Public Assessment Report

Scientific discussion

Gemind
Powder for solution for infusion
200 mg and 1 g

DK/H/1328/001-002/DC

This module reflects the scientific discussion for the approval of Gemind. The procedure was finalised on 22 April 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This assessment report concerns a generic version of Gemcitabine powder for solution for infusion 200 mg and 1 g approved through DCP with Denmark acting as RMS.

Based on the review of the data on quality, safety and efficacy, the application for Gemcitabine, in the treatment of

- Bladder cancer: Treatment of advanced bladder cancer, in combination with cisplatin
- Breast cancer: Treatment of locally advanced or metastatic breast cancer in combination with paclitaxel, in patients experiencing a relapse after (neo) adjuvant chemotherapy. Prior chemotherapy should have included an anthracycline, unless clinically contra-indicated
- Ovarian cancer: Treatment of locally advanced or metastatic epithelial ovarian cancer, in combination with carboplatin, in patients experiencing a releapse after a recurrence-free interval of at least 6 months following platin-based therapy
- Non-small cell lung cancer: Treatment of locally advanced or metastatic non-small cell lung cancer, in monotherapy or in combination with cisplatin
- Pancreatic cancer: Treatment of locally advanced or metastatic adenocarcinoma of the pancreas

was approved on 22 April 2008.

Gemcitabine is an analog nucleoside of cytidine (a pyrimidine nucleoside antimetabolite) with a wide-range activity in a variety of tumors. It is characterised by a mechanism of action which includes cytotoxic self-potentiation, masked DNA chain termination and potent inhibition of DNA repair.

Gemcitabine is a pro-drug that requires intracellular phosphorylation to active di- and triphosphate metabolites, which inhibit DNA synthesis and thereby regulate antitumor activity.

Gemcitabine is clinically used as monotherapy or in combination for the treatment of non-small cell lung cancer, pancreatic cancer, breast cancer, bladder cancer, and in some Member States, for ovarian cancers.

Gemcitabine has a good tolerability and and a very mild side-effect profile. It is administered intravenously and therefore the bioavailability is 100% by definition.

The application is made based on article 10(1) of the Directive 2001/83/EC as amended. The Reference medicinal product authorised in the Community Member States is Gemzar 200 mg and 1 g, powder for solution for infusion; Eli Lilly Nederland BV; The Netherlands.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as solution for infusion in the strengths of 200 mg and 1 g. The strength of 200 mg is packed in 10 ml glass colourless type-I tubular glass vial with bromobutyl rubber stopper and with 20 mm crimp. The 1 g strength is packed in 50 ml glass vial colourless type-I moulded glass vial with bromobutyl rubber stopper and with 20 mm crimp.
Each packaging contains 1 vial.

The excipients are: Mannitol (E421), sodium acetate trihydrate, sodium hydroxide (for pH-adjustment) and hydrochloric acid (for pH-adjustment).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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.

II.2 Drug Substance

The EDMF procedure has been followed for the active substance so the application is submitted in parallel with an EDMF. The active substance gemcitabine hydrochloride is described in the European Pharmacopoeia.

The ASM has provided a discussion (supported by batch analytical results) on potential impurities arising from the starting materials, their carryover into final active substance and whether these impurities need to be included in the specification. The manufacturing process has been satisfactorily validated for the critical process steps.

The control tests and specifications for drug substance product are adequately drawn up and comply with the monograph in Ph.Eur. and additional in-house requirements. The methods have been adequately validated.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 2 years when stored in double polyethylene bags (transparent followed by black) inside a fibre drum is justified.

II.3 Medicinal Product

The chemical-pharmaceutical documentation and Quality Overall Summary presented are of sufficient quality in view of the present European regulatory requirements.

The formulation development of the drug product and process optimisation is described. The product solution is prepared, sterile filtered, filled in vials and lyophilised. For both strengths the product solution is the same, only the fill volume differs.

The manufacturing process has been described and satisfactorily validated on three commercial scale batches of both vial strengths. Batch analysis data for the same commercial batches of both strengths are provided. All results meet the set specifications. All excipients used in the composition of the drug product are described in the Ph.Eur.

The finished product specification covers appropriate parameters for this dosage form. Two impurities which are already present in the drug substance are specified in the drug product specification. Satisfactory validations of the analytical methods have been presented.

Accelerated and long term stability studies have been carried out on commercial scale batches of both strengths. A shelf-life of 30 months is accepted for the finished product as packaged for sale. No special precautions for storage are required. It has been demonstrated that the drug product is photostable and solution stability after reconstitution/compatibility of the drug product with 0.9% sodium chloride solution for injection in different types of packaging has been demonstrated for a period of up to 24 hours when stored at 30°C. The reconstituted solution should not be refrigerated.

The following shelf-life and storage conditions are accepted:

Drug product as packaged for sale:	30 months/ No special precautions for storage.
Reconstituted solution:	24 hours/ Store below 30°C. Do not refrigerate or freeze.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of gemcitabine hydrochloride are well known. As gemcitabine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application contains an adequate overview of the published clinical data. No new pharmacodynamic or clinical data were submitted and none were required. Regarding safety no unexpected concerns were identified.

Description of the Risk Management Plan (RMP) and the pharmacovigilance system

A specific risk-management system as per Article 8.3(ia) of Directive 2001/83 EC as amended is considered not required.

Gemcitabine 200 mg and 1 g powder for solution for infusion is a generic product. With the reference medicinal product of Lilly, marketed under trade names like Gemzar, no special important risks or potential risks have been identified which require additional risk minimisation activities.

An adequate and detailed description of the pharmacovigilance system has been provided by the applicant.

IV.2 Pharmacokinetics

Gemcitabine 200 mg and 1 g, powder for solution for infusion is an aqueous solution intended for iv infusion containing the same active substance in the same concentration as the originator product (Gemzar) that is marketed in most European countries. Therefore, no bioequivalence study is required and all data available for the original product also apply for Gemcitabine 200 mg and 1 g.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gemcitabine is a well-known drug with a very mild safety profile. The presented overviews are adequate. The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

The following commitments have been made during the procedure:

Quality

Commitments made by the active substance manufacturer:

- The long term stability studies will be continued according to the stability protocol as presented in section S.7.1.

Commitments made by the drug product manufacturer:

- The long term stability study of production batches will be continued up to 36 months according to the stability protocol presented in section 3.2.P.8.1.

Summary of Product Characteristics (SPC)

- The applicant has committed to adapt the harmonised SPC as soon as the referral procedure for Gemzar is finalised.

Specific obligations

The applicant has suggested a 3-year PSUR-Cycle for this medicinal product. This has been agreed during the procedures. The product is however not on the PhVWP list with EU harmonised birth dates and consequently the PSUR's should be submitted in accordance with the finalisation date for the procedures (Day 210: 22 April 2008). The applicant is, however, advised to submit the PSURs in accordance with the EU harmonised birth date when Gemcitabine is included in the list.