods, storage conditions and packaging materials have been included on the CEPs. Therefore, the re-test periods and storage conditions can be granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Gemcitabine Fresenius Kabi 40 mg/ml is a clear, colourless to slightly yellow solution with pH 7.0 to 9.0.

The concentrate for solution for infusion is packed in clear, colourless type-I tubular glass vial, closed with a 20 mm flurotec rubber stopper and sealed with flip-off aluminium seal (Green (for 200 mg/5 ml), Blue (for 1000 mg/25 ml) and Purple(for 2000 mg/50 ml) polypropylene flip.

The excipients are: ethanol (96 per cent), sodium hydroxide (E524) (for pH adjustment), hydrochloric acid (E507) (for pH adjustment), water for injections.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The drug product contains ethanol which was included as co-solvent of the drug

substance in order to maintain the drug substance in solution at the pH where the drug substance is most stable. An overage is not applicable.
No bioequivalence study is required since the drug product concerns a parenteral solution, the drug substance concentration is the same as the innovator product.
The compatibility of the drug product with the container closure system and 0.9% NaCl solution medium has been demonstrated. The pharmaceutical development of the drug product was considered to be adequately performed.

Manufacturing process
The concentrate for solution for infusion is manufactured by aseptically preparing the gemcitabine HCl bulk solution. The solution is filtered through a filter into the packaging. Since the manufacturing process involves aseptic filtration as sterilisation step it is considered to be a non-standard process. Process validation data have been submitted on three full-scale bulk batches. Each bulk batch was used to fill three different vial sizes, i.e. 6 ml, 30 ml and 100 ml vials.

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

Quality control of drug product
The product specification includes tests for description, colour, clarity, identification of gemcitabine, assay, related substances, pH, extractable volume, ethanol assay, particulate contamination, bacterial endotoxins, sterility, colour absorbance, related substances and seal integrity. The release and shelf-life limits are identical with the exception of the colour absorbance and any other impurity under the test for related substances, which are widened in the shelf-life specifications.
The analytical methods have been adequately described and validated.
Batch analytical data of 3 pilot-scale batches per volume of the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the drug product have been provided four pilot scaled batches per presentation stored at 25°C/60%RH (12 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are in accordance with the ICH stability guideline. The batches were stored in the proposed packaging materials and stored in both upright and inverted positions and no difference was observed. A slight decrease in assay within 12 months was observed at all conditions. However, this was not considered to be a trend and no out-of-specification results were observed. Based on the submitted data the shelf life of 24 months can be granted.
The stability data of the diluted drug product have been provided. No trends or out-of-specification findings for the diluted drug product are observed after 72 hours. The proposed shelf-life and storage conditions of the diluted drug product of 72 hours at 30°C or 5°C are approvable.
The shelf-life after first opening of 3 days at 25°C has also been substantiated with stability data and was therefore granted.

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.2 Non-clinical aspects

This product is a hybrid formulation of Gemzar, which is available on the European market. 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.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of gemcitabine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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.

As the product is to be administered as an aqueous intravenous solution, no difference in absorption rate or bioavailability between Gemcitabine Fresenius Kabi 40 mg/ml, concentrate for solution for infusion and the reference product is expected. As Gemcitabine Fresenius Kabi 40 mg/ml and the reference product Gemzar 200 mg/1000 mg powder for solution for infusion are pharmaceutically equivalent, also pharmacokinetic bioequivalence can be assumed. Thus, no bioequivalence study is required.

No objection was made against the difference in concentration of 38 mg/ml vs. 40 mg/ml. Since other products are marketed with the same concentration (40 mg/ml) and it provides an advantage with respect to ease of dose calculation for patient administration.

The MAH provided information that no substantial adverse events related to ethanol are to be expected, also in view of the experience with comparable amounts ethanol containing drugs like paclitaxel and other generics of gemcitabine. A relative large amount of alcohol is given in a short period of time: a dose of about 26.5 grams of ethanol per human (based on body surface area of 2 m^2) is administered in half an hour. With respect to the combined use of Gemcitabine Fresenius Kabi and - ethanol containing – paclitaxel, information was provided, but other combinations of Gemcitabine Fresenius Kabi 40 mg/ml with other antineoplastic drugs (e.g. carboplatin and cisplatin) have not been discussed. Nevertheless, many theoretically possible interactions are unlikely to occur with this amount of ethanol. Theoretically possible interactions due to induction by ethanol are unlikely since Gemcitabine Fresenius 40 mg/ml will only be administered as a single dose within a substantial time frame, resulting in only minimal – if any - induction. Also, clinical complications with regard to related ethanol administration are not known and are not envisaged.

Risk management plan
Gemcitabine was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of gemcitabine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
A Referral under Article 30 of Directive 2001/83/EC, as amended (triggered by the European Commission) for the innovator Gemzar was started in 2007 and reached a positive opinion in June 2008 (EMA Procedure Nr: EMA/H/A-30/880). The SPC is in line with the outcome of this Referral. Besides the product texts of the current application are adapted in line with the decision of the PhVWP dated June 2011 related to the risk of adverse reactions due to relative large amount of alcohol after reconstitution.

Readability test

The package leaflet has not been evaluated via a user consultation study. No user testing of the PIL has been submitted. The MAH justifies the absence of a readability test by bridging the PIL of Gemcitabine Fresenius Kabi 40 mg/ml concentrate for solution for infusion to the PIL of Gemcitabine (Kabi) 200 mg/1 g/ 2 g powder for solution for infusion.

The above mentioned PILs have been compared with the following aspects:

- Visual Presentation: dimension, font size and style, pictures, bullet pointing, bolding,
- spacing and any colouring in the PILs.
- Textual: key safety messages, jargon, wording simplicity, and overall linguistic theme.

The Daughter PIL is updated according to the QRD template and contains additional information about the alcohol content of the product but this is written in a very understandable way. Impact on readability is considered unlikely.

The absence of user testing is sufficiently justified.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Gemcitabine Fresenius Kabi 40 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Gemzar powder for solution for infusion 200 mg and 1000 mg. 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. The amount of ethanol present in the product was sufficiently justified and potential interactions are adequately addressed.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the product information for Gemzar, which was harmonised after a referral under Article 30, started in 2007 and concluded positively in June 2008 (EMA Procedure Nr: EMA/H/A-30/880). The SPC, package leaflet and labelling are in the agreed templates.

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 Gemcitabine Fresenius Kabi 40 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 October 2012. Gemcitabine Fresenius Kabi 40 mg/ml, concentrate for solution for infusion was authorised in the Netherlands on 22 May 2013.

The date for the first renewal will be: 4 October 2017.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the long-term stability studies at 25°C/60% RH for up to 36 months after approval on all nine batches of 200 mg/5 ml, 1000 mg/25 ml and 2000 mg/50 ml (3 batches of each presentation).

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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