COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pemetrexed Koanaa 100 mg and 500 mg powder for concentrate for solution for infusion

(pemetrexed disodium hemipentahydrate)

NL/H/3755/001-002/DC

Date: 5 March 2019

This module reflects the scientific discussion for the approval of Pemetrexed Koanaa 100 and 500 mg powder for concentrate for solution for infusion. The procedure was finalised at 23 August 2018. 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 Koanaa 100 and 500 mg powder for concentrate for solution for infusion from Koanaa Healthcare GmbH.

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 (see SmPC section 5.1).

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 (see SmPC section 5.1).

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 (see SmPC section 5.1).

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 and 500 mg powder for solution for injection registered in the Europa through a centralised procedure EU/1/04/290 by Eli Lilly Nederland B.V. since 20 September 2004 (500 mg) and 31 October 2007 (100 mg).

The concerned member states (CMS) involved in this procedure were Malta, Czech Republic and Estonia.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Pemetrexed Koanaa is a white to either light yellow or green-yellow lyophilised powder for concentrate for solution for infusion.

The powder is packed in type I flint glass vial, with a rubber stopper and sealed with an aluminium flip-off seal.

Each vial contains 100 mg or 500 mg of pemetrexed (as pemetrexed disodium hemipentahydrate). After reconstitution with sterile 0.9% NaCl, the solution 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 and diluted drug product is about 300 mOsmol/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, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.), however a Ph.Eur. monograph exists for the related solvate pemetrexed disodium heptahydrate. It is a white to either light yellow or green yellow lyophilised powder. 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. Pemetrexed disodium hemipentahydrate is consistently manufactured. 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.

<u>Manufacturing process</u>
The synthesis of pemetrexed disodium hemipentahydrate consists of eight synthetic steps, and three purification steps. The starting materials are acceptable. No class 1 organic solvents are used. The heavy metal catalyst palladium is used in the first two steps. The specifications for the starting materials, solvents and reagents used are acceptable. The

structure and the polymorphic form of pemetrexed disodium hemipentahydrate were adequately characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for full scale batches stored at 2-8°C (ten batches, 18-36 months) and 25°C/60% RH (six batches, six months). All parameters stayed within specification for the proposed period. Based on the data submitted, a retest period could be granted of 24 months when stored at 2-8°C.

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. A common bulk solution was developed, which is qualitatively equal to the reference product, and which is lyophilised after aseptic filtration. The method of sterilisation has been chosen according to the applicable decision tree and is in line with that of the reference product. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps in the manufacturing process are dispensing, collection of water for injection, compounding, filtration, filling & half stoppering, lyophilisation, sealing & external vial washing, visual inspection, and packaging. This manufacturing process is considered to be a non-standard process, as aseptic processing is used to prepare the final drug product.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three exhibit batches for the 100 mg/vial presentation, and three exhibit batches for the 500 mg/vial.

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 includes tests for description, identification, pH, water content, colour value, light transmission, completeness and clarity of solution, particulate matter, reconstitution time, uniformity of dosage units, bacterial endotoxins, sterility, related substances, assay, and extractable volume. 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 each 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 on three full scale batches of each presentation. The batches were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) in upright and inverted position. The conditions used in the stability studies are according to the ICH stability guideline. On basis of the data submitted, a shelf life was granted of 36 months. No special storage conditions have to be applied. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.
In use stability data has been provided demonstrating that the product remains stable for 24 hours at 2-8°C following reconstitution and dilution.

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 Koanaa 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 Koanaa 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 Koanaa 100 mg and 500 mg powder for concentrate for solution for infusion 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). The quantitative composition of Pemetrexed Koanaa 100 mg and 500 mg powder for concentrate for solution for infusion is 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.

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 Koanaa.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Non-compliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal toxicities • Renal disorders • Gastrointestinal disorders • Interstitial pneumonitis • Radiation pneumonitis

	• Radiation recall • Sepsis • Bullous skin reaction including Stevens-Johnson syndrome and toxic epidermal necrolysis • 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.

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 that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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: two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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 Koanaa 100 mg and 500 mg powder for concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Alimta 100 mg and 500 mg powder for concentrate for solution for infusion. Alimta is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

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 Koanaa with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 August 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse