24 September 2015
EMA/802052/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CIAMBRA

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/003788/0000

Note

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

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List of abbreviations

API	Active pharmaceutical ingredient
ASMF	Active Substance Master File = DMF
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(-DAD)	High performance liquid chromatography (-diode array detector)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-OES	Inductively coupled plasma –optical emission spectrometry
IPC	In process Control
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
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European pharmacopoeia
PRAC	Pharmacovigilance risk assessment committee
QTPP	Quality target product profile
RH	Relative humidity
RMP	Risk Management Plan
SJS	Stevens-Johnson syndrome

SmPC	Summary of Product Characteristics
TEN	Toxic epidermal necrolysis
TGA	Thermo-Gravimetric Analysis
USP	United States Pharmacopoeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Menarini International Operations Luxembourg S.A. submitted on 30 September 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for CIAMBRA, 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 30 May 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

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

Non-small cell lung cancer

CIAMBRA 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.

CIAMBRA is indicated as monotherapy for the maintenance treatment of locally advanced ormetastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

CIAMBRA 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).

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

Information on paediatric requirements

Not applicable

Scientific advice

The applicant received Scientific Advice from the CHMP on 21 February 2013. The Scientific Advice pertained to quality aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Juris Pokrotnieks

- The application was received by the EMA on 30 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 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 30 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 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 assessment overview adopted by PRAC on 10 September 2015.
- The Rapporteur circulated the updated Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 16 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 CIAMBRA.

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion, Ciambra 100 mg or 500 mg Powder for Concentrate for Solution for Infusion which has the same active substance 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 Ciambra is:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Ciambra 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.

Ciambra 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.

Ciambra 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.

Ciambra 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 a powder for concentrate for solution for infusion containing 100 mg/vial or 500 mg/vial of pemetrexed (as disodium salt) as active substance.

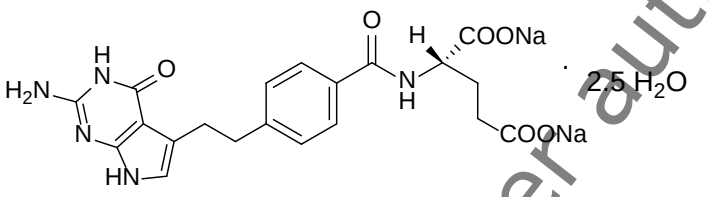
Other ingredients are: mannitol (E421) hydrochloric acid and sodium hydroxide, as described in section 6.1 of the SmPC.

Ciambra powder for concentrate for solution for infusion is available in Type I glass vial with type I chlorobutyl rubber stopper and an aluminium seal with flip off cap, vial is covered with a shrink-wrapped plastic sleeve, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance pemetrexed disodium (hemipentahydrate) is L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-disodium salt, corresponding to the molecular formula $C_{20}H_{19}N_5Na_2O_6 \cdot 2.5H_2O$ and has a relative molecular mass 516.41 g/mol. The active substance has the following structure:



The structure of the active substance has been confirmed by elemental analysis, UV, IR, ^{1}H- and ^{13}C-NMR, UV, Mass Spectrometry and X-ray powder diffraction all of which support the chemical structure.

It appears as a white to almost-white, hygroscopic crystalline powder. It is freely soluble in water, sodium hydroxide (1M); sparingly soluble in ethanol:water mixture (1:1), methanol; very slightly soluble in acetone, ethanol and 2-propanol.

