PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Gemcitabine “Ebewe” 200 mg, powder for solution for infusion
Gemcitabine “Ebewe” 1000 mg, powder for solution for infusion
Ebewe Pharma Ges.m.b.H. Nfg. KG, Austria

gemcitabine 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/1162/001-002/DC
Registration number in the Netherlands: RVG 100734, 100736

26 August 2009

Pharmacotherapeutic group: L01B C05
ATC code: antineoplastic and immunomodulating agents, pyrimidine analogues
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: 6 November 2008
Concerned Member States: decentralised procedure with DE, PT, SE, UK
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 “Ebewe” 200 mg and Gemcitabine “Ebewe” 1000 mg, powder for solution for infusion, from Ebewe Pharma Ges.m.b.H. Nfg. KG. The date of authorisation was on 6 November 2008 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 application concerns a generic application claiming essential similarity with 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).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. This legal basis is considered acceptable for the following reasons:
- The applications refer to a reference product which has been authorised under article 6 of Dir 2001/83/EC as amended for not less than 6/8 years in the EEA.
- The products have the same qualitative and quantitative composition in active substance as the reference product.
- The products have the same pharmaceutical form as the reference product.
- The active substance is not considered a new active substance.

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 “Ebewe” 200 mg and Gemcitabine “Ebewe” 1000 mg 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.

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.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Declarations are included stating that the active substance manufacturer operates in compliance with the detailed guidelines on good manufacturing practice for starting materials.

Active substance

General information
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. Detailed information on the manufacture is included in the DMF. 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.

Except for one alternative method for determination 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 (12 months) and 40°C/75% RH (6 months). The drug substance was packaged in the commercial packaging, i.e. double packed in LDPE bags sealed with twist ties and placed in a HDPE drum or bottle. 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 when stored in the original package to protect from light. Stability data of production scaled batches will be provided post authorisation.

* Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA respectively.

**Medicinal Product**

**Composition**

Gemcitabine “Ebewe” 200 mg contains as active substance gemcitabine hydrochloride equivalent to 200 mg of gemcitabine, and is a white to off-white cake or powder. After reconstitution, the solution contains 38 mg/ml of gemcitabine.

Gemcitabine “Ebewe” 1000 mg contains as active substance gemcitabine hydrochloride equivalent to 1000 mg of gemcitabine, and is a white to off-white cake or powder. After reconstitution, the solution contains 38 mg/ml of gemcitabine.

The excipients for both strengths are: mannitol (E421), sodium acetate (E262), and sodium hydroxide (E524) (for pH adjustment).

**Pharmaceutical development**

The aim was to develop a buffered solution with a good solubility and acceptable pH. A solution for which the pH is adjusted to 5.0, is not stable, a precipitate is formed. Lyophilisation is used as manufacturing process for the powder for solution for infusion. Because of the liability of the drug substance to heat, sterilization by filtration and aseptic filling is applied. In the manufacturing process development the concentration of active ingredient and excipients, the sterilisation method and the freeze-drying cycle have been established. The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs. A comparative impurity profile with the reference products Gemzar 200 mg and Gemzar 1000 mg is included. The impurity profiles are comparable.

The MAH justified the drying temperature used by referring to the eutectic point. However, the drying temperature is 5-10°C above the eutectic point. Therefore, the MAH committed to discuss the possibility of collapsing of the cake during this drying phase.

**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 of three consecutive production scaled batches have been provided for the 1000 mg strength.

**Product specification**

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, water content, dissolution time, uniformity of mass, assay, related substances, bacterial endotoxins, sterility, pH and sub visible particles. The requirements set are in line with the Ph.Eur. monograph for the drug substance and the USP monograph gemcitabine for injection. The release and shelf life requirements were found acceptable. 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 batches from the proposed production sites have been provided, demonstrating compliance with the specification. The MAH committed to submit batch analyses results on production scaled batches for the 200 mg strength as soon as they are available. For the 1000 mg strength these have been provided.

**Package**

The container closure system used for the 200 mg and 1000 mg product is a colourless neutral glass vial, type I, Ph.Eur. of 10 ml and 50 ml respectively, closed with a rubber stopper. The glass vials comply with the Ph.Eur.. The rubber stopper also complies with Ph.Eur.
Stability tests on the finished product
The drug product in the colourless neutral glass vials has been stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). Twelve months of stability data are available. No trends are observed in the stability studies of the drug product. A shelf life of 24 months has been determined. There are no stability data of long term storage in the refrigerator or freezer. Furthermore, no study on fragmentation of the rubber stopper, when punctured cold, is included in the dossier. Therefore the storage condition “Do not refrigerate or freeze” should be applied. The MAH committed to provide stability data of the batches included in the stability studies covering the whole shelf life. The MAH also committed to submit stability data on production scaled batches for the 200 mg strength. The reconstituted solution is also included in the stability studies and a chemical-physical shelf life of 24 hours at 25°C was found appropriate. According to the results of a photostability study, in accordance with ICH guidelines, the drug product is not sensitive to light.

