COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pemetrexed SUN 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11 mg/ml solution for infusion (pemetrexed disodium heptahydrate)

NL/H/5223/001-010/DC

Date: 10 November 2021

This module reflects the scientific discussion for the approval of Pemetrexed SUN 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11 mg/ml solution for infusion. The procedure was finalised at 7 September 2021. 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
HPLC	High-performance liquid chromatography
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 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11 mg/ml solution for infusion, from Sun Pharmaceutical Industries Europe B.V.

The products are 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 section 5.1 of the SmPC).

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 section 5.1 of the SmPC).

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 section 5.1 of the SmPC).

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 products Alimta 100 mg and 500 mg powder concentrate for solution for infusion. The Alimta 100 mg and 500 mg strengths have been registered in the European Economic Area since 20 September 2004 and 31 October 2007, respectively, by Eli Lilly Nederland BV via centralised procedure EMEA/H/C/000564.

The concerned member states (CMS) involved in this procedure were Germany, Spain, France, Italy (except for the 5, 10 and 11 mg/ml strengths) and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC. Pemetrexed SUN differs from the reference product in the dosage form and strength. Alimta is a powder for concentrate for solution for infusion while Pemetrexed SUN is a ready-to-use solution for infusion (infusion bags). The proposed drug product contains the same active substance as the refence medicinal product. The qualitative composition of the drug substance, the route of administration and indication of Pemetrexed SUN are similar as that of the reference product.

II. QUALITY ASPECTS

II.1 Introduction

Pemetrexed SUN are clear colourless to yellow or green-yellow solutions for infusion. The solutions are free from visible particulate matter and have a pH of 6.0 to 8.0 and an osmolality between 275 to 375 mOsmol/kg.

5 mg/ml
Each infusion bag of 100 ml contains 500 mg pemetrexed (equivalent to 551.43 mg pemetrexed disodium and equivalent to 699.0 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 5.0 mg/ml pemetrexed (equivalent to 6.99 mg of pemetrexed disodium heptahydrate).

6 mg/ml
Each infusion bag of 100 ml contains 600 mg pemetrexed (equivalent to 661.71 mg pemetrexed disodium and equivalent to 838.8 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 6.0 mg/ml pemetrexed (equivalent to 8.388 mg of pemetrexed disodium heptahydrate).

6.5 mg/ml
Each infusion bag of 100 ml contains 650 mg pemetrexed (equivalent to 716.85 mg pemetrexed disodium and equivalent to 908.7 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 6.5 mg/ml pemetrexed (equivalent to 9.09 mg of pemetrexed disodium heptahydrate).

7 mg/ml
Each infusion bag of 100 ml contains 700 mg pemetrexed (equivalent to 772.0 mg pemetrexed disodium and equivalent to 978.6 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 7.0 mg/ml pemetrexed (equivalent to 9.79 mg of pemetrexed disodium heptahydrate).

7.5 mg/ml
Each infusion bag of 100 ml contains 750 mg pemetrexed (equivalent to 827.14 mg pemetrexed disodium and equivalent to 1048.5 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 7.5 mg/ml pemetrexed (equivalent 10.485 mg of pemetrexed disodium heptahydrate).

8 mg/ml
Each infusion bag of 100 ml contains 800 mg pemetrexed (equivalent to 882.28 mg pemetrexed disodium and equivalent to1118.4 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 8.0 mg/ml pemetrexed (equivalent to 11.184 mg of pemetrexed disodium heptahydrate).

8.5 mg/ml
Each infusion bag of 100 ml contains 850 mg pemetrexed (equivalent to 937.42 mg pemetrexed disodium and equivalent to 1188.3 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 8.5 mg/ml pemetrexed (equivalent to 11.883 mg of pemetrexed disodium heptahydrate).

9 mg/ml
Each infusion bag of 100 ml contains 900 mg pemetrexed (equivalent to 992.57 mg pemetrexed disodium and equivalent to 1258.2 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 9.0 mg/ml pemetrexed (equivalent to 12.582 mg of pemetrexed disodium heptahydrate).

10 mg/ml
Each infusion bag of 100 ml contains 1000 mg pemetrexed (equivalent to 1102.85 mg pemetrexed disodium and equivalent to 1398.0 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 10.0 mg/ml pemetrexed (equivalent to 13.98 mg of pemetrexed disodium heptahydrate).

