COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(pemetrexed disodium hemipentahydrate)

NL/H/4927/001/DC

Date: 20 October 2020

This module reflects the scientific discussion for the approval of Pemetrexed Sandoz 25 mg/ml, concentrate for solution for infusion. The procedure was finalised at 10 June 2020. 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 Sandoz 25 mg/ml, concentrate for solution for infusion from Sandoz 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 (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 hybrid application claiming essential similarity with the innovator product Alimta 500 mg powder for solution for injection registered in the EEA 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, Bulgaria, Denmark, Finland, France, Greece, Iceland, Ireland, Italy, Lithuania, Norway, Poland, Portugal, Romania, Slovenia, Spain and Sweden.

Pemetrexed Sandoz has the same composition with regard to the active substance i.e. pemetrexed, as Alimta. However, they differ with regards to the pharmaceutical form. Alimta (after reconstitution) and Pemetrexed Sandoz contain the same active moiety, pemetrexed in the same concentration i.e. 25 mg/ml. Pemetrexed Sandoz has same route of administration (intravenous infusion) and same indications as that for Alimta. Consequently, the marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

Pemetrexed Sandoz is a clear, colourless to yellow or green – yellow solution and practically free of particles. Each 1 ml concentrate for solution for infusion contains 25 mg pemetrexed (as pemetrexed disodium hemipentahydrate). The pH of the concentrate is 8.0-9.0.
There are three types of presentations available:

- A vial with 4 ml contains 100 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
- A vial with 20 ml contains 500 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
- A vial with 40 ml contains 1000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

The concentrate is packed in clear, colourless type I glass vial with bromobutyl rubber stopper and aluminium crimp cap with light blue plastic flip-off.

The excipients are sodium thiosulfate pentahydrate (E539), propylene glycol (E1520), hydrochloric acid (for pH adjustment), sodium hydroxide (E524) (for pH adjustment) and water for injection

II.2 Drug Substance

The active substance is pemetrexed as the disodium .2.5 H_2O salt. The 7 H2O salt is described in the European Pharmacopoeia. It is a white or off-white powder. The active substance is soluble in water, hygroscopic, and contains one asymmetric centre, which has the *S*-configuration. Two hydrate forms are known for the disodium salt. Polymorphism is not relevant as the drug product is a solution.

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 seven steps. The starting materials are acceptable. The active substance has been adequately characterised

and acceptable specifications have been adopted for the starting material, solvents and reagents.

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 six batches from the drug product manufacturer and three batches of the drug substance manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for three production batches stored at 5°C (24 months) and 25°C/60% RH (6 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. The main development studies were formulation development and process development. No clinical studies or bioequivalence studies have been performed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps in the manufacturing process are weighing ingredients, compounding and preparation of product solution, sterilisation of filling equipment, sterile filtration, washing and depyrogenation of empty containers, filling and closing of vials, exterior cleaning, terminal sterilisation of vials, sampling for quality control, visual inspection and sampling for quality control. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for a sufficient amount of batches.

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 appearance, clarity and colour of solution, visible and sub-visible particles, pH, extractable volume, identity and content of pemetrexed and sodium thiosulfate, D-pemetrexed, related substances, sterility and bacterial endotoxins. 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 have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three production scale batches of common bulk and three batches of each presentation. The batches were stored at 5°C (2 months bulk and 18 presentations), 25°C/60% RH (12 months bulk and 18 presentations), 30°C/65% RH (12 months bulk and 18 presentations) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations. On basis of the data submitted, a shelf life could be granted of 2 years for the unopened vial when not stored above 25°C and in the original package in order to protect from light. For storage conditions after first opening and dilution of the medicinal product, see SmPC section 6.3.

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 Sandoz 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 Sandoz is intended for hybrid 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 hybrid 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 Sandoz 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). The quantitative composition of Pemetrexed Sandoz 25 mg/ml, 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 Sandoz.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
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 hybrid 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 Alimta for content and the MAH's house style for layout. 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 Sandoz 25 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid 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.

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 Sandoz 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