CBG MEB

Public Assessment Report

Scientific discussion

Gemcitabine Actavis PTC 40 mg/ml, concentrate for solution for infusion

(gemcitabine hydrochloride)

NL/H/3383/001/DC

Date: 21 February 2017

This module reflects the scientific discussion for the approval of Gemcitabine Actavis PTC 40 mg/ml, concentrate for solution for infusion. The procedure was finalised on 11 January 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

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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 Actavis PTC 40 mg/ml, concentrate for solution for infusion from Actavis Group PTC ehf.

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 SmPC.

This decentralised procedure concerns a hybrid 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. Gemcitabine Actavis PTC 40 mg/ml, concentrate for solution for infusion differs from Gemzar in pharmaceutical form (change to solution) and strength (quantitative change to the active substance).

The concerned member states (CMS) involved in this procedure were Bulgaria, Estonia, Ireland, Iceland, Norway, Slovenia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

The product is a clear, colourless or pale yellow solution for intravenous use after dilution with pH of 2.4 ± 0.4 and osmolality in the range of 270 to 280 mOsmol/kg.

Each ml of concentrate for solution for infusion contains 40 mg gemcitabine (as gemcitabine hydrochloride). The concentrate for solution is packed in 5 ml (200 mg), 25 ml (1000 mg) and 50 ml (2000 mg) colourless glass vials (type I) with bromobutyl rubber stoppers and sealed with aluminium caps with a polypropylene disc.

The sterile drug product is to be further diluted in 0.9% sodium chloride to a final concentration in the range between 2–25 mg/ml (2.0 mg/ml, 12 mg/ml and 25 mg/ml). The vial will be packed with or without a protective plastic overwrap.

The excipients are hydrochloric acid (E507) for pH adjustment and water for injections.

II.2 Drug Substance

The active substance is gemcitabine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is soluble in water, slightly soluble in methanol and practically insoluble in ethanol. The manufacturing process consistently yields the β-

isomer. As the drug substance is dissolved in the formulation, issues with polymorphic form and particle size are not expected.

CEP procedures are used for all three 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 Ph.Eur.

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. The additional tests for residual solvents, microbial contamination and loss on drying are acceptable.
Batch analytical data demonstrating compliance with this specification have been provided for several batches (at least one of each manufacturer).

Stability of drug substance
The claimed retest periods are 4 years and 5 years for two of the CEP-holders. Assessment thereof was part of granting the CEP and has been granted by the EDQM. Stability data on the drug substance from the third CEP-holder were provided, stored at accelerated conditions (40°C/75% RH) and at long-term conditions (25°C/60% RH). Based on the data provided, a retest period of 5 years could be granted without specific storage conditions.

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. Sterile filtration is applied followed by aseptic filling. This has been adequately justified by the MAH based on the data of terminally sterilised product by moist heat, where out-of-specification results were observed.

No bioequivalence study is required since the drug product concerns a parenteral solution, the drug substance concentration is the same as the innovator product (after reconstitution), and pH is comparable. An overage is not applicable. Overfills are considered to be necessary as demonstrated by the tests for extractable volume. This is considered acceptable.
The compatibility of the drug product with the container closure system and 0.9% NaCl solution medium after dilution to 2-25 mg/ml has been demonstrated. The chosen dilution range is acceptable in view of the dosing schedule. The pharmaceutical development of the drug product was considered to be adequately performed.

Manufacturing process
The concentrate for solution for infusion is manufactured by dissolution of the active substance in the water for infusion and adjustment of the pH with hydrochloric acid. The solution is filtered into the pre-sterilised packaging. Since the manufacturing process involves filtration as sterilisation step it is considered to be a non-standard process. Process validation data have been submitted on three full scaled batches (one of each presentation). The process is considered to be sufficiently validated.

Control of excipients
All excipients comply with the Ph.Eur. 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 appearance, colour, clarity, identification of gemcitabine, assay, related substances, pH, extractable volume, visible particles sub-visible particles, bacterial endotoxins and sterility. The release and shelf-life limits are identical with the exception of the limit for total degradation impurities and the limit of one known degradation impurity. These limits are widened in the shelf-life specification.
All methods and limits included in the specification are acceptable. There is no test for uniformity of dosage units. Fill weight is tested during filling, and this is considered sufficient to control the mass variation.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from several full scaled batches of each presentation from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the drug product have been provided for two pilot scaled batches stored at 5°C (24 months) and 25°C/60% RH (3 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. Out of specification results were only observed at accelerated conditions. These data confirm that Gemcitabine Actavis PTC 40 mg/ml concentrate for solution for infusion is intended for refrigerated storage (2–8°C). A photostability study demonstrated that the drug product is photostable.
The claimed shelf-life of 18 months stored in the original packaging with the storage condition 2-8°C can be granted.
The MAH has initiated stability studies on three full scaled batches (one of each presentation) stored at 5°C and 25°C/60% RH. These studies will be continued in order to confirm the established shelf-life.

After first opening the chemical and physical in-use stability has been demonstrated for 28 days at 2-8°C and 25°C. The stability after dilution has been tested and no out of specification results were observed after 28 days at 2-8°C and about 25°C diluted with 0.9% NaCl to 2-25 mg/ml and in PVC or PE infusion bag. From a microbiological point of view, the solution for infusion 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 Actavis PTC 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 Actavis PTC 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

Based on the composition, Gemcitabine Actavis PTC provides the same amount of gemcitabine as the reference product for infusion (Gemzar). After reconstitution, the reference product (powder for solution for injection) 200 mg/vial forms a concentrate of 38 mg/ml solution. Further dilution is required before infusion. As the product is to be administered as an aqueous intravenous solution, no difference in absorption rate or bioavailability between Gemcitabine 40 mg/ml concentrate for solution for infusion and the reference product is expected. Although Gemcitabine 40 mg/ml concentrate for solution for infusion and the reference product Gemzar 200 mg/1000 mg powder for solution for infusion have a slightly different composition, these differences are not expected to influence the pharmacokinetics because of the route of administration. The absence of mannitol and sodium acetate in the new formulation is not expected to influence the pharmacokinetics of gemcitabine because the route of administration is intravenous infusion. The small difference in pH level is not expected to influence the pharmacokinetics either.
To conclude, in accordance with Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr** a clinical bioequivalence study is not necessary. The test product 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 Actavis PTC.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Myelosuppression • Severe skin reactions • Pulmonary toxicity • Hypersensitivity • Haemolytic uremic syndrome • Radiosensitisation • Capillary leak syndrome • Posterior reversible encephalopathy syndrome
Important potential risks	• Mutagenicity • Reproductive and developmental toxicity (including male infertility)
Missing information	• Experience with gemcitabine in the paediatric population • Information on clear dosage for 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. This application is different from the reference product in pharmaceutical form and strength. Gemcitabine Actavis PTC is a gemcitabine product to be delivered as concentrate for solution for infusion. Similarity to the reference product has been sufficiently demonstrated based on *in vitro* data. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet 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 with 3 participants, followed by 2 rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gemcitabine Actavis PTC 40 mg/ml, concentrate 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 Actavis PTC with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 January 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