EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2017
EMA/CHMP/270680/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Hospira UK Limited

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/004488/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Pemetrexed Hospira UK Limited
Applicant:	Hospira UK Limited Horizon, Honey Lane Hurley Maidenhead SL6 6RJ UNITED KINGDOM
Active substance:	pemetrexed ditromethamine
International non-proprietary name/Common name:	pemetrexed
Pharmaco-therapeutic group (ATC Code):	antimetabolites, folic acid analogues (L01BA04)
Therapeutic indication(s):	Malignant pleural mesothelioma Pemetrexed Hospira UK Limited in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma. Non-small cell lung cancer Pemetrexed Hospira UK Limited 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). Pemetrexed Hospira UK Limited 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). Pemetrexed Hospira UK Limited 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).
Pharmaceutical form(s):	Powder for concentrate for solution for infusion

Strength(s):	100 mg, 500 mg and 1000 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

Table of contents

List of abbreviations

AS: active substance

ASMF: Active Substance Master File

BSA : Body surface area

Cmax : Maximum measured concentration of drug in plasma

CR : Complete response

CTC : Common toxicity criteria

DNA : Deoxyribonucleic acid

DR: Death receptor

DSC Differential Scanning Calorimetry
FT-IR Fourier Transfom Infrared

GC: Gas Chromatography

h : Hour

HDPE: High Density Polyethylene

HPLC: High performance liquid chromatography

ICH : International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-MS Inductively coupled plasma mass spectrometry
IR Infrared
IV / i.v. : Intravenous

Kd : Dissociation constant

Ki : Binding constant

L : Litre

LDPE: Low Density Polyethylene

MAA : Marketing Authorization Application

mg : Milligram

min : Minute

ml : Millilitre

MPM : Malignant pleural mesothelioma

NLT Not less than
NMR Nuclear Magnetic Resonance
NMT Not more than
NSCLC : Non-small-cell lung cancer

OS : Overall survival

PFS : Progression free survival

Ph. Eur.: European Pharmacopoeia

ppm: parts per million

PR : Partial response

PS : Performance status

RD : Recommended dose

RH: Relative Humidity

SmPC Summary of Product Characteristics

TGA: thermogravimetric analysis

TLSB: triple laminate sunlight barrier bag

UV Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Limited submitted on 28 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Pemetrexed Hospira UK Limited, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 September 2015.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier.

The applicant applied for the following indications:

Malignant pleural mesothelioma

Pemetrexed Hospira UK Limited in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed Hospira UK Limited 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.

Pemetrexed Hospira UK Limited 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.

Pemetrexed Hospira UK Limited 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information and complete quality data. There is no requirement for bioequivalence testing according to the Guideline on the Investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

This application is submitted as a multiple of Pemetrexed Hospira authorised on 20 November 2015 in accordance with Article 82.1 of Regulation (EC) No 726/2004. The submission of this application is due to patent grounds.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Alimta, 500 mg, 100 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 20/09/2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/290/001-002

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Alimta, 500 mg, 100 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 20/09/2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/290/001-002

Scientific advice

The applicant received Scientific Advice from the CHMP on 23 July 2015. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The CHMP and PRAC Rapporteurs appointed by the CHMP were:

CHMP Rapporteur: Alar Irs

PRAC Rapporteur: Claire Ferard

- The application was received by the EMA on 28 April 2016.
- The procedure started on 14 June 2016.
- The CHMP Rapporteur's first Assessment Report was circulated to all CHMP members on 29 June 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 30 June 2016.
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be

sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2016.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 October 2016.
- The CHMP and PRAC Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 November 2016.
- During the meeting on 1 December 2016 the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- The CHMP and PRAC Rapporteur circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 December 2016.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 19 January 2017.
- The CHMP and PRAC Rapporteur circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 February 2017.
- During the meeting on 23 February 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Pemetrexed Hospira UK Limited.

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion. Pemetrexed Hospira UK Limited 100 mg, 500 mg or 1000 mg Powder for Concentrate for Solution for Infusion has the same active substance (pemetrexed) as the centrally approved reference medicinal product Alimta (EU/1/04/290/001-002).

