19 November 2015
EMA/CHMP/828561/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Accord

International non-proprietary name: Pemetrexed

Procedure No. EMEA/H/C/004072/0000

Note

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

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List of abbreviations

ALT : Alanine aminotransferase

AMP : Adenosine monophosphate

AS: active substance

ASMF: Active Substance Master File

AST : Aspartate aminotransferase

AUC : Area under the plasma concentration versus time curve

BSA : Body surface area

CFU : Colony Forming Units

Cmax : Maximum measured concentration of drug in plasma

CR : Complete response

CTC : Common toxicity criteria

DNA : Deoxyribonucleic acid

DR: Death receptor

FT-IR Fourier Transfom Infrared

GC: Gas Chromatography

h : Hour

HDPE: High Density Polyethylene

HPLC: High performance liquid chromatography

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

IV / i.v. : Intravenous

Kd : Dissociation constant

Ki : Binding constant

L : Litre

LDPE: Low Density Polyethylene

MAA : Marketing Authorization Application

mg : Milligram

min : Minute

ml : Millilitre

MPM : Malignant pleural mesothelioma

NMR: Nuclear Magnetic Resonance

NSCLC : Non-small-cell lung cancer

OS : Overall survival

PFS : Progression free survival

Ph. Eur.: European Pharmacopoeia

ppm: parts per million

PR : Partial response

PS : Performance status

RD : Recommended dose

RH: Relative Humidity

TGA: thermogravimetric analysis

TLSB: triple laminate sunlight barrier bag

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 5 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pemetrexed Accord, 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 25 September 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in 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 Accord in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed Accord 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 Accord 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 Accord 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 a bioequivalence study according to (CPMP/EWP/QWP/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

Not applicable

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: John Joseph Borg

- The application was received by the EMA on 5 November 2014.
- The procedure started on 26 November 2014
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 March 2015.
- During the meeting on 26 March 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 24 July 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 August 2015.

- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 September 2015
- During the CHMP meeting on 24 September 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 19 October 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 22 October 2015.
- The Rapporteur circulated an updated Assessment Report to all CHMP members on 5 November 2015

  PRAC RMP Advice and assessment overview, adopted by PRAC on 6 November 2015
- During the meeting on 19 November 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 Accord.

2. Scientific discussion

2.1. Introduction

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

Non-small cell lung cancer

Pemetrexed Accord 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 Accord 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 Accord 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 Accord 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 Accord 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, 500 mg/vial or 1000 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.

Pemetrexed Accord powder for concentrate for solution for infusion is available in Type I glass vial with grey silicon rubber stopper and an aluminium seal with flip off cap. The 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 molecular mass 516.41 g/mol. The active substance has the following structure:

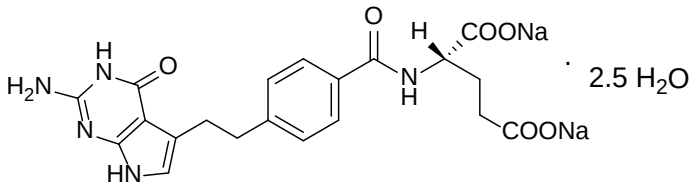

Figure 1: Pemetrexed disodium hemipentahydrate structure.

The structure of the active substance (AS) has been confirmed by elemental analysis, FT-IR, ^{1}H- and ^{13}C-NMR, mass spectrometry and X-ray powder diffraction all of which support the chemical structure.

It appears as a white to off-white, hygroscopic crystalline powder. It is freely soluble in water and insoluble in ethanol.

Pemetrexed disodium contains a single chiral centre at carbon-4 with the absolute S configuration. The formation of desired isomer of pemetrexed is ensured through chirality control of key starting material and the route of synthesis, which is stereoselective. Test for specific optical rotation is one of the control parameters for the desired isomer. 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 thermogravimetric analysis (TGA) and X-ray diffraction. It has been demonstrated that the proposed synthetic route described in the Active Substance Master File (ASMF) yields the desired hemipentahydrate form. It has been also confirmed that polymorphism does not change during manufacture and that the desired polymorph is stable during storage.

Manufacture, characterisation and process controls

The information on the active substance is provided according to the ASMF procedure.

