24 September 2015
EMA/671085/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed medac

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/003905/0000

Note

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

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List of abbreviations

ASMF	Active substance master file
BSA	Body Surface Area
CHMP	Committee for Human Medicinal Products
DMF	Drug master File
DSC	Differential Scanning Calorimetry
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
MS	Mass Spectrometry
NMR	Nuclear magnetic resonance
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
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant medac Gesellschaft für klinische Spezialpräparate mbH submitted on 23 September 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pemetrexed medac, 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 19 December 2013.

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

Non-small cell lung cancer

Pemetrexed medac 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 medac 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 medac 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 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

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Bart Van der Schueren

- The application was received by the EMA on 23 September 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, adopted 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 26 February 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2015.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 June 2015.
- PRAC RMP Advice and assessment overview, adopted 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 by the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 21 August 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 14 September 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 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 medac.

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion. Pemetrexed medac 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 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 medac in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed medac 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 medac 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 medac 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 medac 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 medac 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 or 1000 mg/vial of pemetrexed (as pemetrexed disodium hemipentahydrate) as active substance. After reconstitution, the three presentations result in 25 mg/ml of pemetrexed.

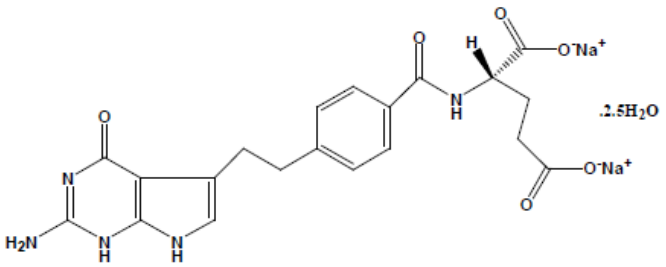
Other ingredients are mannitol, hydrochloric acid and sodium hydroxide.

The product is available in Type I glass vials with rubber (bromobutyl rubber coated with fluoropolymer) stoppers as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

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 hemipentahydrate and has the following structure:



The structure has been confirmed by elemental analysis, infrared (IR) spectroscopy, mass spectrometry (MS), nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectroscopy, UV spectroscopy and identification by chiral HPLC.

The active substance is white or almost white hygroscopic crystalline powder, freely soluble in water, slightly soluble in methanol and insoluble chloroform. Its molecular weight is 516.4 gmol^{-1}, corresponding to the general molecular formula $C_{20}H_{19}N_5O_6Na_2 \cdot 2.5H_2O$.

Pemetrexed disodium hemipentahydrate is an optically active compound due to the stereogenic centre of the glutaminic acid part. Enantiomeric purity is controlled routinely by chiral HPLC. Pemetrexed disodium can exist in an amorphous form or different hydrated forms (pseudo-polymorphs). The most relevant crystalline forms are the hemipentahydrate and the heptahydrate (which has a Ph. Eur. monograph). The form routinely produced by the proposed manufacturing processes is the hemipentahydrate form, as supported by XRPD analysis, thermal (DSC) and water content.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Two ASMFs support the application for Pemetrexed medac.

Manufacture, characterisation and process controls

As described above, the synthesis of pemetrexed disodium hemipentahydrate is documented in two ASMFs supporting this procedure.

Although not identical, both manufacturing methods are quite similar and start from well-defined starting materials with acceptable specifications. Starting materials in both ASMFs were re-defined during the procedure to ensure that steps critical to the quality of the active substance are described in the dossier.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Active substance from both sources is released against the same set of specifications. Batch data indicates that active substance from both sources performs equivalently in secondary manufacture and produces finished product of equivalent quality.

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. Due to its use in advanced cancer therapy, the absence of a full discussion on genotoxic impurities is accepted in accordance with ICH-M7.

