CBG MEB

Public Assessment Report

Scientific discussion

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

(pemetrexed disodium heptahydrate)

NL/H/3289/001-003/DC

Date: 31 October 2016

This module reflects the scientific discussion for the approval of Pemetrexed SUN 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion. The procedure was finalised on 20 January 2016. 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
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 SUN 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion, from Sun Pharmaceutical Industries Europe B.V.

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, Germany, Denmark, Spain, Finland, France, Hungary, Italy, Norway, Poland, Romania, Sweden and the United Kingdom.

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 SUN is a white to either light yellow or green-yellow lyophilised powder.

The powder is packed:
- Per 100 mg in a 10 ml colourless Type-I (good alkali) tubular glass vial with bromobutyl grey rubber stopper and sealed with light green coated seal
- Per 500 mg in a 50 ml colourless Type-I (good alkali) moulded glass vial with bromobutyl grey rubber stopper and sealed with light green coated seal
- Per 1000 mg in a 50 ml colourless Type-I (good alkali) moulded glass vial with bromobutyl grey rubber stopper and sealed with ash grey coated seal

Each vial contains 100 mg, 500 mg or 1000 mg of pemetrexed (as pemetrexed disodium heptahydrate). 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. The osmolality of the reconstituted solution is between 480 and 570 mOsm/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 as the disodium heptahydrate salt, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water, hygroscopic and contains one asymmetric centre, which has the S-configuration. Several hydrate forms are known for the disodium salt, and the heptahydrate is the most stable form. The manufacturer consistently produces pemetrexed disodium heptahydrate. However 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 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 synthesis of pemetrexed consists of two synthetic steps. A key intermediate is manufactured by two manufacturers. One uses a four step synthesis, and the other uses a six step synthesis. Acceptable specifications have been adopted for the starting material, solvents and reagents used.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with tighter limits for enantiomeric purity and bacterial endotoxins, and additional limits for residual solvents and bioburden, in line with, or tighter than, ICH guidelines (residual solvents) and Ph.Eur. limits (bioburden). The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the proposed drug substance specification have been provided for three production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three production scale batches stored at 5°C (18 months) and 25°C/60% RH (6 months), which is acceptable for drug substances intended for storage in a refrigerator.
Storage under long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable throughout the tested period. The claimed retest period of 2 years, with the storage condition "store at temperatures between 2°C and 8°C", is acceptable; based on the available completed 18 months long-term stability studies.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Pharmaceutical development was done by a Quality by Design (QbD) approach, a Quality Target Product Profile (QTPP) was defined, and Critical Quality Attributes (CQAs) were identified. The attributes of the drug substance were evaluated for their effect on the CQAs, a suitable specification was set for the drug substance, to decrease the impact of the drug substance attributes on the drug product CQAs. A formulation was developed that is almost identical to the reference product. Preliminary stability studies demonstrated the compatibility of the used excipients and packaging materials.
The proposed overfills are in line with those of the reference product, according to the instructions for use provided in the SmPC, and are accepted. 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.
It was shown that the drug product is sensitive to heat, and thereby sufficient justification has been

provided for sterilisation by filtration and aseptic filling.

Manufacturing process
Critical parameters of the manufacturing process were studied and optimised by a QbD approach. Critical process parameters were identified. The QTTP, as defined, is logical, considering the type of product. The CQAs and CPPs also make sense, in view of the type of process. The risk assessments performed were not on a quantitative basis, but expressed as high, low and medium; this is acceptable, considering the justifications provided. Risk assessment was performed at the beginning and also at the end; this strategy is acceptable. No multivariate studies were performed, and no design space is included in the product manufacturing process.

The main steps in the manufacturing process are: heat treatment of all silicon tubing, sterilisation of the rubber stoppers, preparation of the bulk solution, washing and depyrogenation of the vials, filling of the vials, freeze drying, capping of the vials, leak detection and visual inspection, and labelling and packing. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the specifications of the most recent version of the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification and includes tests for description, identification, water content, clarity and absorbance of the reconstituted solution, constitution time, pH, osmolality, particulate contamination, bacterial endotoxins, sterility, uniformity of dosage units, related substances, assay of mannitol, and content of pemetrexed. 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 three batches of every presentation from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three production scale batches, of every presentation, stored at 25°C/60% RH (18-24 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. For 500 mg and 1000 mg product no clear up or downward trends were observed for any of the tested parameters. For the 100 mg product a slow increase is observed for total impurities, however, always remaining below 0.5% after 18 months. Therefore, no special storage conditions have been applied. Based on the provided stability data under accelerated conditions for 6 months and long term conditions for at least 18 months the proposed shelf-life of 24 months can be accepted. A photostability study was performed according to ICH guidelines, showing that all presentations are not light sensitive and are stable in the market pack.

Information about the stability of the product after reconstitution to a concentration of 25 mg/ml and further dilution with 0.9% sodium chloride, to a final concentration of 8.5 mg/ml, has been provided. The reconstituted solution was found to be stable up to 24 hours when stored at 2-8°C. From a microbiological point of view, the product should be used immediately.

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

Summary table of safety concerns as approved in RMP:

Important identified risks	• Bullous skin reactions including Stevens Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) • Gastrointestinal disorders • Interstitial pneumonitis • Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities

	• Radiation pneumonitis • Radiation recall • Sepsis • Renal events • Bone marrow suppression
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 package leaflet (PL) 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: a pilot test, followed by two rounds with 10 participants each. The 14 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pemetrexed SUN 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 SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 January 2016.

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