Pemetrexed disodium contains a single chiral centre at carbon-4 with the absolute S configuration. The stereoisomeric purity of the active ingredient depends on the purity of the starting material involved in the synthesis and on the stereoselectivity of the synthetic steps to give pemetrexed disodium hemipentahydrate. Enantiomeric purity is tested in the active substance by specific chiral HPLC. Pemetrexed disodium is known to exist in two crystalline hydrate forms, a 2.5 mole hydrate (hemipentahydrate) form and a 7 mole hydrate (heptahydrate) form. The different polymorphs can be differentiated by four analytical techniques: infrared spectroscopy (IR), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray diffraction. All batches of pemetrexed disodium produced by active substance manufacturer contain exclusively hemipentahydrate. It has been demonstrated that validation batches manufactured by the proposed synthetic route described in ASMF contain exclusively the hemipentahydrate form. In addition evidence has been provided that the polymorphic form of active substance has not been changed during storage time.

Manufacture, characterisation and process controls

Pemetrexed disodium hemipentahydrate is synthesized in a six-step process from four well-defined starting materials with acceptable specifications. Following a risk assessment no critical steps have been identified. Reprocessing and reworking has been described in sufficient detail. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

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 characterised and are well discussed with regards to their origin and fate.

The active substance is packaged in nitrogen atmosphere in four low-density polyethylene (LDPE) bags, which are placed into thermo-sealed aluminium bag. This latter is placed into a HDPE drum, which is stored in a metal drum. The primary packaging material conforms to the requirements of the relevant European Directives and the Ph.Eur. monograph 3.1.3.

Specification

The active substance specification includes tests and limits for: appearance (visual), appearance (colour and clarity) of solution (Ph. Eur.), identity (Ph. Eur.), pH (Ph. Eur.), water content (Ph. Eur), assay (HPLC), related substances (HPLC), enantiomeric purity (chiral HPLC), residual solvents (GC), palladium content (ICP-OES), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).
The specifications of the active substance are [PB1]based on Ph.Eur. monograph for Pemetrexed Disodium Heptahydrate. The principle is acceptable because the only difference is in the hydration degree. The omission of the parameter “Heavy metals” in the specification of active substance has been justified; Potential genotoxic impurities are controlled in final active substance in accordance with the relevant guidelines.

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 results for three commercial scale batches manufactured by the proposed manufacturer and three pilot scale batches by a different manufacturer were presented. The results comply with the proposed specification.

Stability

Stability data on three pilot batches (manufactured by a different manufacturer) and on three commercial scale batches (by the proposed manufacturer) were presented. The commercial scale batches were packaged in packaging intended for marketing while the pilot batches without the external metal drum, was not used for these studies since the worst case was considered. Stability results for the pilot batches were provided for six months under accelerated (40°C/75% RH), for up to 12 months under intermediate condition at 30°C/65% RH and up to 24 months at long term condition 25°C/60% RH. For the commercial batches stability results were provided up to 6 months at both accelerated (40°C/75% RH) and long term conditions (25°C/60% RH and 30°C/75% RH). Stability studies were conducted according to the ICH guidelines.

The following parameters were tested: appearance, water content, related substances (by HPLC), assay (by HPLC), enantiomeric purity, microbiology. Analytical procedures used in stability studies are the same as described for release which were shown to be stability indicating.

Apart from some out of specification results due to wrong sampling/packaging procedure of the stability samples, no significant change in any of the tested parameters was observed over the time-points evaluated at long-term or accelerated conditions.

In addition a fourth pilot batch was stored at 25°C/60%RH and refrigerated conditions (2 – 8 °C/ ambient air atmosphere) were performed to investigate the behaviour of pemetrexed disodium hemipentahydrate without inert atmosphere. The active substance was packed in 2 LDPE bags at air, placed into HDPE container. The stability results up to 1 month at refrigerated conditions and up to 15 days at 25°C/60%RH are compliant with the specification.

Forced degradation studies were performed pilot batch to identify the main degradation compounds. The effect of pH, heat and hydrogen peroxide on solution of active substance was studied and effect of light (photostability), pH, heat and oxidation on solid state of active substance was studied. Based on the results pemetrexed disodium hemipentahydrate in solid state is stable at high temperature under nitrogen atmosphere until 6 days. When stored under not controlled atmosphere it is stable for 3 days at 60 °C and for 24 h at 70 °C. The photostability study as per ICH, on solid state demonstrated no significant degradation in the samples. The active substance in solution is stable in water solution (pH 7.5-8.4), while significant degradation is observed at high pH. Studies show that oxidation is likely mechanism of degradation of active substance.

