Public Assessment Report

Scientific discussion

Gemcitabine SUN 10 mg/ml solution for infusion

(gemcitabine hydrochloride)

NL/H/3313/001/DC

Date: 2 November 2017

This module reflects the scientific discussion for the approval of Gemcitabine SUN 10 mg/ml solution for infusion. The procedure was finalised on 30 September 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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 SUN 10 mg/ml solution for infusion from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for:

- the treatment of locally advanced or metastatic bladder cancer in combination with cisplatin.
- the 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, the treatment of patients with unrespectable, 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 SUN 10 mg/ml differs from Gemzar in the pharmaceutical form and the strength (quantitative change to the active substance). The 10 mg/ml strength falls within the approved dosage and administration requirements of the innovator product.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Italy, Norway, Poland, Romania, Sweden, Slovak Republic 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

Gemcitabine SUN is a clear, colourless solution for infusion and free from visible particulate matter. The solution has a pH range of 6.0 – 8.0 and an osmolality range of 350-450 mOsmol/kg.

Every ml of solution contains 10 mg gemcitabine (as hydrochloride). The product is available in 7 quantities: 120 ml, 140, 160 ml, 170 ml, 180 ml, 200 ml and 220 ml corresponding to 1200 mg, 1400 mg, 1600 mg, 1700 mg, 1800 mg, 2000 mg and 2200 mg gemcitabine (as hydrochloride). The solution is ready for infusion by intravenous route and does not require further dilution.

The solution for infusion is supplied sterile in flexible multilayer M312 plastic infusion bags overwrapped with an aluminium pouch. The Minitulipe infusion bag stopper consists of a spike port with a chlorobutyl (latex-free) joint, and a polyolefin connector tubing is used.

The excipients are sodium chloride, sodium hydroxide (for pH adjustment), hydrochloride acid (for pH adjustment) and water for injection.

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 a white or almost white powder, which is soluble in water, slightly soluble in methanol and practically insoluble in acetone. The finished product is a solution for infusion; therefore the particle size and polymorphic form of the drug substance will not have an impact on 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 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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur and additional tests for residual solvents, bacterial endotoxins and bioburden. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance
A re-test period of 60 months was adopted under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM

II.3 Medicinal Product

Pharmaceutical development
The development of Gemcitabine SUN is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and its functions explained. Additionally, the proposed ranges for the osmolality and pH have been sufficiently justified. The development activities were aimed towards achieving a stable solution for infusion. The product differs in pharmaceutical form, but delivers the same dose as the reference product Gemzar, without the need for reconstitution and any dilution before use. The product is a hybrid product for parenteral use and therefore exempted from bioequivalence studies.

Manufacturing process
The product is manufactured using conventional manufacturing techniques. Gemcitabine hydrochloride is dissolved in solution of water for injections with sodium chloride, the pH is adjusted by addition of sodium hydroxide and optionally by addition of hydrochloric acid. Water for injections is added to make up the volume. The bulk solution is filtered twice and filled into the terminally sterilised infusion bags. Process validation data on the product have been presented for three production scale batches of every proposed drug product presentation.

Control of excipients
The excipients used in the proposed finished product are commonly used for parenteral products and comply with the relevant Ph. Eur. monograph.

Microbiological attributes
The container-closure integrity was tested for the Gemcitabine SUN by a microbiological challenge test and a sterility test. For the sterility test the final primary packaging material was analysed as per Ph. Eur. For both tests the results were satisfactory. Therefore, the integrity of the container-closure system had been confirmed.

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, identification, pH, % transmittance at 650nm, absorbance at 420nm, osmolality, water loss, extractable volume, volume variation, particulate matter, related substances, sterility, bacterial endotoxins, assay for sodium chloride and assay of gemcitabine. 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 three batches of every proposed presentation from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for fifteen commercial scale batches stored at 25°C/40%RH (up to 36 months, depending on the presentation) and 40°C/25%RH (6 months) in accordance with ICH stability guideline for products stored in semi-permeable containers. The results show that all the batches remain within specifications, with no significant changes at accelerated and long term conditions.
A water loss study at accelerated conditions has been performed at the development stage and the obtained results met the requirement. Results from all parameters tested in the photostability study are well within the limits and no changes occurred due to the exposure to light when stored in the proposed package.
On the basis of the submitted data the claimed shelf-life of 24 months, without further conditions and the additional statement “do not refrigerate or freeze” can be granted.

The MAH has provided test results demonstrating that the Gemcitabine SUN solution for infusion, 10 mg/mL is compatible with IV infusion sets for 30 minutes when stored at room temperature (20°C-25°C).

From a microbiological point of view, after opening the infusion bag the solution should be used immediately. There is no in-use shelf life.

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 SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments were made:

- The MAH has committed that a weight loss study will be performed at long term condition (25°C and the reference relative humidity of 40% RH) on the first three commercial batches of 120 ml, 200 ml and 220 ml in order to ensure compliance to weight loss requirements.
- The MAH has committed to monitor the levels of critical non-volatile leachables for continued compliance at or near proposed shelf- life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Gemcitabine SUN is intended for hybrid 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

Gemcitabine SUN solution for infusion 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 Sun 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 SUN.

- Summary table of safety concerns as approved in RMP

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

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 SUN is the only gemcitabine product to be delivered as solution for infusion in infusion bags. This has benefits for the caregivers since handling of the cytostatic drugs with its risks for the personnel is thereby minimised. 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 study consisted of 15 questions and three rounds, including the pilot. 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 SUN 10 mg/ml 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.

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 SUN solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 September 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3313/1/IA/001	Submission of a European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph; Updated certificate from an already approved manufacturer	-	14-09-2016	Approved	-
NL/H/3313/1/IA/002	Change in immediate packaging of the finished product; replacement or addition of a supplier	-	20-10-2016	Approved	-
NL/H/3313/1/II/003	Change in immediate packaging of the finished product; Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/ immunological medicinal products.	PL SmPC	19-06-2017	Approved	-
NL/H/3313/1/IA/004	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; Secondary packaging site	-	08-05-2017	Approved	-