The active substance is packaged by one of the manufacturers into a polyethylene bag filled with an inert gas tightly sealed with a cable tie, which is placed into a second polyethylene bag and a heat sealed aluminium/LDPE bag. This bag is then placed into a HDPE container. The other manufacturer packs the active substance in doubly heat-sealed LDPE bags with an intermediate silica gel pouch, packed inside a triple laminated sunlight barrier bag and stored inside an HDPE drum. All materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

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

Specification

A unified specification is provided for active substance from both sources by the finished product manufacturer, and is based on the Ph. Eur. monograph for the heptahydrate salt. The active substance specification includes tests for appearance, identity (IR, HPLC, sodium test (Ph. Eur.)), clarity, colour and pH of solution (Ph. Eur.), water content (Ph. Eur.), heavy metals (Ph. Eur.), residual solvents (GC), impurities (HPLC), enantiomeric purity (HPLC), assay (HPLC), bacterial endotoxins (Ph. Eur.) and microbial contamination (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 have been provided in both ASMFs.

Batch analysis data on three commercial scale batches of the active substance from one manufacturer and eight from the other were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on eight commercial scale batches of active substance from one of the ASMF holder stored in the intended commercial package for up 36 months under long term conditions (5 ºC ± 3 ºC), for up to 12 months under intermediate conditions (15 ºC / 60% RH) and for up to 3 months under accelerated conditions (25 ºC / 60% RH), according to the ICH guidelines, were provided. The parameters tested were description, identification, water content, clarity and appearance of solution, pH, D-isomer content, related compounds, assay, bacterial endotoxin and microbial limit. The analytical methods used were the same as for release and were stability indicating. Out of specification results were observed for impurities under accelerated conditions, but no significant trends were observed under intermediate or long term conditions. Forced degradation studies (base hydrolysis, acid hydrolysis, oxidation, thermal degradation) including photostability were performed on one batch. It was concluded that the active substance is sensitive to base, acid oxidation but stable to thermal degradation. A minor amount of an oxidation impurity was formed during photostability testing, but all results were within the specification.No racemisation occurred under any condition. For the active substance from this source, the stability results justify the proposed retest period of 36 months at 5 ºC stored in its original packaging for the active substance from this source.

Stability data on three commercial scale batches of active substance from the other ASMF holder stored in the intended commercial package for up 36 months under long term conditions (5 ºC ± 3 ºC), and for up to 6 months under accelerated conditions (25 ºC / 60% RH), according to the ICH guidelines, were provided. The parameters tested were appearance, enantiomeric purity, clarity, colour and pH of solution, water content, assay, and impurities. The analytical methods used were the same as for release and were stability indicating. No significant trends in any of the parameters tested were observed under accelerated or long term conditions. Photostability testing following the ICH guideline Q1B and forced degradation studies (base and acid hydrolysis, oxidation and UV exposure) were performed on one batch. It was concluded that the active substance is photostable under the conditions tested and sensitive to base, acid and oxidation. The stability results justify the proposed retest period of 36 months stored in its original packaging under argon or nitrogen atmosphere at 5 ºC ± 3 ºC in the proposed container, for the active substance from this source.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of the pharmaceutical development was to develop a finished product equivalent to Alimta. The same disodium salt as in the reference medicinal product is used. As mentioned above, a different hydrate form than the one used in the reference medicinal product is used for Pemetrexed medac. Since the active substance is fully solubilised during the manufacture of the finished product, this has no impact. Therefore a biowaiver can be granted from the quality point of view.

As the active substance is sensitive to oxidation and vulnerable to hydrolysis in aqueous environment it is formulated as a lyophilised powder, and stored under nitrogen in type I glass vials as the reference medicinal product. The product is manufactured and stored under an inert atmosphere to prevent oxidation of the bulk solution and the final product. Terminal sterilisation by heat or radiation was deemed to be unsuitable due to instability of the finished product. Thus, the finished product is manufactured by sterile filtration followed by aseptic processing.

The excipients used in the formulation are the same as for the reference medicinal product, namely mannitol (bulking agent), HCl and NaOH (pH adjusting agents). All excipients are well known pharmaceutical ingredients and their 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.

Pemetrexed medac 100 mg/vial and 500 mg/vial presentations are dose and qualitatively identical to the reference medicinal product. For Pemetrexed medac, an additional, dose-proportional 1000 mg/vial presentation has been developed. The 100 mg/vial presentation contains an over-fill of 5% in order to allow correct dosing. The reconstitution method is adequately described in section 6.6 of the SmPC. There is no overfill in the 500mg/vial and 1000mg/vial presentations.

With regards to the manufacturing process development, the same composition of the bulk solution was used for the manufacture of the three presentations. It was demonstrated that 50 mg/ml bulk solutions of pemetrexed and mannitol were stable when stored at 25 °C in the dark, and no precipitation occurred when stored in the fridge for 24 hours. Therefore, this concentration was selected for further development. The lyophilisation process development was discussed in depth and included the evaluation of electrical resistance and freezing/melting properties, as well as crystallization studies. With respect to the filling dose and vial dimensions, the 500 mg presentation was deemed to be the most critical in terms of filling height and vial diameter. Therefore, this presentation was used for the development trials, which focused on: low content of residual water in the final product; short reconstitution time; colour and clarity of the reconstituted solution; aspect of the lyophilized cake; process economy.Overall, the combination of fast freezing with annealing allowed preparing the lyophilized matrix with the desired physicochemical properties and adequate stability. Based on these results, the freeze drying cycle for the 500 mg/vial presentation was scaled up and adjusted for the 100 mg/vial and 1000 mg/vial presentations.

Since the finished product is administered as an aqueous intravenous solution (0.9% NaCl as stated in the SmPC) with 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 was conducted.

The primary packaging is a colourless type I glass vial with a rubber lyo stopper and aluminum cap with flip-top. The material complies with Ph. Eur. and EC 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 involves the following steps: bulk solution preparation; sterile filtration of the bulk solution; filling; lyophilisation; capping of the vials. The process is considered to be a non-standard manufacturing process. The in-process controls are adequate for this type of manufacturing process. They consist of pH at compounding, filter integrity test before and after filtration, bioburden

before pre-filtration and before sterile filtration, nitrogen filter integrity, fill weight, container closure integrity and oxygen content after capping.

Process validation was carried out on three validation batches per strength. The data presented demonstrate 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 appearance, reconstitution time, colour, clarity and pH of reconstituted solution (Ph. Eur.), particulate contamination (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), identification (HPLC, UV), assay (HPLC), impurities (HPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for three commercial-scale batches of each presentation of the finished product (100 mg/vial, 500 mg/vial and 1000 mg/vial) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data on three commercial scale batches of the finished product stored under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH) for up to 24 months, and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided for 100 mg/vial and 500 mg/vial presentations. For the 1000 mg/vial presentation, 12 months long term and 6 months accelerated stability data were provided. Vials were stored upright. The batches of finished product were manufactured at the proposed commercial site and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, reconstitution time, colour, clarity and pH of reconstituted solution, particulate contamination, water content, identification, assay, impurities and sterility. The analytical procedures used are stability indicating. No significant trends were observed in any of the presentations and conditions tested.

In addition, one batch of each of the presentations of the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All results remained within the specifications and no significant trends were observed.

In addition, an in-use stability study was carried out on one batch of each presentation after reconstitution with the prescribed volume of saline (0.9% sodium chloride solution) in an inverted vial. It revealed a slight assay decrease and an increase of an unspecified impurity, but the solution remained within the specification for up to 24 hours.

Compatibility studies with the infusion bag were performed on the two most extreme dilutions (20 mg/ml and 2 mg/ml). The reconstituted samples were stored for 24 hours in the dark at 2-8 ºC or in daylight at ambient temperature. Although a slight decrease in assay and an increase in an unspecified impurity was observed in some of the samples stored in daylight all results remained within the specification limits.

