CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Gemcitabine 200 mg Pharmachemie B.V., powder for solution for infusion
Gemcitabine 1000 mg Pharmachemie B.V., powder for solution for infusion
Pharmachemie B.V., the Netherlands

gemcitabine (as hydrochloride)

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/1240/01-02/DC
Registration number in the Netherlands: RVG 101090, 101091

4 February 2010

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:	24 February 2009
Concerned Member States:	Decentralised procedure with IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 200 mg Pharmachemie B.V. and Gemcitabine 1000 mg Pharmachemie B.V., powder for solution for infusion from Pharmachemie B.V. The date of authorisation was on 24 February 2009 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 generic application claiming essential similarity with the innovator product Gemzar, powder for solution for infusion 200 mg and 1000 mg (NL 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(1) of Directive 2001/83/EC.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application taking into account the formulation intended for parenteral administration.

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 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 200 mg Pharmachemie B.V. and Gemcitabine 1000 mg Pharmachemie B.V. are products for parenteral use, these two formulations are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their reference product.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted, as this is not required for a generic medicinal product.

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 these product types 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 drug substance consists of white to off white solids and is freely soluble in water, slightly soluble in methanol, practically insoluble in alcohol or polar organic solvents.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Gemcitabine hydrochloride is synthesized in a five step process. This process is reflected in a flow diagram providing molecular structures of starting materials and intermediates. The drug substance has been adequately characterized. The drug substance has the same polymorphic form as the Ph.Eur. reference standard. The solvents used during the manufacturing process are adequately limited in the drug substance specification.

Specification
The active substance specification is in line with the Ph.Eur. with adequate additional requirements for residual solvents, polymorphic forms and microbiological quality. Batch analytical data demonstrating compliance with these specifications have been provided for 6 batches of various sizes.
Except for one alternative method for determination (in-house) of residual solvents, Ph.Eur. methods are used. The analytical methods have been adequately described.

Stability of drug substance
Stability data on the active substance have been provided for 3 pilot scaled batches during storage at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The drug substance was adequately stored. For the stability studies at accelerated storage conditions no trends were observed. Also no trends were observed in the stability studies at long term storage conditions. The results all comply with the specification. The solid drug substance is stable with respect to degradation, but sensitive to light. Based on the data provided, a retest period of 12 months was granted for the powder *'when stored in the original package to protect from light'*.

** 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 200 mg Pharmachemie B.V. contains as active substance gemcitabine hydrochloride equivalent to 200 mg of gemcitabine, and is a white or almost white compact aggregate. After reconstitution, the solution contains 38 mg/ml of gemcitabine.

Gemcitabine 1000 mg Pharmachemie B.V. contains as active substance gemcitabine hydrochloride equivalent to 1 g of gemcitabine, and is a white or almost white compact aggregate. After reconstitution, the solution contains 38 mg/ml of gemcitabine.

The 200 mg powder for solution for infusion is packed in 10 ml colourless glass vials (type I) with bromobutylic rubber stopper and sealed with aluminium seals with grey polypropylene caps, with or without a protective plastic overwrap.

The 1000 mg powder for solution for infusion is packed in 50 ml colourless glass vials (type I) with bromobutylic rubber stopper and sealed with aluminium seals with grey polypropylene caps, with or without a protective plastic overwrap.

The excipients for both strengths are: mannitol E421, sodium acetate trihydrate, and sodium hydroxide 1 N (for pH adjustment).

Pharmaceutical development
Lyophilisation is used as manufacturing process for the powder for solution for infusion. Because of the lability of the drug substance to heat, sterilization by filtration and aseptic filling is applied. The excipients used (sodium acetate, sodium hydroxide, mannitol and water for injections) are common in a lyophilized powder for infusion. All excipients comply with the Ph.Eur. The packaging materials are usual and suitable for the product at issue. For justification of the drying temperature in the first drying phase, the glass transition temperature and collapse temperature have been included. The eutectic point is determined using the temperature time curves.

Manufacturing process
The drug product is prepared under aseptic conditions in order to maintain the sterility of the product. The in-process controls and critical steps have been sufficiently described. Process validation data on the product have been provided for 3 batches of each strength. Since lyophilisation is a non-standard manufacturing process, process validation data of three consecutive production scaled batches have been provided.

Container closure system
The container closure system used for the 200 mg and 1 g product is a colourless neutral glass vial, type I, Ph.Eur. of 10 ml and 50 ml respectively, closed with a halobutyl rubber stopper with a cap. The glass vials comply with the Ph.Eur. The halobutyl rubber stopper is a type I rubber and complies with Ph.Eur. 3.2.9. The cap used for closing the vials is a grey polypropylene disk and aluminium cap. Adequate specifications have been provided.

Microbiological attributes
The drug product is a sterile powder for solution for infusion. The sterility is ascertained due to limited content of potentially microbiological contaminating agents in the raw materials, routine controle of microbial contamination prior to filtration, a manufacturing process with 2 phases of sterilisation by filtration using the same type of filter and control of sterility on batch release. This is sufficient.

Compatibility
Compatibility with other products than those claimed for the reference product have not been proposed.
The MAH has included information on stability of the reconstituted solution in 0.9% NaCl at room temperature for 24 hours. After 24 hours for the 38 mg/ml solution an increase in sub-visible particles is seen. No increase in impurities or decrease in assay is observed. The pH remains stable over time.