In conclusion, the proposed re-test period of 2 years under inert atmosphere (nitrogen) and under 30 °C when the active substance is stored in the proposed packaging is adequately supported by the stability data provided and is acceptable. Compatibility study with primary packaging materials has been provided.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The objective of pharmaceutical development was to develop a product generic to Alimta. The Quality Target Product Profile (QTPP) has been described as a sterile lyophilised powder with appropriate reconstitution time, with specified assay and impurities content and compliant to Ph. Eur. requirements.

Ciambra powder for concentrate for solution for infusion is presented in two strengths: 100 mg/vial and 500 mg/vial. The product is a sterile lyophilised powder that must be reconstituted and then diluted with a suitable intravenous solution prior to administration. Sodium chloride solution for injection (0.9%) is proposed to be used for reconstitution of the powder and preparation of the final solution for infusion. There are no accompanying reconstitution diluent(s) with this product. Each 100 mg vial and 500 mg vial are reconstituted respectively with 4.2 ml or 20 ml of commercially available 0.9% Sodium Chloride Injection, without preservatives. The reconstituted solution contains 25 mg/ml of pemetrexed. The required amount of the reconstituted pemetrexed solution is further diluted to 100 ml in 0.9% Sodium Chloride Injection prior to intravenous infusion. The reconstitution instructions are identical to those of the reference product.

A comprehensive comparison between the reference product batches of Alimta 100 mg and 500 mg and industrial scale batches of generic Ciambra 100 mg and 500 mg produced at the proposed manufacturing site has been conducted considering their qualitative and quantitative compositions, container closure characterisation, physico-chemical properties and head space analysis. Comparative analytical data of three batches of the proposed (generic) product and three batches of the reference product Alimta for each strength to confirm the equivalence were presented. Ciambra can be considered comparable with the reference product regarding chemical-physical parameters like assay, impurities, pH, osmolality, appearance, reconstitution time and in-use stability studies. The same pharmaceutical form has been developed as that of the reference product. The same active substance salt as the reference product is used.

The excipients used in Ciambra 100 mg and 500 mg are the same ones used in the composition of reference product Alimta and are in compliance with both European Pharmacopeia (Ph. Eur.) and USP. No specific compatibility studies are performed but since the qualitative composition of Ciambra is the same as the reference product, this was found acceptable.

Filling of vials was studied to determine the required overfill required to enable the targeted extractable volume from the vial after reconstitution using the same reconstitution procedure as for reference product Alimta. Based on the results appropriate overfill has been determined.

Development of proposed lyophilisation cycle to be used for production of Ciambra 100 mg and 500 mg lyophilised powders has been developed in a development site, scaled up to pilot batches in a second manufacturer (pilot site) and scaled-up to the commercial manufacturing scale at the proposed site.

The preparation of the bulk solution was investigated in order to optimise the process.
Main development work included determination of the critical conditions and parameters during lyophilisation process. Further optimisation work was done to establish the conditions during sublimation in order to keep critical quality attributes of drug product, within specified acceptance criteria.
In addition a design of experiment study on the freeze drying cycle was conducted on 500 mg strength for determining the relationship between factors affecting a process and the output of process. It is concluded that the currently validated process parameters ensure consistent quality of finished product. Proven acceptable ranges have been set but no design space is claimed.

Scaling up from the laboratory scale to the pilot-scale and production scale is described and analytical results of finished product compared. All drug product batches produced at the pilot site and the propose site were lyophilised applying the same cycles. It was concluded that product manufactured at different sites during development showed comparable quality.
The sterilisation method by aseptic filtration was selected after consideration of the requirements of the guideline CPMP/QWP/054/98 – "Decision trees for the selection of sterilization methods" (Annex to Note for Guidance on Development Pharmaceutics). The suitability of the filter type and the parameters for the filtration of the bulk solution was demonstrated.

