CBG MEB

Public Assessment Report

Scientific discussion

Pemetrexed Synthon 25 mg/ml, concentrate for solution for infusion

(pemetrexed diarginine)

NL/H/3920/001/DC

Date: 27 June 2018

This module reflects the scientific discussion for the approval of Pemetrexed Synthon 25 mg/ml, concentrate for solution for infusion. The procedure was finalised on 8 November 2017. 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Synthon 25 mg/ml, concentrate for solution for infusion, from Synthon B.V.

The product is indicated for:

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

Non-small cell lung cancer
Pemetrexed Synthon 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 Synthon 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 Synthon 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 500 mg powder for concentrate for solution for infusion (EU/1/04/290) which has been registered in the EU by Eli Lilly Nederland B.V. since 22 September 2004.

The concerned member state (CMS) involved in this procedure was Luxembourg.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

Scientific advice
Scientific advice was given by different EU-member states before an application for marketing authorisation was submitted. The scope of the advices concerned the concentration of the product, the differences in excipients and a waiver for bioequivalence studies.
It was concluded that arginine, cysteine and propylene glycol are excipients often used in powder for solution for infusions and in solutions for infusion. The MAH was advised to include in the submission a justification of the use of these excipients and to demonstrate (e.g. pH, osmotic value, impurities) similarity between test and innovator product after reconstitution.

II. QUALITY ASPECTS

II.1 Introduction

Pemetrexed Synthon is a clear, colourless to slightly yellow to brown, brown yellow or green yellow concentrate for solution for infusion. The pH of the concentrate is between 8.3 and 9.0.

Pemetrexed Synthon is packed in Type I glass vials containing 4 ml, 20 ml or 40 ml of concentrate. The vials are closed with a rubber stopper (bromobutyl), a cap and a flip-top.

One vial of 4 ml concentrate (ivory flip-top) contains 100 mg pemetrexed (as pemetrexed diarginine).
One vial of 20 ml concentrate (blue flip-top) contains 500 mg pemetrexed (as pemetrexed diarginine).

One vial of 40 ml concentrate (green flip-top) contains 1000 mg pemetrexed (as pemetrexed diarginine).

The excipients are L-arginine, L-cysteine, propylene glycol, citric acid and water for injections.

II.2 Drug Substance

The active substance is pemetrexed diarginine, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.) as diacid. The Ph.Eur. includes a monograph for pemetrexed disodium heptahydrate. Pemetrexed is a white or almost white powder, almost insoluble in water, very slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride. The aqueous solubility of pemetrexed is higher at pH ≥8. Since pemetrexed is administered as a solution, polymorphism, moisture content and particle size distribution are not relevant for the quality of the drug product. Pemetrexed has one centre of chirality. It is marketed as the (S)-enantiomer.

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 described synthesis comprises eight synthetic steps, with the isolation of three intermediates. The starting materials of this synthesis are acceptable. Adequate controls are applied for the starting materials, reagents and intermediates. The synthesis has been described in sufficient detail. The characterisation data is appropriate.

Quality control of drug substance
The applied controls and limits are, where applicable, in line with the Ph.Eur. monograph for pemetrexed disodium heptahydrate. In-house methods are applied for the determination of solvents, assay and impurities, and identification and enantiomeric purity. The methods have adequately been described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three small scale batches.

Stability of drug substance
Results of stability studies with three batches, stored for 18 months at 5°C and 6 months at 25°C/60% RH, have been provided. Based on the data submitted, a retest period could be granted of 24 months when stored at 5°C, in the original packaging, under inert atmosphere.

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.
Different to the reference product, which is a powder for a concentrate (25 mg/ml) for solution for infusion and contains only mannitol as excipient, the proposed product is a concentrate that only needs to be diluted with 5% glucose. Pharmaceutical development has been adequately performed.

The excipients are usual for a solution for infusion. According to the non-clinical assessment, the different formulation of Pemetrexed Synthon is not expected to have an impact on the pharmacology or safety. The formulation development has adequately been performed and described. The inclusion and concentration of the anti-oxidant has been adequately justified. Differences compared to the reference product have been discussed and justified.