11 mg/ml
Each infusion bag of 100 ml contains 1100 mg pemetrexed (equivalent to 1213.14 mg pemetrexed disodium and equivalent to 1537.8 mg of pemetrexed disodium heptahydrate). One ml of the solution for infusion contains 11.0 mg/ml pemetrexed (equivalent to 15.378 mg of pemetrexed disodium heptahydrate).

All strengths of Pemetrexed SUN are supplied in two different packaging types. They are packed sterile in flexible multilayer non-PVC infusion bags overwrapped with an aluminium pouch along with an oxygen scavenger. The infusion bag stopper (Polycarbonate Minitulipe M95A spike port) consists of a spike port with a chlorobutyl (latex-free) 6321 GS joint, and a polyolefin RFT connector tubing is used. Also, the solutions for infusion are supplied sterile in flexible multilayer non-PVC infusion bags overwrapped with an aluminium pouch with a transparent window along with one oxygen scavenger and one oxygen indicator. The infusion bag stopper consists of a polycarbonate Minitulipe M95A spike port with a chlorobutyl (latex-free) 6321 GS joint, and polyolefin RFT connector tubing is used.

Different colour coding employed for printing different strength on overwrap is laid down for aiding in differentiating between the product strengths.

The excipients are sodium chloride, sodium hydroxide (for pH adjustment), concentrated hydrochloric acid (for pH adjustment) and water (for injection).

II.2 Drug Substance

The active substance is pemetrexed disodium heptahydrate, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white or almost white powder, freely soluble in water, very slightly soluble in anhydrous ethanol and

practically insoluble in methylene dichloride. The solubility in aqueous solution is pH dependent. The active substance is hygroscopic and contains one asymmetric centre, which has the *S*-configuration. Several hydrate forms are known for the disodium salt. Pemetrexed disodium heptahydrate is consistently manufactured.

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 consists of the synthesis of an intermediate form, followed by the manufacturing of the final active substance. The key intermediate form is produced at two production sites, in three or six steps. From the intermediate form, the final form is produced in three steps at one production site. Adequate specifications have been adopted for starting materials, solvents and reagents. Detailed process flow diagrams and detailed descriptions of all steps are provided, including details on temperatures, stirring times, in-process controls, raw-material input details, equipment details, and yields. No additional manufacturing steps, like blending or milling are described. The active substance has been 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., with tighter limits for enantiomeric purity and bacterial endotoxins. Additional limits are in line with, or tighter than, ICH guidelines (residual solvents) and Ph. Eur. limits (bioburden). Batch analytical data demonstrating compliance with the 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 eight production scale batches stored at 5°C and 25°C/60% RH in accordance with applicable European guidelines. For three batches, 18 months long-term and six month accelerated data are available. For the five other batches, only the initial time point is presented. The batches were stored in double Alu/LDPE bags, kept in a LDPE bag, kept in HDPE container. Both 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. Based on the data submitted, a retest period could be granted of two years, when stored temperatures between 2°C and 8°C.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions are explained. The MAH has used elements of a Quality by Design approach during the pharmaceutical development, including identification of Critical Quality Attributes (CQA) and the selection of Critical Process Parameters (CPP). Justifications for the risk assignments are provided. Furthermore, the MAH has also presented control strategies to reduce or control risks.

Adequate formulation optimisation studies have been performed including temperature cycling studies, pH stability studies, photostability, sterility and several compatibility studies. The results of these studies were acceptable. Terminal sterilisation was selected as the method of sterilisation for Pemetrexed SUN. A detailed risk assessment report on leachables and extractables from the primary and secondary packaging material is provided. It is sufficiently supported that the risk to patient safety due to extractables and leachables is low.

The same excipients are used as in the reconstituted and diluted reference products. The compatibility study results support that the active substance is compatible with the excipients of Pemetrexed SUN. It is clearly stated that no overages are used, based on the validation, batches analyses, and stability data. The fill volume is found adequate to ensure that the requirement for delivered dose is met at release, based on the process validation and batch release data.