Based on available stability data, the shelf-life of 36 months without any special storage conditions as stated in the SmPC is acceptable, and specific instructions for use have been included in section 6.3 of the SmPC.

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. As requested by the CHMP, the applicant redefined the proposed starting materials to ensure that all critical steps of the synthetic process are described in the dossier. 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.

2.2.6. Recommendations for future quality development

Not applicable.

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 Medac manufactured by Medac Gesellschaft für klinische Spezialpraparate mbH 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 medac has the same active substance, indications, route of administration, method of administration, instructions for reconstitution with sodium chloride 9 mg/ml (0.9 %) solution for injection without preservatives, 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 medac are: 100 mg/vial, 500 mg/vial and 1000 mg/vial.

The composition of Pemetrexed medac 100 mg and 500 mg vial and Alimta 100 mg and 500 mg vial are similar. Excipients used in the 100 and 500 mg formulations are qualitatively the same than the originator.

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.

All the formulations should be reconstituted with sodium hydrochloride 9 mg/ml (0.9%) solution for injection, without preservative, resulting in a solution containing 25 mg/ml 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 medac, 100 mg and 500 mg, powder for concentrate for solution for infusion, has the same active substance as the reference medicinal product, Alimta. The same salt (sodium) is used as in the innovator's product. The only difference between the reference product Alimta and the test product is the hydratation of the salt of the active substance which do not raise any concern regarding efficacy and safety. There are no excipients interacting with the drug substance, the disposition of the drug substance is therefore not affected. Furthermore, Pemetrexed medac has the same indications, posology, pharmaceutical form, route of administration, method of administration, instructions for reconstitution with sodium chloride 9 mg/ml (0.9 %) solution for injection without preservatives and strength after reconstitution as Alimta when used in accordance with the conditions defined in the SmPC.

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 medac 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 medac 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 medac 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion from a clinical point of view.

2.5. 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 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/or CHMP.

The CHMP endorsed the Risk Management Plan version 4 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 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 medac, 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

