EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/700366/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Hospira

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/003970/0000

Note

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

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List of abbreviations

CHMP	Committee for Human Medicinal Products
ASMF/DMF	Active Substance Master File /Drug master File
EC	European Commission
EMA	European Medicines Agency
EU	European Union
GC	Gas chromatography
GI	Gastrointestinal
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
LoD	Limit of Detection
LoQ	Limit of Quantification
MAA	Marketing authorisation application
NfG	Note for Guidance
NIR	Near infrared spectroscopy
Ph. Eur.	European pharmacopoeia
PRAC	Pharmacovigilance risk assessment committee
RH	Relative humidity
RMP	Risk Management Plan
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TEN	Toxic epidermal necrolysis
UV	Ultraviolet
API	Active pharmaceutical ingredient
BSA	Body Surface Area
NfG	Note for Guidance
RMP	Risk Management Plan
USP	United States Pharmacopoeia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Limited submitted on 10 October 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pemetrexed Hospira, 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 20 February 2014.

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 in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Malignant pleural mesothelioma:

Pemetrexed Hospira 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 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 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 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 cf.CPMP/QWP/EWP/1401/98 Rev. 1.

Information on paediatric requirements

Not applicable

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 100 mg & 500 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 100 mg & 500 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 did not seek scientific advice at the CHMP.

Licensing status

Pemetrexed Hospira has been given a Marketing Authorisation in Australia on 22 November 2011, in Korea on 28 August 2012, in New Zealand on 22 June 2012 and in Hong Kong on 13 August 2012.

An application was filed in the following countries: Canada, Malaysia, Thailand, Taiwan, USA and China.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alar Irs

- The application was received by the EMA on 10 October 2014.
- The procedure started on 29 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 January 2015.
- PRAC RMP Advice and assessment overview as endorsed by PRAC on 12 February 2015.
- During the meeting on 26 February 2015, 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 27 February 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2015.
- PRAC RMP Advice and assessment overview as endorsed by PRAC on 9 July 2015.
- During the CHMP meeting on 23 July 2015, 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 24 August 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 September 2015.

- PRAC RMP Advice and assessment overview as endorsed by PRAC on 10 September 2015.
- The Rapporteur circulated an updated Assessment Report to all CHMP members on 15 September 2015.
- During the meeting on 24 September 2015, 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.

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion. Pemetrexed Hospira 100 mg, 500 mg or 1000 mg Powder for Concentrate for Solution for Infusion has the same active substance and the same excipients in comparable amounts to the centrally approved reference medicinal product Alimta (EU/1/04/290/001-002). After reconstitution, each vial contains 25 mg/ml of pemetrexed.

The claimed indication for Pemetrexed Hospira is:

Malignant pleural mesothelioma

Pemetrexed Hospira 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 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 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 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 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 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 disodium salt hemipentahydrate) as active substance.

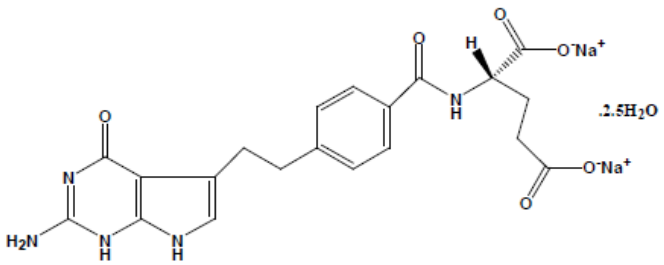
Other ingredients are mannitol, hydrochloric acid and sodium hydroxide.

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

2.2.2. Active substance

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

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



Molecular formula: $C_{19}H_{21}N_5Na_2O_6.[H_2O]_{2.5}$ - Relative molecular mass: 516.4 $gmol^{-1}$

The active substance is a white to off-white hygroscopic crystalline solid, freely soluble in water but practically insoluble in organic solvents. It has one chiral centre which originates in one of the starting materials and which is tested in the active substance by specific optical rotation and chiral HPLC.

Two hydrate form of pemetrexed disodium are known. The heptahydrate has a Ph. Eur. monograph whilst the hemipentahydrate used in this product is routinely produced by the given manufacturing processes.

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 two manufacturing sites (one of them is

involved in intermediate manufacture).

Pemetrexed is synthesized in seven stages using commercially available well defined starting materials with acceptable specifications. Staring materials were re-defined during the procedure as a result of major objections, thus ensuring that steps critical to the quality of the active substance are controlled.