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 “Ebewe” 200 mg and Gemcitabine “Ebewe” 1000 mg, powder for solution for infusion are parenteral formulations and fulfill 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 “Ebewe” 200 mg and Gemcitabine “Ebewe” 1000 mg, 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 product can be used instead of its reference product.

Risk management plan
Gemcitabine hydrochloride 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 hydrochloride 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
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
As the product information for this product is identical to the texts harmonized during the Gemzar Referral, no readability test was deemed necessary.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Gemcitabine “Ebewe” 200 mg and Gemcitabine “Ebewe” 1000 mg, 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 of the Gemzar Referral to the CHMP. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other gemcitabine hydrochloride containing products.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gemcitabine “Ebewe” 200 mg and Gemcitabine “Ebewe” 1000 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 July 2008. Gemcitabine “Ebewe” 200 mg and Gemcitabine “Ebewe” 1000 mg were authorised in the Netherlands on 6 November 2008.

A European harmonised birth date has been allocated (12-01-1995) and subsequently the first data lock point for gemcitabine is January 2010. The first PSUR will cover the period from July/August 2008 to January 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: September 2010.

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

Quality - medicinal product
- The MAH committed to investigate the possibility of collapsing of the drug product, when the product temperature becomes higher than the eutectic temperature.
- The MAH committed to provide batch analysis results of three production scaled batches for the 200 mg strength.
- The MAH committed to provide stability data of the batches included in the stability studies covering the whole shelf life.
- The MAH committed to submit stability data on production scaled batches for the 200 mg strength.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.</td>
<td>NL/H/1162/001-002/IA/001</td>
<td>IA</td>
<td>29-09-2008</td>
<td>14-10-2008</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>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.</td>
<td>NL/H/1162/001-002/IA/002</td>
<td>IA</td>
<td>29-08-2008</td>
<td>14-10-2008</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>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.</td>
<td>NL/H/1162/001-002/IA/003</td>
<td>IA</td>
<td>29-09-2008</td>
<td>14-10-2008</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>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.</td>
<td>NL/H/1162/001-002/IA/004</td>
<td>IA</td>
<td>29-09-2008</td>
<td>14-10-2008</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in the name of the medicinal product.</td>
<td>NL/H/1162/001-002/IB/005</td>
<td>IB</td>
<td>29-09-2008</td>
<td>6-11-2008</td>
<td>Approval</td>
<td>N</td>
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<tr>
<td>Repeat use procedure with BE, BG, CY, CZ, DK, EE, EL, ES, FI, HU, IE, IT, LT, LU, LV, MT, NO, PL, RO, SI and SK.</td>
<td>NL/H/1162/001-002/E/001</td>
<td>E</td>
<td>24-11-2008</td>
<td>22-02-2009</td>
<td>Approval</td>
<td>Y, Annex I</td>
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</table>
ANNEX I – Repeat use procedure (NL/H/1162/001-002/E/001)

The Repeat use procedure started on 13 January 2009. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states (BE, BG, CY, CZ, DK, EE, EL, ES, FI, HU, IE, IT, LT, LU, LV, MT, NO, PL, RO, SI and SK), on the basis of the data submitted, considered that essential similarity has been demonstrated for Gemcitabine “Ebewe” 200 mg and 1000 mg with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finished on 22 January 2009.

The date for the first renewal will be: 21 August 2013. This is in line with the date of the first granted MA of the procedure (UK: 22 August 2008).

A European harmonised birth date has been allocated (12-01-1995) and subsequently the first data lock point for gemcitabine is January 2010. The first PSUR will cover the period from July/August 2008 to January 2010, after which the PSUR submission cycle is 3 years. The second PSUR will cover the period from January 2010 to January 2013 and will be submitted latest 21 February 2013 together with the application for renewal.

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

- The MAH committed to submit a type II variation within 1 month (not later than 22 March 2009) to address the following items:
  
  - Update of the dossier
    1) description of the packaging material with the specification of the primary packaging material; 2) composition of sodium acetate trihydrate in form used with batch formula; 3) references given in the specification of the vials should be the monographs, 4) references given in the specification of the stopper should be the monographs, and 5) provide available stability data (containing proposed shelf life).
  
  - Update of the PL
    1) including the sentence ‘The expiry date refers to the last day of the month’, and 2) Addition of the list of names in the member states.
  
  - Immediate packaging
    As the vial for the 1000 mg strength is greater than 10 ml full labelling should be used. The MAH committed to adapt the text for the vial label of the 1000 mg strength together with the next planned variation.
  
  - Outer packaging
    1) Addition of ‘cytotoxic’ and 2) Change of the sentence ‘Discard any unused content according to standard practice for cytotoxic agents’.