Public Assessment Report

Scientific discussion

Pemetrexed BioOrganics 100 mg, 500 mg and 1000 mg, powder for concentrate for solution for infusion

(pemetrexed disodium hemipentahydrate)

NL/H/3327/001-003/DC

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This module reflects the scientific discussion for the approval of Pemetrexed BioOrganics 100 mg, 500 mg and 1000 mg, powder for concentrate for solution for infusion. The procedure was finalised on 22 October 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 Pemetrexed BioOrganics 100 mg, 500 mg and 1000 mg, powder for concentrate for solution for infusion from BioOrganics BV.

The product is indicated for:

Malignant pleural mesothelioma
Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer
Pemetrexed in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

Pemetrexed is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Alimta 100 mg and 500 mg. Alimta has been registered in Europe through a centralised procedure (EU/1/04/290) by Eli Lilly Nederland B.V. since 20 September 2004.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, France, Germany, Italy, Spain and the UK.

The marketing authorisation for the 100 mg and 500 mg strengths has been granted pursuant to Article 10(1) of Directive 2001/83/EC (generic medicinal product). For the 1000 mg strength the legal base is Article 10(3) of Directive 2001/83/EC (hybrid medicinal product), as the quantitative composition in terms of drug substance differs from the reference product.

II. QUALITY ASPECTS

II.1 Introduction

Pemetrexed BioOrganics is a white to light yellow powder.

The powder is packed in type I glass vials with a rubber stopper (bromobutyl- or chlorobutyl elastomer, coating of e.g. Teflon), an aluminium cap and an ivory (100 mg), blue (500 mg) or green (1000 mg) flip-top.

Each vial contains 100 mg, 500 mg or 1000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate). The vial sizes are 10 ml, 25 ml and 50 ml, respectively. After reconstitution, each vial contains 25 mg/ml of pemetrexed. The pH of the reconstituted solution is between 6.6 and 7.8. Further dilution is required.
Depending on the body surface but up to a dose of 1700 mg, the osmolality of the reconstituted and further diluted solution is between 280 and 500 milliosmole/kg.

The excipients are mannitol, hydrochloric acid (for pH-adjustment) and sodium hydroxide (for pH-adjustment).

II.2 Drug Substance

The active substance is pemetrexed disodium hemipentahydrate is not described in the European Pharmacopoeia (Ph. Eur.), however, a Ph. Eur. monograph exists for the related solvate pemetrexed disodium heptahydrate. The active substance is freely soluble in water, hygroscopic, and contains one asymmetric center, which has the S-configuration. Several hydrate forms are known for the disodium salt. Polymorphism is not relevant as the drug substance will be completely dissolved to prepare the drug product.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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/EMA 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
The manufacturing process of one manufacturer consists of five synthetic steps and the formation of the disodium hemipentahydrate salt. No class I solvents or heavy metal catalysts are used. The manufacturing process of the other ASMF holder consists of six synthetic steps and the formation of the disodium hemipentahydrate salt; no class I solvents are used in the process.
The manufacturing processes have been sufficiently described and validated.

Quality control of drug substance
The drug substance specification of the MAH is based on the Ph. Eur. monograph for pemetrexed disodium heptahydrate, with wider limits for pH, and additional limits for residual solvents (in line with the ICH guideline on residual solvents) and microbiological contamination (in line with the Ph.Eur.). The wider limits for pH are due to the different hydrate form of the drug substance at issue. Batch analytical data from have been provided for three and six batches of the two ASMF holders, demonstrating compliance with the drug substance specification.

Stability of drug substance
Stability data on the active substance have been provided for three production-scale batches stored at 5°C ± 3°C (36 months) and 25°C ± 2°C/60% RH (6 months), which is acceptable for drug substances intended for storage in a refrigerator. A retest period of 36 months is applied.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. A common bulk solution was developed, which is qualitatively equal to the reference product, and which is lyophilised after aseptic filtration. The main development studies concentrated on the lyophilisation process. The product at issue was shown to be comparable with the reference product with regard to appearance, osmolality, pH, assay, and impurities.
An overfill is applied for the 100 mg presentation, in line with the overfill used for the reference product. No overfill is required for the 500 mg and 1000 mg presentations. The instruction for reconstitution, as provide in section 6.6 of the SmPC is in line with the used overfill. The new presentation of 1000 mg/vial is acceptable, as it will allow for the use of a single vial for the maximum daily dose of 850 mg, instead of using two vials of 500 mg/vial.
Sufficient information has been provided that the drug product is sensitive to heat and thereby the choice for sterilization by filtration followed by aseptic filling is justified.