The claimed indications for this generic application are:

Malignant pleural mesothelioma

Pemetrexed Hospira UK Limited in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed Hospira UK Limited 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.

Pemetrexed Hospira UK Limited 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.

Pemetrexed Hospira UK Limited 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.

As monotherapy or in combination with cisplatin the recommended dose of Pemetrexed Hospira UK Limited is 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Pemetrexed Hospira UK Limited must be reconstituted and further diluted prior to use. After reconstitution, each strength of the proposed product contains 25 mg/ml of pemetrexed.

About the product

Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Mode of action

In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase.

The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT.

Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 100 mg/vial, 500 mg/vial and 1000 mg/vial of pemetrexed (as ditromethamine dihydrate) as active substance. After reconstitution with sterile water for injections, the three presentations result in 25 mg/ml of pemetrexed. Once reconstituted, further dilution with 5% glucose solution for injection is required before administration.

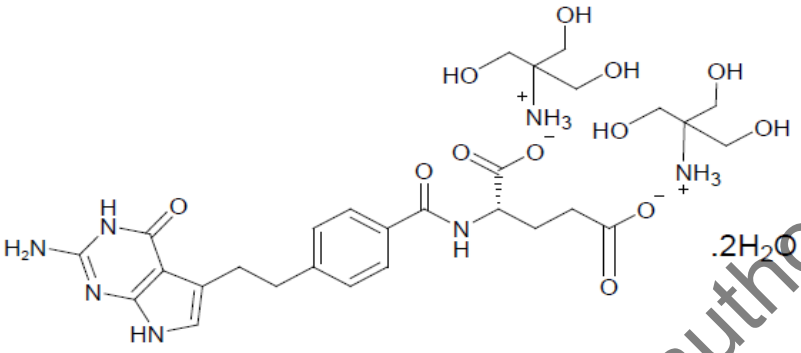
The other ingredient of the formulation is mannitol (E 421).

The product is available in clear, type I glass vials with bromobutyl rubber stoppers as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of pemetrexed ditromethamine dihydrate is L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-ditromethamine dihydrate and it has the following structure and properties:



Molecular formula: $C_{28}H_{47}N_7O_{14}$ - Relative molecular mass: 705.68 $gmol^{-1}$

The structure of the active substance has been confirmed by elemental analysis, IR, UV, ^{1}H- and ^{13}C-NMR, mass spectrometry, X-ray powder diffraction, DSC, TGA and Specific optical rotation all of which support the chemical structure.

The active substance is a white to cream colour crystalline solid, with or without a green/yellow tinge, slightly hygroscopic. It has a pH dependent solubility in water. It has one chiral centre which originates in one of the starting materials and which is tested in the active substance by chiral HPLC.

Polymorphism has been observed for pemetrexed ditromethamine dihydrate. Manufacturing process followed consistently produces the same crystalline pemetrexed ditromethamine dihydrate form. The crystallinity of the active substance is not critical to the bioavailability of the finished product since the product is administered as an intravenous infusion following reconstitution and dilution of the lyophilized dosage form. Hence the absence of polymorphism control in the active substance specifications is considered justified.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

The active substance is sourced from one supplier using three manufacturing sites (two of them are involved in intermediate manufacture).

Pemetrexed is synthesized in eight stages using commercially available well defined starting materials with acceptable specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Potentially genotoxic impurities were demonstrated not to be detected in the active substance and are thus not routinely tested for.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is packaged in a polyethylene bag, filled with nitrogen, which complies with Ph. Eur. requirements. This bag is placed inside a black polythene bag along with two oxygen absorbers filled with nitrogen and tied. This second bag is placed in continuous liner bag tied both sides with two pull ties. This above bag is placed in triple laminated aluminium bag along with one silica gel pouch and sealed with a vacuum, nitrogen flushing & sealing machine (VNS sealer). Finally the packed samples are kept in HDPE container with a lid and this outer container is also sealed.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC, tromethamine content, enantiomer), colour, clarity and pH of solution (Ph. Eur.), water content (Ph. Eur.), enantiomeric purity (HPLC), assay (HPLC), related substances (HPLC), tromethamine content (potentiometric titration), residual solvents (GC), acetic acid content (ion suppression chromatography (IC)), ρ-Toluene Sulfonic acid content (HPLC), palladium content (ICP-MS), residue on ignition (Ph. Eur.), bacterial endotoxins (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

Batch analysis data on three production scale batches of active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three production scale batches of active substance stored in the proposed commercial package for up to 24 months under long term conditions (5±3 ºC) and 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Samples were tested for appearance, identity by IR, related substances and enantiomeric purity, water content, assay. All tested parameters were within the specifications.