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Non-compliance with folic acid and vitamin B12 regimens, manifested mainly as haematological and gastrointestinal toxicities	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.2 Posology and method of administration:* "To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation (see section 4.4). Patients must take oral folic acid or a multivitamin containing folic acid (350 – 1,000 µg) on a daily basis. At least five doses of folic acid must be taken during the seven days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive an intramuscular injection of vitamin B12 (1,000 µg) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed." *4.4 Special warnings and precautions for use:* "(…), all patients treated with pemetrexed must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment-related toxicity (…)." *5.2 Pharmacokinetic properties* "Oral folic acid and intramuscular vitamin B12 supplementation do not affect the pharmacokinetics of pemetrexed." *Patient Information Leaflet (PIL):* The PIL includes similar information as the SmPC in lay language.	None
Renal disorders	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	The Summary of Product Characteristics (SmPC) includes the following information: *4.2 Posology and method of administration:* "Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration blood chemistry tests should be collected to evaluate renal and hepatic function." *4.4 Special warnings and precautions for use:* "Patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 ml/min) should avoid taking non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and aspirin (> 1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration (…)." "In patients with mild to moderate renal insufficiency eligible for pemetrexed therapy NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (…)." "Serious renal events, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes." *4.5 Interaction with other medicinal products and other forms of interaction* "In patients with normal renal function (creatinine clearance ≥ 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin at higher dose (≥ 1.3 g daily) may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be made when administering higher doses of NSAIDs or aspirin, concurrently with pemetrexed to patients with normal function	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(creatinine clearance ≥ 80 ml/min)." *4.8 Undesirable effects:* Renal toxicities/disorders are listed as undesirable effects with common to very common frequency. "Uncommon cases of acute renal failure have been reported with pemetrexed alone or in association with other chemotherapeutic agents (…)." *Patient Information Leaflet (PIL):* The PIL includes "acute renal failure" as an uncommon and "kidney abnormal blood test" as very common side effects. A wording is included that the patient should inform the doctor about a history of kidney problems and the use of NSAIDs.	
Gastrointestinal disorders	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.4 Special warnings and precautions for use:* "Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment." *4.8 Undesirable effects:* Gastrointestinal toxicities/disorders are listed as some of the most commonly reported undesirable effects (frequency: common to very common). *Patient Information Leaflet (PIL):* The PIL includes similar information as the SmPC in lay language.	None
Interstitial pneumonitis	*Prescription only medicine* Pemetrexed medac must only be administered under	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.8 Undesirable effects:* "In clinical trials, cases of interstitial pneumonitis with respiratory insufficiency, sometimes fatal, have been reported uncommonly in patients treated with pemetrexed." *Patient Information Leaflet (PIL):* The PIL lists 'interstitial pneumonitis (scarring of the air sacs of the lung)' as a side effect with uncommon frequency.	
Radiation pneumonitis	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.4 Special warnings and precautions for use:* "Cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radiosensitising agents." *4.8 Undesirable effects:* "Uncommon cases of radiation pneumonitis have been reported in patients treated with radiation either prior, during or subsequent to their pemetrexed therapy (…)." *Patient Information Leaflet (PIL):* The PIL includes similar information as the SmPC in lay language. Radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) is listed as an uncommon side effect.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Radiation recall	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.4 Special warnings and precautions for use:* "Cases of radiation recall have been reported in patients who received radiotherapy weeks or years previously." *4.8 Undesirable effects:* "Rare cases of radiation recall have been reported in patients who have received radiotherapy previously (…)." *Patient Information Leaflet (PIL):* The PIL includes similar information as the SmPC in lay language. Radiation recall (a skin rash like severe sunburn) is listed as a rare side effect.	None
Sepsis	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.8 Undesirable effects:* "Summary of safety profile … Other undesirable effects include renal toxicities, increased aminotransferases, alopecia, fatigue, dehydration, rash, infection/sepsis and neuropathy." "Sepsis, sometimes fatal, has been commonly reported during clinical trials with pemetrexed." *Patient Information Leaflet (PIL):* The PIL includes similar information as the SmPC in lay language.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bullous skin reactions including SJS and TEN	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.8 Undesirable effects:* "Summary of the safety profile … Rarely seen events include Stevens-Johnson syndrome and Toxic epidermal necrolysis." "Rare cases of bullous conditions have been reported including Stevens-Johnson syndrome and Toxic epidermal necrolysis which in some cases were fatal." *Patient Information Leaflet (PIL):* The PIL includes similar information as the SmPC in lay language.	None
Bone marrow suppression	*Prescription only medicine* Pemetrexed medac must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy. *The Summary of Product Characteristics (SmPC) includes the following information:* *4.2 Posology and method of administration* "Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count." *4.4 Special warnings and precautions for use* "Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anaemia (or pancytopenia) (…). Myelosuppression is usually the dose-limiting toxicity. Patients should be monitored for myelosuppression during therapy and pemetrexed should not be given to patients until absolute neutrophil count (ANC) returns to ≥ 1,500 cells/mm³ and platelet count returns to ≥ 100,000 cells/mm³. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	haematologic toxicity seen from the previous cycle (…).” *4.8 Undesirable effects:* “Summary of safety profile: The most commonly reported undesirable effects related to pemetrexed, whether used as monotherapy or in combination, are bone marrow suppression manifested as anaemia, neutropenia, leukopenia, thrombocytopenia (…)” *Patient Information Leaflet (PIL):* The following side effects associated with bone marrow suppression are listed: Low white blood cells (frequency: very common), Low haemoglobin level (anaemia) (frequency: very common), Low platelet count (frequency: very common), Pancytopenia-combined low counts of white cells, red cells and platelets (frequency: uncommon).	

2.6. 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.

2.7. 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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Alimta. The bridging report submitted by the applicant has been found acceptable.

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 Medac in the following indications:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed medac 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 medac 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 medac 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.