Manufacturing process

The manufacturing process consists of preparation of the bulk solution, filtering of the bulk solution, followed by filling of the bags. Finally, the bags are terminally sterilised. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches per strength, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Microbiological attributes

The microbial attributes were evaluated to assure manufacturing controls, finished products quality and container closure integrity. The container closure integrity was evaluated by a microbial challenge test and a sterility test. The microbial challenge test results were satisfactory and the same configuration for primary and secondary packaging material qualified for sterility assurance and the integrity of container closure system was confirmed.
The sterility test showed that Pemetrexed SUN in the final pack complies for sterility testing as per Ph. Eur. (General Chapter 2.6.1). This confirms the integrity of container closure system used.

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 by high-performance liquid chromatography (HPLC) and UV, pH, osmolality, extractable volume, weight loss, particulate contamination, related substances, sterility, bacterial endotoxins and assays of sodium chloride and pemetrexed. The release and shelf life limits are identical. However, the following tests are only tested at release: identification by UV, extractable volume, and assay of sodium chloride. 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 full scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three full scale batches per strength stored at 40°C/NMT 25% RH for six months, and at 25°C/40% RH for twelve months. A bracketing approach has been applied to the use of the proposed packaging during the stability studies. This is deemed justified. The conditions used in the stability studies are according to the ICH stability guideline. After six months at long term and accelerated conditions, an increase in some impurities was observed, however, all remain within specification. No changes are observed in any of the other parameters measured at both conditions.

Photostability studies were performed in accordance with ICH recommendations and showed that the products are stable when exposed to light. However, data do show that there is an increase of related substances when exposed to light, although, the levels remain within specification. On basis of the submitted data, a shelf life has been granted of two years when stored in the original package and protected from light.

Chemical and physical in-use stability of Pemetrexed SUN in infusion bag once removed from overwrap was demonstrated for 30 days at room temperature if protected from light and seven days at room temperature if not protected from light. From a microbiological point of view, the product should be used immediately, in-use storage times and condition prior to use are the responsibility of the user and would not be longer than 24 hours at room temperature, unless aseptic technique is used for spiking sterile IV administration infusion set.

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 have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pemetrexed SUN are intended for substitution of the innovator products, 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

These products are hybrid formulations of Alimta which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 disodium heptahydrate 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. Since this procedure concerns a hybrid application for an aqueous intravenous solution, the MAH has submitted justification for a biowaiver of the bioequivalence study.

IV.2 Pharmacokinetics

No new pharmacokinetic studies were considered needed for this hybrid application. The MAH presented bibliographical data to describe the absorption, bioavailability, distribution,

elimination, excretion and metabolism of dobutamine. Sufficient references were provided to support the presented data on pharmacokinetics.

Biowaiver

Both Pemetrexed SUN and Alimta are administered as aqueous intravenous solutions and contain the same active substance at similar concentrations at time of infusion. According to the *Guideline on the investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product." Since there are no excipients that interact with pemetrexed (e.g. complex formation), or otherwise affect the disposition of pemetrexed, there is no requirement for a bioequivalence study. Hence, a biowaiver has been granted.

Clinical efficacy and safety

Pemetrexed SUN differ from the reference products in dosage form and strength. Both differences have been justified, since both products are aqueous solutions with a similar qualitative composition of drug substance, route of administration and indications. Therefore, it may be considered as therapeutic equivalent, with the same clinical efficacy and safety profile as known for the active substance of the reference medicinal products. The drug products can be used instead of the reference products.

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.

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

Important identified risks	• None
Important potential risks	• Medication errors
Missing information	• None

The MAH adequately described the risk of medication errors in the RMP. In addition, a warning is included in the SmPC, PIL and labelling. The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for this risk and that no additional pharmacovigilance activities are required.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Alimta. No new clinical studies were conducted. The MAH demonstrated through bibliographical data that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference products. A clinical overview with relevant references was provided and no new clinical studies were required. Changes in

pharmaceutical form and strength have been adequately discussed and are acceptable. Adequate risk minimisation measurements are described to minimise the risk of medication errors.

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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test with three 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pemetrexed SUN 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11 mg/ml solution for infusion have a proven chemical-pharmaceutical quality and are hybrid forms of Alimta 100 mg and 500 mg powder concentrate for solution for infusion. Alimta are well-known medicinal products with established favourable efficacy and safety profiles.

Since both the reference and current products are intended for parenteral use, no bioequivalence study was deemed necessary. A biowaiver has been granted. Clinically relevant changes that were made compared to the reference products have been adequately addressed and the clinical efficacy and clinical safety profiles were considered acceptable.

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 7 September 2021.

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