Forced degradation studies (under heat, light, water hydrolysis, acid hydrolysis, base hydrolysis, oxidation) showed that the active substance ditromethamine is stable under stress conditions like higher temperature and light in line with ICH Q1B. Significant degradation was observed in water hydrolysis, acid hydrolysis, base hydrolysis and the active substance was also shown to be sensitive to oxidation.

The stability results justify the proposed re-test period of 24 months when stored at 5±3 ºC in the original packaging.

2.2.3. Finished medicinal product

Pharmaceutical development

Pemetrexed ditromethamine 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion is a sterile lyophilized formulation, which is intended for initial reconstitution with sterile water for injections (resulting in a solution of 25 mg/ml pemetrexed) and further dilution to 100 ml with 5% glucose solution prior to administration as an intravenous infusion.

The aim of development was to produce a finished product equivalent to the reference medicinal product Alimta which is a lyophilised powder containing only the active substance, mannitol, and pH adjusting agents (HCl or NaOH). The same pharmaceutical form has been developed as that of the reference product. An additional 1 g/vial presentation was also developed to facilitate administration of the finished product to patients exceeding a body surface area (BSA) of 1 m^2.

A different salt form of the active substance (pemetrexed ditromethamine dihydrate) has been selected for the proposed product compared to the reference product (pemetrexed disodium). Based on comparative physicochemical studies it was concluded that there are no significant differences in physicochemical properties of the two different salt forms.

The same excipient (i.e. mannitol) is used in the proposed formulation and in the reference product however, contrary to the reference product, no pH adjusting agents (sodium hydroxide, hydrochloric acid) have been used. The excipient used is a well-known pharmaceutical ingredient whose quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in section 2.2.1 above.

To demonstrate pharmaceutical equivalence, comparative testing was performed on exhibit batch samples of the proposed finished product and the reference product 100 mg/vial presentations.

The pH of reconstituted finished product is slightly lower than the pH of the reconstituted reference medicinal product (pH 6.6 – 7.8) but is considered appropriate in terms of product solubility and is within clinical recommendations for intravenous administration. The observed osmolarity for reconstituted finished product solution is lower than that of the reference product due to the difference in recommended diluents for reconstitution. The tonicity of the finished product in sterile water for injection is considered to be acceptable for intravenous administration.

Physicochemical properties of the solution for infusion at concentrations reflective of the point of administration were also investigated. The solution of pemetrexed ditromethamine for infusion is to be prepared using 5% glucose solution, whereas the solution for infusion of the reference product is to be prepared using sodium chloride 0.9 % solution. The applicant was asked to provide data to demonstrate the compatibility of the finished product with 0.9% sodium chloride solution. No compatibility study with 0.9% sodium chloride solution was provided. The applicant justified that the formulation was developed for reconstitution in sterile water for injection and further dilution in 5% glucose solution only and that this is reflected in the proposed labelling. The approach followed by the applicant (i.e. use of 5% glucose solution only for preparing the admixed solution) was accepted taking into account that this approach has already been accepted for other centralized procedures on the basis of the existence of a relevant usage patent regarding administration of the product in saline (Pemetrexed Fresenius Kabi EMEA/H/C/3895 and Armisarte EMEA/H/C/4109). Given the difference in API salt and proposed diluent, the applicant provided comparative physicochemical studies to demonstrate equivalence between the proposed product and Alimta.

The pH of the admixed proposed finished product is slightly lower than that of the admixed reference product, but this difference is not considered clinically significant. Osmolarity of the proposed finished product solution after reconstitution and dilution over the concentration range anticipated at point of administration based on recommended dose is lower than the osmolarity range observed for the reference product over the same concentration range however the tonicity of the admixed solution of the proposed finished product is considered acceptable for intravenous administration and the difference is not considered to be of clinical significance.