Manufacturing process
The main steps in the manufacturing process are preparation of the bulk solution, sterile filtration, filling of the vials, lyophilisation, capping of the vials, labelling and packing.
The product is manufactured using conventional manufacturing techniques for sterile lyophilized drug products, which are sensitive to heat sterilization. As the product is manufactured by aseptic processing, the manufacturing process is considered a non-standard process. Process validation data

on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with the specifications of the most recent version of the European Pharmacopoeia. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, reconstitution time, colour, clarity, and pH of the reconstituted solution, particulate contamination, uniformity of dosage units, water content, identification, assay, impurities, sterility, and bacterial endotoxins. The release and shelf-life requirements/limits are identical. The drug product specification is acceptable.
The analytical methods have been adequately described and validated, and the method for identification, assay and purity was found to be stability indicating. Batch analytical data from the proposed production site have been provided on three production-scale batches of each presentation, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three production-scale batches of each presentation, stored at 25°C/60% RH (18-24 months), 40°C/75% RH (6 months), and 30°C/75% RH (24 months, only 100 mg and 500 mg presentations). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Ph. Eur. Type 1 clear glass vials with bromobutyl rubber stoppers and sealed with flip-off aluminium seals.
No clear up or downward trends were observed for any of the tested parameters, for any of the presentations, under any of the conditions. A photostability study has been performed in line with guideline ICH Q1B, demonstrating that the product was not sensitive to light.
Based on the provided stability data, the proposed shelf-life of 36 months has been granted. No special storage conditions have to be applied for all presentations.

Stability data on the product after reconstitution to a concentration of 25 mg/ml have been provided, as described in the SmPC section 6.6, and further dilution with 0.9% sodium chloride to 100 ml infusion volume, to a final concentration of 1.05 mg/ml and 10 mg/ml. The reconstituted solution was found to be stable up to 24 hours when stored at 2 – 8°C and at 25°C (ambient temperature).

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 Pemetrexed BioOrganics has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pemetrexed BioOrganics is intended for generic 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 generic formulation of Alimta, 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

Pemetrexed 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

Pemetrexed BioOrganics 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). This is also valid for the 1000 mg strength. Therefore, Pemetrexed BioOrganics 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 Pemetrexed BioOrganics.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities - Bone marrow suppression - Gastrointestinal disorders - Renal disorders - Sepsis - Bullous skin reaction including SJS and TEN - Interstitial pneumonitis - Radiation pneumonitis - Radiation recall
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

PSUR
In accordance with the EURD list, no PSURs are required for generic products containing pemetrexed, referring to the 100 mg and 500 mg strength. For the pemetrexed 1000 mg strength, which is registered as a hybrid medicinal product with legal base Art. 10(3), a PSUR will be submitted with the 3-year frequency.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Alimta. No new clinical studies were conducted. The MAH demonstrated similarity based on *in vitro* data. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The current package leaflet (PL) of the reference product Alimta 100 mg and 500 mg has been used as a basis for the PL of Pemetrexed BioOrganics 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion.
The MAH submitted a bridging report, including a comparison between the leaflets to evaluate the differences. The differences are mainly editorial. A few differences pertain to the additional strength of 1000 mg. The PL does not substantially differ from the PL of the reference product and has an approved house style. Therefore it was agreed that no additional user testing is necessary.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pemetrexed BioOrganics 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion. has a proven chemical-pharmaceutical quality. The 100 mg and 500 mg strengths are generic forms of Alimta 100 mg and 500 mg; the 1000 mg strength is a hybrid form. Alimta 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 Pemetrexed BioOrganics with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 October 2015.

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