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 and heat sealed which complies with Ph. Eur. requirements and Commission Regulation No. 1183/2012. The polyethylene bag is then placed into a secondary polyethylene bag, which is also heat sealed. This bag is inserted into an aluminium foil bag and heat sealed.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC, UV, sodium test (USP), colour, clarity and pH of solution (Ph. Eur.), assay (HPLC), enantomeric purity (HPLC), related substances (HPLC), residual solvents (GC), water content (Ph. Eur.), heavy metals (USP), specific optical rotation (USP), chloride (USP), sulfate (USP), bacterial endotoxins (Ph. Eur.) and total aerobic microbial count (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 packaging simulating 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, clarity and colour of solution, specific optical rotation and optical isomer, impurities, water content, bacterial endotoxins and microbial limits. In addition, supportive stability data was provided on additional seven batches of active substance for up to 24 months under long term conditions and on five additional batches, for up to 36 months at -20 ºC (a further long term condition). Forced degradation studies show the active substance is sensitive to oxidation. Active substance from this source has a re-test period of 24 months when stored at -20 ºC and 12 months when stored at 5±3 ºC in the original packaging.

2.2.1. Finished medicinal product

Pharmaceutical development

The aim of development was to produce a finished product bioequivalent to the reference medicinal product Alimta which is a lyophilised powder containing only the active substance, mannitol, and pH adjusting agents HCl or NaOH. An additional 1 g/vial presentation was also developed to facilitate administration of Pemetrexed for Injection in patients exceeding a body surface area (BSA) of 1 m^2. The active ingredient, route of administration, dosage form, and reconstitution instructions are the same as that of the reference product Alimta marketed by Eli Lilly. The proposed finished product uses a different hydrate form to the reference medicinal product, but since it is fully solubilised during formulation, this has no impact. It is however more unstable and thus needs to be stored under controlled conditions. The excipients used are the same as for the reference medicinal product and are well known pharmaceutical ingredients 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. An over-fill of vials is used in order to ensure the claimed amount can be withdrawn from vials following reconstitution. The reconstitution method is adequately described in section 6.6 of the SmPC.

Since the finished product is administered as an aqueous intravenous solution in the same concentration as Alimta, the excipients are qualitatively and quantitatively equivalent, and the active substance is freely soluble in aqueous media, no bioequivalence study is required.

The active substance is unstable to oxygen. Thus, all manufacture is carried out under a nitrogen atmosphere. In addition to purging, the pH is controlled during the compounding process and the formulation temperature is maintained below 25°C.

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. Lyophilisation development activities determined cycle parameters which allowed the frozen sample matrix to be satisfactorily freeze-dried below the critical temperature.

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. The in-process controls (pH, assay of solution during compounding, bioburden, filter integrity test during filtration, filter integrity test during nitrogen filtration and fill weight control during filling process) are 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. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description of cake, reconstitution time, description of 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 the 100 mg/vial and 500 mg/vial strength stored under long term conditions for up to 36 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. Stability data were also provided for three production scale batches of 1g/vial strength stored under long term conditions for up to 6 months at 25 ºC / 60% RH 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 specifications except for pH, related substances and water content (wider limits at shelf-life). Shelf-life limit were considered appropriate except for the shelf-life limit for total impurities. The applicant agreed to consider further tightening of the shelf-life limit for total impurities when stability study is completed. The analytical procedures used are the same as for release and are stability indicating.

Stress studies were performed by storing the drug 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 drug product.

Stress testing was also demonstrated during the method validation by degrading a reconstituted (25 mg/mL) finished product sample. Portions of the reconstituted product were stressed with acid, base, heat, oxidation (H_2O_2) and light. The data demonstrated that the product is susceptible to degradation by harsh heat, oxidation, basic, acidic and light conditions.

An extractable study was performed on the bromobutyl rubber closure. Results demonstrated compatibility of the closures for freeze-dried powders and aqueous solution.

A reconstitution study was conducted using one batch of the 100 mg/vial, which when reconstituted with 0.9% Sodium Chloride has the same strength (25 mg/mL) as the 500 mg/vial and 1 g/vial presentations thus is also representative of the 500 mg/vial and 1 g/vial presentations. The key attributes that were monitored were pH, description of solution, assay, related substances and particulate matter. The results of the experiments demonstrated that the finished product when reconstituted with 0.9% sodium chloride injection is stable for up to 24 hours at room temperature (25°C exposed to normal room light) or refrigerated (5°C ± 3°C protected from light). Studies were performed to demonstrate compatibility 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 m2 and 2.7 m^2. The results from both studies were acceptable and support the label claim regarding stability of the subject finished product when co-mixed with intravenous solutions as prescribed in the SmPC. The studies also demonstrated that the proposed finished product is comparable to the reference medicinal product when diluted in the 0.9% Sodium Chloride Injection and stored for 24 hours at either room temperature or refrigerated conditions.

A transport study was performed in which the effects of temperature cycling were investigated to determine the effect of transportation on the stability of the proposed finished product. This study demonstrated that the proposed finished product is stable when subjected to freezing, thawing and temperatures of up to 40°C/75%RH during transportation over a 12 day period. All results obtained are within the proposed specification.