An over-fill of vials is used in order to ensure the claimed amount can be withdrawn from vials following reconstitution.

The active substance is unstable to oxygen and slightly hygroscopic. Thus, all manufacture is carried out under a nitrogen atmosphere and humidity control environment.

Terminal sterilisation by heat or radiation was demonstrated to be unsuitable due to instability of the finished product. Thus, the finished product is manufactured by sterile filtration followed by aseptic processing.

The primary packaging is clear, colourless type I glass vials with bromobutyl rubber stoppers. The vials are sealed with aluminium crimp caps with a flip-off cap. The materials comply with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product

The manufacturing process consists of four main steps: compounding and pre-filtration; sterile filtration and filling; lyophilisation; stoppering and further packaging. The process is considered to be a non-standard manufacturing process.

Critical steps and process parameters that are considered critical for the quality of the product were identified and are controlled by in-process controls adequate for this type of manufacturing process..

Major steps of the manufacturing process have been validated on three production scale batches of each strength. Hold time study results support the proposed holding times. Initially two different production scale batch sizes were proposed for each strength. Process validation was performed only with the smallest production batch size proposed. Since the process is a non-standard process, the larger proposed batch size was not accepted. The applicant agreed that increase of batch size would be requested post-approval via variation once the relevant process validation studies are conducted. It has been demonstrated that the manufacturing process is capable of producing finished product of the intended quality in a reproducible manner.

Product specification

The finished product specification includes appropriate tests for this kind of dosage form including description of cake, reconstitution time, description of reconstituted solution, colour and pH of solution (Ph. Eur.), particulate matter (Ph. Eur.), identification (UV, HPLC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), assay (HPLC), related substances (HPLC), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analysis results are provided for three pilot scale batches of 100 mg/vial presentation, three pilot scale batches of the 500 mg/vial strength, and three production scale batches of the 1000 mg/vial presentation confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for three pilot scale batches of each of the strengths stored for up to 18 months at 25 ºC / 60% RH (long term conditions) and 30 °C/75% RH (intermediate condition) and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. Vials were stored in both upright and inverted positions. Samples were tested according to the release analytical methods with the exception of the assay and related substances

method. This method was initially the same test method as proposed for active substance but was modified after 6 months' time point to provide better separation of degradation impurities. The analytical procedures used are stability indicating.

For the 500 mg/vial and 1000 mg/vial presentations, no significant changes have been observed.

With respect to the 100 mg/vial presentation, out of specification results were observed for related substances at accelerated conditions. Therefore the following storage condition "Store below 30° C" is adopted.

Stress studies were performed by storing the finished product under freezer conditions (-20°C ±5 °C) for 1 month. Results showed that the freeze-thaw conditions had no impact on the stability of the finished product.

A forced degradation study was performed on finished product samples exposed to acid, base, heat, oxidation (H_2O_2) and light (UV) . The results demonstrated that the reconstituted finished product is susceptible to strong heat and strong light conditions whereas the finished product remained unaffected under these conditions. In addition the active substance has been demonstrated to be not sensitive to light, hence there is no need for additional storage restrictions.

An extractable study was performed on the container-closure system. The results of the extractables and leachables studies indicate that the primary packaging components are appropriate for use with the finished product. It was concluded that leachable chemical compounds identified were at levels that do not present safety concerns to patients receiving the finished product.

The reconstitution studies were conducted using one batch of the 100 mg/vial and one batch of the 1000 mg/vial presentation, which when reconstituted with sterile water for injections have the same strength (25 mg/mL) as the 500 mg/vial presentation. The reconstitution studies performed on the 100 mg/vial presentation and 1000 mg/vial presentation are therefore considered to also be representative of the 500 mg/vial presentations. The key attributes that were monitored were pH, description of solution, assay, related substances and particulate matter. The results showed that the finished product is chemically stable for up to 24 hours after reconstitution with sterile water for injections when stored at 5°C ± 3°C and at 25°C. Studies were performed to demonstrate compatibility of the reconstituted and diluted solution with polyvinyl chloride and polyolefin lined infusion bags. Each study was performed at two concentrations 5 mg/mL and 14 mg/mL, to support the dosage range for patients with Body Surface Areas between 1.0 m^2 and 2.7 m^2. The results from both studies were acceptable and support the in-use stability of 24 hours at refrigerated temperature and 25°C as prescribed in the SmPC. The studies also demonstrated that the stability of the proposed finished product when diluted in 5% glucose solution and stored for 24 hours at refrigerated temperature and 25°C is comparable to the stability of the reference finished product diluted in the 0.9% Sodium Chloride Injection.