Pemetrexed disodium hemipentahydrate is synthesized in a 10-step process from three well-defined starting materials with acceptable specifications. The starting materials were redefined during the evaluation so that critical steps are conducted under GMP. Following the redefinition of starting materials critical steps have been identified. Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials, intermediate products 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 triple low-density polyethylene (LDPE) bags, which are placed into triple laminate sunlight barrier bag (TLSB) bag and heat sealed. A desiccant is placed in between secondary and tertiary bag. The latter bag is placed into a high-density polyethylene (HDPE) container. The primary packaging material is of food grade and in compliance with current Ph. Eur. requirements and Commission Regulation 1183/2012.

Specification

The active substance specification includes tests and limits for: description, appearance (colour and clarity) of solution (Ph. Eur.), solubility (Ph. Eur.), identity (Ph. Eur.), pH (Ph. Eur.), water content (Ph. Eur), specific optical rotation (Ph. Eur.), sodium content, heavy metals (Ph. Eur.), assay (HPLC), related substances (HPLC), chiral purity (D-isomer content) (HPLC), residual solvents (GC), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The specification of the active substance is based on Ph.Eur. monograph for Pemetrexed disodium heptahydrate. The principle is acceptable because the only difference is in the hydration degree. Potential genotoxic impurities have been sufficiently discussed and shown that they are not carried over in the final active substance.

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 were presented. The results comply with the proposed specification.

Stability

Stability data on three commercial scale batches packaged in packaging intended for marketing and stored for six months under accelerated (25 °C ± 2 °C / 60% RH ± 5% RH) and up to 36 months at long term condition 5 °C ± 3 °C were presented. Results from another four commercial scale batches stored for up to 36 months under long term conditions were also presented. Stability studies were conducted according to the ICH guidelines.

The following parameters were tested: description, appearance (colour and clarity) of solution, identification, pH, water content, assay, related substances, chiral purity (D-isomer content), microbial limits and bacterial endotoxins. Analytical procedures used in stability studies are the same as described for release which were shown to be stability indicating. All tested parameters remained within the specification apart from an impurity which increased significantly and was out of specification at 36 months.

Forced degradation (photo, thermal, high humidity, acid hydrolysis, base hydrolysis and oxidation conditions) and photostability studies have been carried out. The results obtained from these studies indicate that the AS is stable at high humid condition, thermal and light exposure (as per ICH) and acidic condition, but significant degradation was observed in alkaline and oxidative conditions.

In conclusion, the proposed re-test period of 24 months at 2 °C to 8 °C when the active substance is stored under inert atmosphere (nitrogen) in the proposed packaging, in order to protect from moisture and humidity, is adequately supported by the stability data provided and is acceptable.

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 powder for concentrate for solution for infusion. The same pharmaceutical form has been developed as that of the reference product.

The same active substance salt as the reference product is used.

For the 100 mg /vial and the 500 mg /vial, a comparative profile of the test product and the reference product was provided. For the 1000 mg /vial presentation the composition is proportional to that of the approved presentations of the reference product.The final concentration after reconstitution is 25 mg/ml for all three presentations, as is for Alimta. Compatibility of the product with 0.9% sodium chloride to be used for reconstitution and dilution, at the recommended temperatures, has also been demonstrated. The reconstitution instructions are identical to those of the reference product.

The excipients used are the same ones used in the reference product, Alimta. No preservatives or antioxidants are used. Excipients-active substance compatibility studies have not been performed, however, these are not deemed necessary since, as mentioned above, the same excipients are used in the reference product.

The manufacturing process has been optimised with regard to the solubilisation of the active substance, the pH of the bulk solution, the headspace gas, the vial fill volume, the bulk holding and its compatibility with equipment. As a result of these studies the mixing conditions were established, the pH range of the bulk solution has been set, the use of nitrogen to minimise oxidation of the active substance has been decided, the fill volume and overfill have been defined to facilitate delivery of the labelled amount, holding time and conditions of the unfiltered and filtered pemetrexed bulk solution have been established and compatibility with the equipment was demonstrated.
Further optimization studies were carried out particularly focusing on the lyophilisation cycle in order to establish suitable conditions followed by scaling up studies at the commercial manufacturing facility.
The sterilisation method is aseptic filtration and it has been satisfactorily justified on the basis of the active substance chemical stability in line with the guideline CPMP/QWP/054/98 – “Decision trees for the selection of sterilization methods” (Annex to Note for Guidance on Development Pharmaceutics). The filters used in the aseptic filtration process have been validated with regard to microbial retention, compatibility, integrity and extractable substances. The nitrogen gas used in vials during filling is filtered through a 0.22µm filter to ensure its sterility.

