CBG MEB

# Public Assessment Report

# Scientific discussion

# Gemcitabine Koanaa 200 mg and 1000 mg powder for solution for infusion

# (gemcitabine hydrochloride)

## NL/H/3502/001-002/DC

## Date: 19 December 2016

**This module reflects the scientific discussion for the approval of Gemcitabine Koanaa 200 mg and 1000 mg powder for solution for infusion. The procedure was finalised on 15 June 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

## List of abbreviations

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| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDQM | European Directorate for the Quality of Medicines |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gemcitabine Koanaa 200 mg and 1000 mg powder for solution for infusion, from Koanaa Healthcare Limited.

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.
- 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.
- 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 SmPC.

This decentralised procedure concerns a generic application claiming 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 September 2014 the registration was withdrawn due to commercial reasons in the Netherlands.

The concerned member states (CMS) involved in this procedure were France, Malta 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

Gemcitabine Koanaa is a white to off-white lyophilized powder, or cake, for solution for infusion.

After reconstitution with 0.9% sodium chloride solution, the solution contains 38 mg/ml gemcitabine (as hydrochloride). Reconstituted solution is a clear, colourless to light straw-coloured solution. Further dilution of reconstituted solution with 0.9% sodium chloride solution for injection at a concentration range of 2–25 mg/ml will have pH of 2.7-3.3.

The powder is packed in a Type I flint glass vial, with a rubber stopper and sealed with an aluminium flip-off seal.

The excipients are mannitol, sodium acetate anhydrous, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

## 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 to almost white powder, which is soluble in water, slightly soluble in methanol and practically insoluble in acetone. Particle size and polymorphic form of the active substance are not deemed critical since it is dissolved during the manufacturing process of the drug product.

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 Ph.Eur.

Manufacturing process
A CEP has 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 is in line with the Ph.Eur. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for 3 full scaled batches.

Stability of drug substance
The active substance is stable for 4 years when stored under the stated conditions. The stability data are evaluated by the EDQM as part of granting the CEP

## 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 excipients and container closure system are typical for powders for solution for infusion and accepted. It has been adequately demonstrated that the reconstituted solution remains stable regarding physicochemical aspects and regarding microbiological purity.

No bioequivalence study is required since the drug product concerns a parenteral solution, the drug substance concentration (after reconstitution) is the same as the innovator product, and pH is comparable. A qualitative and quantitative comparison of the composition of both products is given as well as an impurity profile comparison of a batch of Gemcitabine Koanaa and a batch of Gemzar. The compatibility with the proposed reconstitution solution has been demonstrated. The pharmaceutical development of the drug product was considered to be adequately performed.

Manufacturing process
The manufacture of the drug product comprises preparation of the bulk solution, sterile filtration and filling into glass vials, and lyophilisation. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for 3 commercial scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. or other relevant pharmacopoeia. These specifications are acceptable.

Microbiological attributes
Tests for sterility and bacterial endotoxins are included in the specification of the drug product. Hence the sterility test is performed according to Ph.Eur chapter 2.6.1. The results demonstrate that the product is sterile from a microbiological point of view.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, pH, water content, reconstitution time, colour of reconstituted solution, uniformity of dosage units, particulate contamination, bacterial endotoxins, sterility, related substances and assay. Release and shelf-life specifications are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 3 commercial scaled batches per strength 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 3 batches per strength stored at 25°C/60% RH (6–12 months) and stored at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the same vials which will be used for commercial packaging. No trends are observed in any of the tested parameters at both storage conditions. The drug product is not photosensitive. The proposed shelf-life of 24 months and storage condition 'no special storage conditions' are acceptable.

The in-use period after first opening of 28 days is supported by chemical studies. After reconstitution chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view however 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 Koanaa has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No following post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Gemcitabine Koanaa 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 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

Gemcitabine Koanaa is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Gemcitabine Koanaa 200 mg and 1000 mg powder for solution for infusion is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. 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 Koanaa.

Summary table of safety concerns as approved in RMP:

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| Important identified risks | • Severe skin reaction (toxic epidermal necrolysis and Steven Johnson Syndrome)<br>• Hypersensitivity<br>• Myelosuppression<br>• Pulmonary toxicity<br>• Radiosensitisation<br>• Haemolytic uraemic syndrome (HUS)<br>• Posterior reversible encephalopathy syndrome (PRES)<br>• Capillary leak syndrome |
| Important potential risks | • Mutagenicity<br>• Reproductive and developmental toxicity (including male infertility)<br>• Use during lactation |
| Missing information | • Experience with gemcitabine in the paediatric population<br>• Information on clear dosage recommendation in patients with hepatic or renal impairment |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Gemzar. No new clinical studies were conducted. Gemcitabine Koanaa is a parenteral formulation and fulfils the requirements for an exemption from bioequivalence studies. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test, followed by two rounds with 10 participants each. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gemcitabine Koanaa 200 mg and 1000 mg powder for solution for infusion has a proven chemical-pharmaceutical quality and is a generic 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.

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 Koanaa with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 June 2016.

## 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 |
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