COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(pemetrexed disodium)

NL/H/4114/001-002/DC

Date: 28 January 2020

This module reflects the scientific discussion for the approval of Pemetrexed Waverley 100 mg and 500 mg powder for concentrate for solution for infusion. The procedure was finalised at 28 November 2019. 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 Waverley 100 mg and 500 mg powder for concentrate for solution for infusion from Waverley Pharma Europe Limited.

Malignant pleural mesothelioma
Pemetrexed powder for concentrate for solution for infusion in combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer
Pemetrexed powder for concentrate for solution for infusion in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology (see SmPC section 5.1).
Pemetrexed powder for concentrate for solution for infusion 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 powder for concentrate for solution for infusion 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 mg and 500 mg powder for solution for injection (EU/1/04/290) which has been registered in the EEA by Eli Lilly Nederland B.V. since 31 October 2007 (100 mg) and 20 September 2004 (500 mg).

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Germany, Spain, Ireland, Luxembourg, Poland, Slovenia, Slovakia, and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

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

The powder is packed in 10 ml Type I clear glass vial with chlorobutyl grey rubber stopper containing 100 mg of pemetrexed, sealed with dark grey aluminium flip off seal.

The content of 100 mg vials should be reconstituted with 4.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative. This results in a solution containing 25 mg/ml pemetrexed. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8.
The appropriate volume of reconstituted pemetrexed solution must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.

The excipients are mannitol (E421), hydrochloric acid (E507) (for pH adjustment) and sodium hydroxide (E524) (for pH adjustment).

II.2 Drug Substance

The active substance is pemetrexed as the disodium 2.5 H_2O salt. The 7 H_2O salt is described in the European Pharmacopoeia (Ph.Eur.). The drug 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 substance will be completely dissolved in the preparation of 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 manufacturing process has been adequately described. The proposed synthesis of the drug substance consists of six synthetic steps and the formation of the disodium hemipentahydrate salt, and a final purification step. Satisfactory in process controls and

controls on key intermediates have been established in order to ensure production of an active substance of consistent quality.

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. The specification includes tighter limits regarding purity tests, and additional tests and limits are provided on some quality aspects. Batch analytical data demonstrating compliance with this specification have been provided for twelve batches.

Stability of drug substance
Stability data have been submitted of eight production batches stored at 5°C (long term) up to 48 months and three production batches at 25°C/60% RH (accelerated) during 6 months, in the proposed packaging. All results remained within specification limits. In addition, stability results have been provided for two annual batches of pemetrexed disodium with the revised Ph.Eur. specification stored under long term conditions for 24 months and 18 months respectively. No significant changes or trends in Ph.Eur. impurities A–D levels were observed. Based on the data submitted, a claimed retest period could be granted of 36 months when stored in tightly closed container at 2-8°C to protect from light and moisture.

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 concentrated on selection of the solvent and order of mixing, the hold time of bulk solution before lyophilisation and the lyophilisation process. Chemical-physical properties of the current product are comparable to those of the innovator product. Pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing processes consists of dispensing, bulk solution preparation, pH measurement and volume makeup, primary filtration, online filtration and filling and partial stoppering, lyophilisation, crimping, external decontamination, visual inspection and packaging. Given the manufacturing process contains a critical lyophilisation step, the manufacturing process is regarded non standard for both strengths.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with 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, reconstitution time, completeness and clarity of solution, average weight of cake, assay, related substances, particulate contamination, sterility, bacterial endotoxins and seal integrity. 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 production scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product are included for three production scale batches. The batches have been stored up to 36 months at 25°C/60% RH, and 6 months at 40°C/75% RH.

The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed container closure systems. No significant changes or trends were observed in any of the parameters studied, and all results remained within the specified limits. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

Based on the provided stability data a shelf-life was granted of 24 months when stored in the proposed packaging, without special storage conditions.

Stability data have been provided demonstrating that the product remains stable for 24 hours following reconstitution, when stored at refrigerated temperature. 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 Waverley 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 Waverley 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 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Pemetrexed 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 100 mg powder for concentrate for solution for infusion.

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

Important identified risks	• Bullous skin reaction including SJS and TEN • Gastrointestinal disorders • Interstitial pneumonitis • Noncompliance with folic acid and vitamin B12 regimes manifested mainly as haematological and gastrointestinal toxicities • Radiation pneumonitis • Radiation recall • Sepsis • Renal disorders • Bone marrow suppression
Important potential risks	--
Missing information	--

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: a pilot test with four participants, followed by 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 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 solution for injection. 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 Waverley with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 November 2019.

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