The following statement is also included in the SmPC "Chemical and physical in-use stability of reconstituted and infusion solutions of Pemetrexed Hospira UK Limited were demonstrated for 24 hours at refrigerated temperature and 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C."

A transport study was performed to investigate the effects of temperature cycling during transportation on the stability of the proposed finished product. This study demonstrated that the product is stable when subjected to freezing, thawing and temperatures of up to 40°C/75% RH over a 12 day period during transportation. The tested parameters were: description, description of solution, pH, clarity of

solution, colour of solution, assay, related substances, water content, reconstitution time and particulate matter. All results obtained were within the proposed specification.

Based on available stability data, the proposed shelf-life of 18 months with a special storage condition "store below 30 °C" for the 100 mg/vial presentation, and 24 months without special storage conditions for 500 mg/vial and 1000 mg/vial presentations, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pemetrexed Hospira UK Limited manufactured by Hospira is considered unlikely to result in any significant increase in the combined sales volumes for all pemetrexed containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion and conclusion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of pemetrexed are well known. No non-clinical data were submitted with this application. Published literature has been reviewed and is

considered of suitable quality. Therefore, the CHMP agreed that no further non-clinical studies are required.

The change in formulation (the difference in the tromethamine salt) between the proposed product Pemetrexed (as ditromethamine) for Injection and the reference product Alimta are fully characterized by the Applicant through in silico studies (data not shown) and literature data. Generally, the scientific literature submitted is relevant for the pemetrexed and tromethamine. There is a lack of the safety pharmacology published studies; however the extensive clinical experience with pemetrexed could substitute the lack of some preclinical data.

The Applicant demonstrated that in a watery environment, both Pemetrexed (as ditromethamine) for Injection and Alimta contain the same amount of pemetrexed as free base.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Pemetrexed Hospira UK Limited and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for powder for concentrate for solution for infusion containing pemetrexed.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of pemetrexed based on published literature. The SmPC is in line with the SmPC of the reference product.

CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) in its current version, is of particular relevance.

Exemption

Pemetrexed Hospira UK Limited has the same active substance, indications, route of administration, method of administration, dosage form and posology as Alimta, but has instructions for reconstitution with sterile water for injection and dilution with 5% glucose solution, rather than sodium chloride 9 mg/ml (0.9%) solution.

Alimta is available in two presentations in the European market: 100 mg/vial and 500 mg/vial of pemetrexed (as pemetrexed disodium).

The proposed presentations of Pemetrexed Hospira UK Limited are: 100 mg/vial, 500 mg/vial and 1000 mg/vial.

The 1000 mg formulation is not available for the originator product but the qualitative composition of the new presentation, 1000 mg/vial, is comparable to the composition of the 100 mg and 500 mg vials.

Biowaiver

No bioequivalence studies have been submitted.

According to the Guideline on the Investigation of bioequivalence (CPMP/EWP/QWP/1401/98), bioequivalence studies are generally not required if the product is to be administered as an aqueous IV solution containing the same active drug substance in the same concentration as the currently authorised product. Pemetrexed solution is intended for IV use and contains the same active drug substance in a concentration (25 mg/mL) similar to the concentration of 100 mg/vial and 500 mg/vial presentations of Alimta and therefore, no bioequivalence studies are required.

The active substance in Pemetrexed Hospira UK Limited is Pemetrexed ditromethamine instead of Pemetrexed disodium as in Alimta 100 mg/500 mg powder for concentrate for solution for infusion. After reconstitution with sterile water for injections, the three presentations result in 25 mg/ml of pemetrexed. Once reconstituted, further dilution with 5% glucose solution for injection is required before administration. In the solution for intravenous infusion the active moiety remains the same irrespective of the salt form.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were submitted.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

Pemetrexed Hospira UK Limited, 100 mg, 500 mg and 1000 mg, powder for concentrate for solution for infusion, has the same active substance as the reference medicinal product, Alimta.

