CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Gemcitabine Accord 100 mg/ml concentrate for solution for infusion Accord Healthcare 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/2136/001/DC
Registration number in the Netherlands: RVG 109019

25 June 2012

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:	19 March 2012
Concerned Member States:	Decentralised procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, HU, IE, IT, LT, LV, MT, NO, PL, PT, RO, SE, SK
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 Accord 100 mg/ml concentrate for solution for infusion from Accord Healthcare B.V. The date of authorisation was on 19 March 2012 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 concentrate for solution for infusion) 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).

After reconstitution the reference product has a concentration of 38 mg/ml, whereas the concentration of Gemcitabine Accord is 100 mg/ml. The concentration of none of the registered gemcitabine products is as high as Gemcitabine Accord. The rationale for developing a higher concentration is to minimise the amount of ethanol content compared to currently approved generic concentrates for solution for infusion of gemcitabine.

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 Accord 100 mg/ml, concentrate for solution for infusion is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98).

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, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white or almost white crystalline powder/solid, which is soluble in water, slightly soluble in methanol and practically insoluble in ethanol.

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 new 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 per drug substance manufacturer. The specifications are in line with the Ph.Eur. with additional tests for microbial contamination and loss on drying. 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 per batch size.

Stability of drug substance
At long term (36 months) and accelerated (6 months) conditions no change in any of the parameters was observed. Based on the submitted data the re-test period of 36 months 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 Accord is a clear, colourless to slightly yellow solution with pH in the range of approximately 6.0 to 7.5 and osmolarity is 1000 mOsmol/l undiluted and in the range of approximately 270 to 330 mOsmol/Litre after dilution with 0.9 % sodium chloride solution at a concentration of 0.1 mg/ml gemcitabine.

The concentrate for solution for infusion is packed in 2, 10, 15 and 20 ml type I clear glass vials sealed with rubber stoppers and aluminium flip-off seals.

The excipients are: macrogol 300, propylene glycol, ethanol anhydrous, sodium hydroxide (for pH adjustment), concentrated hydrochloric acid (for pH adjustment).

Pharmaceutical development

The development of the product has been described, the choice of excipients was justified. No bioequivalence study is required since the drug product concerns a parenteral solution. The osmolarity of 1000 mOsmol/l has been adequately discussed.

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 first aseptically preparing a solution of several excipients. The gemcitabine HCl is dissolved in this solution. The solution is filtered through 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 two full-scale batches of the 2, 10, 15 and 20 ml vials.

Control of excipients

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

Microbiological attributes

The product must meet USP/Ph.Eur. requirements of sterility until shelf life. The drug product contains the preservative 44% dehydrated alcohol. A preservative efficacy test has been performed demonstrating the preserving capabilities.

Quality control of drug product

The product specification includes tests for description, identification, identification of the alcohol content, pH, water content, extractable volume, particulate matter, sterility, bacterial endotoxins, chromatographic purity, assay, alcohol content, limit of ethylene glycol and diethylene glycol, clarity and colour of solution and a preservative efficacy test. The release and shelf-life limits are identical with the exception of the pH which is widened in the shelf-life specifications. Furthermore, a slight change in the colour intensity in the specification is made. The drug product specification is acceptable. All analytical methods have been adequately described and validated.

Batch analytical data of 2 full-scale batches per strength of the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the drug product (all fill volumes) have been provided for two full-scale batches with the Flurotec coated rubber stopper stored at 25°C/60%RH (18 months) and 40°C/75%RH (6 months). Furthermore, stability data on the drug product (2 and 20 ml) have been provided for two full-scale batches with the Teflon coated rubber stopper stored at 25°C/60%RH (6 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. An increase in pH was observed at all conditions. However, no out-of-specification results were observed. A photostability study demonstrated that the drug product is photostable.

In line with the guideline on stability testing, the claimed shelf life of 24 months without special storage conditions has been granted.

In-use stability

Chemical and physical in-use stability after dilution to 0.1 mg/ml and 10 mg/ml in 0.9% sodium chloride solution has been demonstrated for 60 days at 25°C and 2°C to 8°C.

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic condition.

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. 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 is a well-known active substance with established efficacy and tolerability. Since the product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorized product, no bioequivalence study is required.

After reconstitution, the reference product Gemzar has a concentration of 38 mg/ml, whereas the concentration of Gemcitabine Accord is 100 mg/ml. The concentration of none of the registered gemcitabine products is as high as Gemcitabine Accord. The rationale for developing a higher concentration is to minimise the amount of ethanol content in to the products compared to currently approved generics of gemcitabine. To minimise the risk of overdosing instructions and warnings regarding higher concentration of product compared to the other gemcitabine products are added to the SmPC, PIL and labelling, attending physicians at the different concentration for preparation/dilution and administration of this product.

In worst case scenario, by which no NaOH and HCl were needed to set the pH at 7.5, Gemcitabine Accord contains 470,15 mg/ml (= 47.0 w/v) ethanol. For the treatment of breast cancer the recommended dose of gemcitabine is 1250 mg/m^2, meaning that 25 ml Gemcitabine Accord is administered to patients with a body surface area of 2 m^2 . This volume could contain a maximum of 11.75 gram ethanol (corresponding to about 250 ml beer with 5% alcohol). The reference drug does not any contain ethanol. However, a comparable product that was recently approved by the decentralized procedure contains 395,0 mg/ml (= 39, 5 % w/v) ethanol. For the treatment of a breast cancer patient with a body surface area of 2 m^2 62.5 ml of this generic containing in total 24.69 mg ethanol, is needed. Ethanol might influence potential pharmacological concomitant drug interactions and possible additional side effects, especially as gemcitabine concentrate is administrated intravenous in a sort time period (30 minutes).

Gemcitabine Accord concentrate for solution for infusion is filled in glass vials containing 200 mg up to 2000 mg gemcitabine (2 mg/200 mg, 10 ml/1000 mg, 15 ml/ 1500 mg, and 20 ml/2000mg). These amounts of gemcitabine fit into the approved dosage regimens.

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 SPC is in line with to the earlier approved SPCs of gemcitabine by different DCPs. This product contains ethanol and therefore appropriate warnings on possible side effects due to ethanol (for instance CNS side effects and AE in hepatic failure) have been added to section 4.4 of the SPC.

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. Fourteen questions were presented to the respondents with respect to the ability to find and understand the information. The results have shown that the information most relevant to the patient can be found (98.57%) and understood (98.57%) in a good way. No recommendations are suggested to the structure and presentation of the patient information leaflet, and none are deemed necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Gemcitabine Accord 100 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 MAH provided explanation for the higher gemcitabine concentration. The amount of ethanol present in the product was sufficiently justified.

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 Accord 100 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 31 January 2012. Gemcitabine Accord 100 mg/ml concentrate for solution for infusion was authorised in the Netherlands on 19 March 2012.

The date for the first renewal will be: 31 January 2017.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH committed to continue the stability study up to 60 months on the batches already included in the stability study.

Quality - medicinal product

- The MAH committed to perform full-scale process validation on the first commercial batch of each of Gemcitabine Injection 100 mg/ml, 2 ml, 10 ml, 15 ml and 20 ml.
- The MAH committed to continue the stability studies to the end of the period shown for each batch and storage condition. Any results, which are out of specification, will be reported to the authorities.
- The MAH committed to subject the first commercial batch of Gemcitabine Injection 100 mg/mL, 10 ml and 15 ml to six months accelerated study at 40°C/75% RH and real time study at 25°C/60% RH throughout the approved shelf-life.

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