Manufacturing process
The manufacturing process comprises the manufacture of the bulk solution, filtration of the bulk solution, filling into vials and subsequent terminal sterilisation by autoclavation. The manufacturing

process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three small scale batches of each presentation in accordance with the relevant European guidelines.

Control of excipients
The specification for L-cysteine is largely in line with the Ph.Eur monograph for cysteine hydrochloride monohydrate and is acceptable. The test methods are pharmacopoeial tests. For the other excipients reference is made to 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 appearance, colour of solution, clarity of solution, pH of solution, particulate matter, identification of pemetrexed, assay of pemetrexed and cysteine, related substances, enantiomeric purity, extractable volume, bacterial endotoxins and sterility. 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
The results have been provided of stability studies with three batches of each presentation stored for 12 months at long-term and six months at accelerated conditions. On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are “do not freeze”.

Chemical and physical in-use stability of infusion solution of pemetrexed after dilution with 5% glucose solution for injection was demonstrated for 24 hours in the dark at refrigerated temperature (2-8°C).

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 Synthon 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 Synthon 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 Synthon 25 mg/ml, 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).

Although the pharmaceutical form of the concerned product (concentrate) is different from the reference product (lyophilised powder), after reconstitution and dilution, the concentration of pemetrexed in the final infusion solution is the same. Differences in excipients are not expected to influence the pharmacokinetic profile of pemetrexed. The choice and concentration of L-arginine and target pH have adequately justified, also based on the results of stability studies. Although not specifically tested, it is well-known and also clear from the decrease observed in assay at lower levels of anti-oxidants, that addition of an anti-oxidant is required for a concentrate for solution for infusion of pemetrexed. The proposed anti-oxidant and its concentration have adequately been justified by the performed studies. Also the positive impact of different levels of propylene glycol, usefulness of citric acid as anti-oxidant synergist and the impact of pH on stability has been properly investigated. No significant influence was observed on total impurity level for solution with pH between 8.5 - 9.4. The concentrate can be steam sterilised at standard sterilisation conditions (121°C for 15 minutes).

Pemetrexed Synthon may be considered as pharmaceutically 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 Clinical safety

For some patients, pemetrexed is used in combination with cisplatin. The excipient L-arginine is incompatible with cisplatin. Therefore, for combination treatments of pemetrexed and cisplatin intravenous lines should be flushed after administration of Pemetrexed 25 mg/ml concentrate for solution for infusion.

IV.4 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 Synthon.

Summary table of safety concerns as approved in RMP:

Important identified risks	Bone marrow suppression Bullous skin reaction including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) Gastrointestinal disorders Interstitial pneumonitis Noncompliance with folic acid and vitamin B_{12} regimens manifested mainly as haematological and gastrointestinal toxicities Radiation pneumonitis

	Radiation recall Renal disorders Sepsis
Important potential risks	Medication error*
Missing information	None

*the dilution should be performed as described in the MAH's SmPC.

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

IV.5 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 submitted justification for request of a biowaiver for the drug product. A comparative bioavailability study between de innovator product and Pemetrexed Synthon was not required as the final solution is aqueous and administered intravenously.
Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to of Alimta 100 mg and 500 mg powder for concentrate for solution for infusion. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pemetrexed Synthon 25 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Alimta 500 mg powder for concentrate for solution for infusion. 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. Although the pharmaceutical form of the concerned product (concentrate) is different from the reference product (lyophilised powder), after reconstitution and dilution, the concentration of pemetrexed in the final infusion solution is the same. Differences in excipients is not expected to influence on the pharmacokinetic profile of pemetrexed. The concerned product, Pemetrexed Synthon 25 mg/ml concentrate for solution for infusion is considered similar to the innovator Alimta.

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 Synthon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 November 2017.

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
NL/H/3920/1/IA/001	To update sections 4.4 and 4.8 of the SmPC and section 4 of the PL to implemented the wording agreed by the EMA following the outcome of the PRAC recommendation adopted at 11 January 2018	SmPC and PL	14-5-2018	Approval	