Furthermore, Pemetrexed Hospira UK Limited has the same indications, posology, pharmaceutical form, route of administration and strength as Alimta after it is reconstituted with sterile water for injection and diluted with 5% dextrose,

Pemetrexed (as ditromethamine) for Injection is conjugated to a tromethamine salt instead of sodium salt. The Applicant demonstrated that in a watery environment, both Pemetrexed (as ditromethamine) for Injection and Alimta contain the same amount of pemetrexed as free base.

There are no concerns with Pemetrexed Hospira UK Limited from a clinical efficacy point of view.

No new studies have been conducted and none are required under the provisions of the Note for Guidance on the investigation of Bioequivalence and Bioavailability (CPMP/EWP/QWP/1401/98/Rev. 1): “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”.

Pemetrexed Hospira UK Limited is proposed to be diluted in 5% glucose solution.

The clinical overview supports the indications and covers adequately the clinical pharmacology, efficacy and safety of the product. It is expected that the physician will take the general health status of the patient into account before treating patients with Pemetrexed Hospira UK Limited.

As the active substance pemetrexed is widely used and well- known, the applicant has not provided additional clinical studies but a justification that further studies are not needed. The CHMP agrees with the justification.

The proposed SmPC of the applied product is in line with the SmPC of Alimta, with the exception of the instructions for reconstitution and dilution.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Pemetrexed Hospira UK Limited and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Table: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• *Renal disorders* • *Non-compliance with folic acid and vitamin B_{12} regimens, manifested mainly as haematological and gastrointestinal toxicities* • *Radiation pneumonitis* • *Radiation recall* • *Gastrointestinal disorders* • *Interstitial pneumonitis* • *Sepsis* • *Bullous skin reactions including Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEC)* • *Bone marrow suppression*
Important potential risks	• *None*
Missing information	• *None*

Pharmacovigilance plan

There are no pharmacovigilance studies, activities, or additional risk minimisation measures ongoing or planned.
Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The 1000 mg strength does not exist for the reference originator Alimta. Therefore, PRAC and CHMP estimate that, even if not listed as a specific risk in the RMP of Pemetrexed Hospira UK Limited, the risk of medication error should be under specific surveillance by the MAH. Should a significant increase in the frequency of reported medication errors be detected, the MAH should report this as a signal.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal disorders	Proposed text in SmPC sections 4.4 and 4.8 and PIL in section 4	None
Non-compliance with folic acid and vitamin B_{12} regimens, manifested mainly as haematological and gastrointestinal toxicities	Proposed text in SmPC section 4.2 and PIL in section 3	None
Radiation pneumonitis	Proposed text in SmPC sections 4.4 and 4.8 and PIL in section 4	None
Radiation recall	Proposed text in SmPC sections 4.4 and 4.8 and PIL in section 4	None
Gastrointestinal disorders	Proposed text in SmPC sections 4.4 and 4.8	None
Interstitial pneumonitis	Proposed text in SmPC section 4.8 and PIL in section 4	None
Sepsis	Proposed text in SmPC section 4.8 and PIL in section 4	None
Bullous skin reactions including SJS and TEN	Proposed text in SmPC section 4.8 and PIL in section 4	None
Bone marrow suppression	Proposed text in SmPC sections 4.4 and 4.8	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 7.0 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion. The reference product Alimta is indicated for

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Alimta 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.

Alimta 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.

Alimta 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Bioequivalence testing with the reference product is not required under the provisions of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98/Rev.1) since the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised product.

Although a new presentation of 1000 mg is introduced by the Applicant compared to the reference product, the application is still considered to be a generic application as the reconstituted product has the same concentration as the reference product regardless of the presentation. Therefore, the introduction of the 1000 mg presentation is considered acceptable.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pemetrexed Hospira UK Limited is favourable in the following indication:

Malignant pleural mesothelioma

Pemetrexed Hospira UK Limited in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed Hospira UK Limited 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).

Pemetrexed Hospira UK Limited 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).

Pemetrexed Hospira UK Limited 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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.