The product is packaged in clear, type I glass vials, rubber stopper and aluminium flip-off cap. The vial is covered with a shrink wrapped plastic sleeve. Compatibility of the stopper to the reconstituted solution has been tested on inverted vials of drug product. The study report has been provided and results represent a worst-case scenario exposure and they are not considered to raise any concern regarding genotoxicity or carcinogenicity in humans.

Manufacture of the product and process controls

The main steps of the manufacturing process are preparation of bulk solution, sterile filtration of the bulk solution, aseptic filling of vials, lyophilisation and closing of the vials. Water for injections is used as processing solvent during the manufacturing process and is evaporated during freeze-drying step and is not part of the final formula. Nitrogen is used as inert gas for solution preparation, filtration and closing of vials. Satisfactory information regarding the sterilisation of the primary packaging material has been presented.

Critical steps and process parameters that are considered critical for the quality attributes of the product were evaluated by risk assessment performed during process validation at the proposed site.
The following process steps and respective process control parameters are defined as critical:
preparation of the bulk solution, aseptic filling of vials, lyophilisation and closing of vials. Adequate in-process controls re in place for this type of manufacturing process.

In accordance with Annex II to the guideline on process validation the aseptic manufacturing process by sterile filtration in combination with a lyophilisation process is considered a non-standard

manufacturing process. Process validation has been performed on three consecutive production scale batches for both 10 ml (100 mg strength) and 50 ml (500 mg strength) vials. Media fill validation is applied by the proposed manufacturer in line with the requirements of the Guidance PIC/S PI 007-6 "Recommendation on the Validation of Aseptic Processes" and Annex 15 to the EU Guide to GMP. The applied bracketing approach covers the manufacturing process of Ciambra 100 mg and 500 mg and is acceptable. 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 and shelf life specifications include appropriate tests and limits for this kind of dosage form including appearance (visual), particulate (visible and subvisible) matter (Ph. Eur.), clarity and colour of the reconstituted solution (Ph. Eur.), reconstitution time, water content (Ph. Eur.), pH of the reconstituted solution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), oxygen headspace (Ph. Eur.), osmolality in reconstituted solution (Ph. Eur.), identification (HPLC, HPLC-DAD), assay (Ph. Eur.), impurities (HPLC), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The impurities from active substance and drug product degradation are controlled as single unspecified impurities in the finished product specifications in line with current ICH Q3B guideline on "Impurities in New Medicinal Products" for the maximum daily dose.

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 data are provided on three pilot scale batches for each strength manufactured at the pilot site (not proposed manufacturer), one pilot batch and three commercial batches for each strength manufactured at proposed manufacturing site. Full analytical testing as per the proposed drug product specification was performed. Results were in line with proposed specifications and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The same batches have been placed on stability studies.

Stability of the product

Stability studies have been conducted on 2 pilot batches (one per strength) and 6 commercial batches (three per strength) manufactured at proposed manufacturing site packaged in the proposed packaging in accordance with ICH requirements. Stability results were provided for up to 12 at long-term conditions (25 ºC / 60% RH and 30 ºC / 75% RH) and for six months under accelerated conditions (40°C/75% RH).
Stability data were also provided for 6 older pilot scale batches (three per strength) in the proposed packaging and manufactured at the pilot site (not proposed manufacturer) for up to 18 months at long-term conditions (25 ºC / 60% RH and 30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40°C/75% RH).
Parameters tested as per the stability protocol: appearance of the powder, particulate contamination (visible/subvisible) of the reconstituted solution, colour and clarity of the reconstituted solution, water content, reconstitution time, pH of the reconstituted solution, closure integrity, identification (HPLC), assay, purity tests, sterility and bacterial endotoxins. All the results met the specification and did not show any trend in any storage condition.