Product specification
The drug product specification includes tests for appearance, identity, water content, dissolution time, uniformity of dosage units, assay, related substances, bacterial endotoxins, sterility, pH and sub visible particles. The release and shelf-life requirements are acceptable.
The analytical methods used are adequately described and where necessary adequately validated. Furthermore the method for assay and related substances is sufficiently stability indicating. Batch analysis

results have been provided for 3 batches of each strength, demonstrating compliance with the release specification.

Stability tests on the finished product
The drug product in the colourless neutral glass vials has been stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) for at least three production-scale batches of each strength. The studies will be continued up to 36 months. No trends or changes are observed. The MAH committed to provide results of the ongoing studies. In view of the stability data provided, the claimed shelf-life of 24 months was granted, with the additional storage condition "Do not refrigerate or freeze".
The reconstituted solution is also included in the stability studies and a shelf life of 24 hours at 2-8ºC or 25°C is justified. According to the results of a photostability study, in accordance with ICH guidelines, the drug product is not sensitive to light.

Photostability
A photostability study has been provided. The study is performed according to the NfG on photostability testing on two batches after six months of storage at accelerated storage conditions. A photostability study will also be performed after 36 months of storage under long term storage conditions. Appearance, assay, related substances, pH and particulate matter have been tested. The results remain well within the specification and no trends are observed.

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 generic formulation of Gemzar powder for solution for infusion 200 mg and 1000 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 hydrochloride 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 hydrochloride is a well-known active substance with established efficacy and tolerability.

Gemcitabine 200 mg Pharmachemie B.V. and Gemcitabine 1000 mg Pharmachemie B.V., powder for solution for infusion are parenteral formulations and fulfil 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Gemcitabine 200 mg Pharmachemie B.V. and Gemcitabine 1000 mg Pharmachemie B.V., powder for solution for infusion are 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 products can be used instead of their reference products.

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 postauthorisation 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
The content of the SPC approved during the decentralised procedure is identical to the harmonized product information of the Gemzar Referral to the CHMP under Article 30 of Directive 2001/83/EC as amended (EMEA/H/A-30/880, harmonisation of the SPC) which was finalized during the June 2008 CHMP meeting, with the exception of the product particulars.

Readability test
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 two rounds with 10 participants each. Participants were aged in the range of 18 to 65+ years. Twelve participants were male and 8 were female. None of them had ever used the product before and all of them never participated in a readability test before. A questionnaire of 17 questions which addresses the most critical information for appropriate use of the product and additional important issues in the sections 1-4 was used. Two of the 17 questions were gender specific. For each question it was evaluated whether participants could find the relevant information and could express it in their own words.
The leaflet passed the readability test and no significant changes were considered essential.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Gemcitabine 200 mg Pharmachemie B.V. and Gemcitabine 1000 mg Pharmachemie B.V., powder for solution for infusion have a proven chemical-pharmaceutical quality and are generic forms 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 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 harmonized product information from the Gemzar CHMP Referral. 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 200 mg Pharmachemie B.V. and Gemcitabine 1000 mg Pharmachemie B.V., powder for solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 October 2008. Gemcitabine 200 mg Pharmachemie B.V. and Gemcitabine 1000 mg Pharmachemie B.V., powder for solution for infusion were authorised in the Netherlands on 24 February 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from October 2008 to October 2011.

The date for the first renewal will be: 14 October 2013.

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

<u>Quality - medicinal product</u>

- The MAH committed to provide results of the ongoing stability studies.

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
NSCLC	Non-Small Cell Lung Cancer
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
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/ intermediate in the manufacturing process of the active substance; from a manufacturer currently approved.	NL/H/1240/001 -002/IA/001	IA	3-12-2008	17-12-2008	Approval	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance; from a new manufacturer (replacement or addition); other substances.	NL/H/1240/001 -002/IA/002	IA	3-12-2008	17-12-2008	Approval	N
Change in any part of the (primary) packaging material not in contact with the finished product formulation.	NL/H/1240/001 -002/IA/003	IA	3-12-2008	17-12-2008	Approval	N
Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance; other changes to a test procedure, including replacement or addition of a test procedure.	NL/H/1240/001 -002/IB/004	IB	3-12-2008	2-1-2009	Approval	N
Minor change in the manufacture of the finished product.	NL/H/1240/001 -002/IB/005	IB	3-12-2008	2-1-2009	Approval	N
Increase in batch size for finished product.	NL/H/1240/001 -002/II/006	II	16-1-2009	17-3-2009	Approval	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/ intermediate in the manufacturing process of the active substance; from a new manufacturer (replacement or addition); other substances.	NL/H/1240/001 -002/IA/007	IA	12-5-2009	26-5-2009	Approval	N
Addition of a finished product manufacturer and site of release.	NL/H/1240/001 -002/II/008	II	23-1-2009	10-6-2009	Approval	N
Change in the name of the medicinal product for NL and IT.	NL/H/1240/001 -002/IB/009	IB	9-3-2009	8-4-2009	Approval	N
Minor change in the manufacture of the finished product.	NL/H/1240/001 -002/IB/010	IB	7-5-2009	6-6-2009	Approval	N
Change in any part of the (primary) packaging material not in contact with the finished product formulation.	NL/H/1240/001 -002/IA/011	IA	27-5-2009	10-6-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/1240/001 -002/IA/012	IA	27-5-2009	10-6-2009	Approval	N
Change to batch release	NL/H/1240/001	IA	27-5-2009	10-6-2009	Approval	N

arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; not including batch control/testing.	-002/IA/013					
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; not including batch control/testing.	NL/H/1240/001 -002/IA/014	IA	13-7-2009	27-7-2009	Approval	N