Based on available stability data, the shelf-life is 3 years with no special storage condition. The shelf-life is acceptable and included in the SmPC. The following statement is also included in the SmPC "Chemical and physical in-use stability of reconstituted and infusion solutions of Pemetrexed Hospira powder for concentrate for solution for infusion has been demonstrated for up to 24 hours after reconstitution of the original vial when stored below 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."

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

2.2.2. 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. Staring materials were re-defined during the procedure as a result of major objections, thus ensuring that steps critical to the quality of the active substance are controlled. 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.

At the time of the CHMP opinion, there was a minor unresolved quality issues related to finished product shelf-life limit for total impurities that have no impact on the Benefit/Risk ratio of the product.

2.2.3. 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.

2.2.4. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The shelf-life limit should be tightened for total impurities within the specifications of the medicinal product when the stability study is completed.

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 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 are submitted with this application. Published literature has been reviewed and is considered of suitable quality.

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.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Exemption

Pemetrexed Hospira has the same active substance, indications, route of administration, dosage form and posology as Alimta.

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 are: 100 mg/vial, 500 mg/vial and 1000 mg/vial.

The composition of Pemetrexed Hospira 100 mg and 500 mg vial and Alimta 100 mg and 500 mg vial are similar. A quantitative composition comparison of the applied and the reference product is provided below.

Composition	Pemetrexed Hospira			Alimta®	
	100 mg/vial	500 mg/vial	1000 mg/vial	100 mg/vial	500 mg/vial
Active ingredient					
Pemetrexed	Pemetrexed disodium equivalent to pemetrexed 100 mg	Pemetrexed disodium equivalent to pemetrexed 500 mg	Pemetrexed disodium equivalent to pemetrexed 1000 mg	Pemetrexed disodium equivalent to pemetrexed 100 mg	Pemetrexed disodium equivalent to pemetrexed 500 mg
Inactive ingredients					
Mannitol	106.4 mg*	500 mg	1000 mg	106.4 mg	500 mg
Hydrochloric acid	q.s.	q.s	q.s	q.s	q.s
Sodium hydroxide	q.s	q.s	q.s	q.s	q.s

*Pemetrexed for Injection has an overfill to ensure the complete withdrawal of the labeled amount of drug product. For full details please refer to Module 3.2.P.1.
q.s: quantity sufficient

The qualitative composition of the new presentation, 1000 mg/vial, is comparable to the composition of the 100 mg and 500 mg vials.

Both products are intended for intravenous use and must be reconstituted and further diluted prior to use. After reconstitution each presentation of both the proposed product and the originator product contains 25 mg/ml of pemetrexed.

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.

2.4.2. Pharmacokinetics

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

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, 100 mg and 500 mg, powder for concentrate for solution for infusion, has the same active substance and the same excipients in comparable amounts as the reference medicinal product, Alimta. Furthermore, Pemetrexed Hospira has the same indications, posology, pharmaceutical form, route of administration and strength after reconstitution as Alimta.

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.

There are no concerns with Pemetrexed Hospira 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".

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Pemetrexed Hospira and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and is deemed acceptable and sufficiently up-to-date. This is in accordance with the relevant guideline and additional clinical/bioequivalence studies were not considered necessary. The CHMP considers that there are no objections to approval of Pemetrexed Hospira 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion from a clinical point of view.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Non-compliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities Renal disorders Gastrointestinal disorders

Summary of safety concerns	
	Interstitial pneumonitis Radiation pneumonitis Radiation recall Sepsis Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) Bone marrow suppression
Important potential risks	None
Missing information	None

Pharmacovigilance plan

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, 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

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities	Proposed text in SmPC section 4.2 and PIL section 3	None
Renal disorders	Proposed text in SmPC section 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 section 4	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Radiation pneumonitis	Proposed text in SmPC sections 4.4 and 4.8 and PIL section 4	None
Radiation recall	Proposed text in SmPC sections 4.4 and 4.8 and PIL section 4	None
Sepsis	Proposed text in SmPC section 4.8 and PIL section 4	None
Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Proposed text in SmPC section 4.8 and PIL section 4	None
Bone marrow suppression	Proposed text in SmPC sections 4.4 and 4.8 and PIL section 4	None

2.7. PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

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. However, the applicant provided a clinical overview on these clinical aspects based on information from published literature which 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

A benefit/risk ratio comparable to the reference product Alimta 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 decision that the benefit-risk balance of Pemetrexed Hospira in the following indications:

Malignant pleural mesothelioma

Pemetrexed Hospira 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 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 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 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.

is favourable and 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).

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.

- **Additional risk minimisation measures**

Not applicable.

- **Obligation to conduct post-authorisation measures**

Not applicable.