Forced degradation studies were also performed where samples were stress tested (temperature, composition of acidic, basic, oxidative and light exposure). Based on this study the analytical method were shown to be stability indicating.

Photostability studies

The photostability testing on one pilot batch per strength following the ICH Q1B guideline (CPMP/ICH/279/95) was conducted. The parameters tested were: appearance of the powder, particulate contamination (visible/subvisible) of the reconstituted solution, colour and clarity of the reconstituted solution, pH of the reconstituted solution, water content, identification (HPLC), assay, purity tests, sterility, bacterial endotoxins. None of them showed any significant change and results met specification.

In-use stability studies

In-use stability studies on the reconstituted solution (concentrate solution 25 mg/ml) and solution for infusion (minimum and maximum concentrations, 3 mg/ml and 12 mg/ml, respectively) have been performed in upright and in inverted position of the vials for reconstituted solution and in the polyvinylchloride laminated bag (equipped with an infusion kit) and polyolefin laminated infusion bags for further diluted solution were performed including infusion set. In-use stability study has been performed at temperature (5±3) °C and room temperature at time points 12 h and 24 h. One pilot and one commercial scale batch have been used for this study. The batches used for the in-use studies stability were stored for 6 months at accelerated storage conditions (40°C/75% RH).

Parameters tested: appearance of the powder, particulate contamination (visible/subvisible) of the reconstituted solution, colour and clarity of the reconstituted solution, pH of the reconstituted solution, identification (HPLC), assay, purity tests, sterility and bacterial endotoxins.
Based on the results the following storage instructions are proposed: Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature or 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, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions (section 6.3 of SmPC). However because the in-use study was conducted on batches previously stored under accelerated conditions it is recommended that they are also performed on the reconstituted and diluted solutions (pemetrexed concentrate for solution for infusion 25 mg/ml and pemetrexed solution for infusion 3 mg/ml and 12 mg/ml, respectively) at final shelf-life point (see 2.2.6 Recommendations for future quality development).

On the basis of the overall available stability data, the shelf life of 24 months without any special storage conditions during the proposed shelf-life as stated in section 6.3 and 6.4 of the SmPC is accepted

Adventitious agents

No excipients of human or animal origin are 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. Ciambra can be considered pharmaceutically comparable with the reference product. The product is manufactured by aseptic processing which is considered as a non-standard process and therefore full process validation data have been provided confirming the

manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The choice of the sterilization method has been sufficiently justified and supported by data. 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. 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:

to perform in-use stability studies on the reconstituted and diluted solutions (pemetrexed concentrate for solution for infusion 25 mg/ml and pemetrexed solution for infusion 3 mg/ml and 12 mg/ml, respectively) at final shelf-life point for one batch of 100 mg and one of 500 mg strength.

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. However the Applicant has conducted some non-clinical studies to assess the tolerability of clinical dose form of Ciambra which are presented below. The impurity profile has been discussed and was considered acceptable.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

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

2.3.2. Toxicology

Published toxicity data, genotoxicity, reproductive and developmental toxicity were provided. Information available in the SmPC of Alimta was also included. In addition, the Applicant has conducted some non-clinical studies to assess the tolerability of the clinical dose form of Ciambra: (a) a local tolerance study after acute i.v., p.v. or i.a. administration in rabbits, (b) an investigation on the potential for human red blood cell haemolysis and (c) genotoxic studies on impurities and synthesis intermediates. The results from these studies showed that the clinical dose of Ciambra is well tolerated.

Local tolerance

The tolerance of Pemetrexed arising from single intravenous (intended clinical route), paravenous and intra-arterial administration (non-intended routes) of the test item was investigated in female New Zealand White rabbits. Three groups (one for each route of administration) of 6 female rabbits each were used. The animals were treated in the left and right ear with the test or control item, respectively. A dose volume of 0.5 mL/site was injected through the intravenous and intra-arterial routes while a volume of 0.2 mL/site was injected through the paravenous route. The resulting reaction to treatment was assessed approximately 1 hour after dosing and daily thereafter. The first three animals/group were sacrificed approximately 24 hours after dosing, while the remaining three animals per group were sacrificed 7 days after treatment. Histopathological evaluation of the injection sites was performed for each animal. No relevant irritation was observed at the sites of injection.

Other toxicity studies

Haemolysis:

Erythrocyte osmotic fragility (haemolysis) was assessed on blood samples, taken from healthy male donors, after treatment with the test item Pemetrexed. The test item was reconstituted in physiological saline at 10 mg/mL. Solutions at 500, 300 and 100 mg/mL were prepared in physiological saline and used for treatment. A single experiment was performed. The experiment included positive, negative and vehicle controls and test item solutions prepared as above described. Samples were incubated for 3 hours at 37 □ 2°C in a water bath in static condition. At the end of the incubation time, samples were centrifuged, supernatants were diluted with Drabkin's Solution and read at 540 nm. The supernatant haemoglobin concentration of each sample was obtained from a calibration curve.

No haemolysis was observed in blood samples exposed to the test item at any concentration tested.

No haemolysis was observed in blood samples treated with negative or vehicle controls. Treatment with the positive control Tween 80 yielded 92% haemolysis, indicating the correct functioning of the assay system. It is concluded that the test item Pemetrexed does not induce haemolysis under the reported experimental conditions.

Toxicity of impurities:

Furthermore, genotoxic tests (Ames test and/or micronuclei in human lymphocytes) were conducted by the Applicant on synthesis intermediates, MEN19150, MEN19151 and impurities.

In conclusion, all intermediates and impurities tested were considered as non-genotoxic apart from the intermediate Methyl 4-(3-bromo-4-oxobutyl) benzoate.

2.3.3. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Ciambra manufactured by Menarini International Operations Luxembourg S.A. 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.

2.3.4. Discussion and conclusion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of pemetrexed are well known. Published literature has been reviewed and is considered of suitable quality. The non-clinical data submitted with this application did not raise any concern.

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

The active substance contained in Alimta is pemetrexed disodium heptahydrate whereas the active substance contained in Ciambra is pemetrexed disodium hemipentahydrate. The hydrate form of the drug substance does not affect bioavailability of the drug product since the drug substance is dissolved in water for injection during the formulation process and the drug product is administered as an intravenous infusion. The Applicant states that once dissolved in water and lyophilized, the final drug product is identical to the reference product Alimta.

Ciambra contains the same qualitative and quantitative composition in active substance, indications, route of administration, dosage form and posology as Alimta.

Ciambra does not contain a different salt, ester, ether, isomer, mixture of isomers, complex or derivative of an active substance than the reference medicinal product.

The Applicant has provided information that the excipients contained in the proposed formulation are the same and in the same quantity as the ones contained in the reference product formulation.

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

Ciambra, 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, Ciambra has the same indications, posology, pharmaceutical form, route of administration and strength after reconstitution as Alimta.

There are no concerns with Ciambra 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 Ciambra 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 Ciambra 100 mg and 500 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 1.2 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 1.3 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

Summary of safety concerns	
	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 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
Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None
Renal disorders	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None
Gastrointestinal disorders	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Interstitial pneumonitis	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None
Radiation pneumonitis	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None
Radiation recall	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None
Sepsis	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None
Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None
Bone marrow suppression	Ensure awareness via product information. Prescription only medicine. Use restricted in hospitals.	None

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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the format and layout of the package leaflet of pemetrexed 100 mg and 500 mg, powder for concentrate for solution for infusion, is consistent with the one of the originator.

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/majority decision that the benefit-risk balance of Ciambra in the following indications:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Ciambra 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.

Ciambra 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.

Ciambra 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.