The product is packaged in clear, type I glass vials, silicon rubber stopper and aluminium flip-off cap. Integrity of the container and compatibility of the container, the stopper and the lyophilisate as well as the reconstituted solution has been confirmed on inverted vials of finished product.

Manufacture of the product and process controls

The main steps of the manufacturing process are: preparation of bulk solution, pre-filtration, sterile filtration of the bulk solution, aseptic filling of vials, lyophilisation and sealing 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. Bioburden is checked before and after the first filtration and, filter integrity testing is performed pre and post filtration. 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.

Steps and process parameters that are considered critical for the quality of the product were identified. The following process steps and respective process control parameters were defined as critical: preparation of the bulk solution, aseptic filtration and filling of vials and sealing of vials. The bioburden limit prior to second filtration, filter integrity testing before and after filtration, fill weight during filling and filter integrity testing of the sterilizing filter used for nitrogen are all considered as critical parameters in the manufacturing process.

Adequate in-process controls are in place for this type of manufacturing process. The batch size for each strength has been clearly defined at the time of submission.

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 to be a non-standard manufacturing process. Process validation has been performed on three commercial scale batches for each strength 100 mg/ vial, 500 mg/ vial and 1000 mg/ vial for all proposed batch sizes. A media fill study is performed to evaluate the aseptic manufacturing, filling and lyophilization procedures. The media fill study is carried out to simulate aseptic filtration and the filling process at worst case conditions. 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), identification (HPLC, HPLC-DAD), identification of sodium (chemical reaction), uniformity of dosage units (Ph. Eur.), oxygen headspace content, assay (HPLC), related substances (HPLC), water content (Ph. Eur.), clarity and colour of the reconstituted solution (Ph. Eur.), reconstitution time, pH of the reconstituted solution (Ph. Eur.), particulate matter (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The limits of impurities are based on the maximum daily dose and are in line with ICH guideline Q3B(R2). It has been demonstrated that no isomer conversion occurs during the manufacturing process of the drug product. Thus the justification for not including the test for D-isomer in the finished product specification is considered acceptable.

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

Batch analysis data were provided on three commercial scale batches for each strength manufactured at proposed manufacturing site. Additional batch analysis data were provided on two commercial scale batches for the 100 mg/vial and the 500 mg/vial strength. 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.

Stability of the product

Stability studies have been conducted on three commercial scale batches per strength manufactured at proposed manufacturing site and packaged in the proposed packaging in accordance with ICH requirements. Stability results were provided for samples stored in upright position for up to 36 months at long-term conditions (25 ºC / 60% RH) and for six months under accelerated conditions (40 °C/75% RH).
Stability data were also provided for another four commercial scale batches for the 100 mg /vial and 500 mg /vial two in the proposed packaging and manufactured at the proposed manufacturer for up to 24 months at long-term conditions. Finally three additional batches of the 500 mg /vial strength manufactured at an alternative larger batch size have been studied for up to 9 months stored in upright and inverted position under long term conditions.
The parameters tested as per the stability protocol were: appearance of the powder, particulate contamination of the reconstituted solution, colour and clarity of the reconstituted solution, water content, reconstitution time, pH of the reconstituted solution, assay, related substances, sterility and bacterial endotoxins. Analytical

procedures used in stability studies are the same as described for release. All the results met the specification and did not show any trend under any storage condition.

Forced degradation studies were also performed where samples were stress tested under heat, moisture, acidic, alkaline, oxidative and light conditions. It has been demonstrated that the product does not show significant degradation when exposed to heat, water, UV and fluorescent light. Significant degradation occurred when the product was exposed to acidic, alkaline, oxidative conditions. Based on this study the analytical methods were shown to be stability indicating.

Photostability studies

A photostability study has been carried out on one batch of the 500 mg/vial strength as per ICH requirement. The results showed no significant impact of light on the product and suggest that the product is not sensitive to light.

In-use stability studies

Reconstitution: Since the nominal concentration of the reconstitution solution is the same for all the strengths, a reconstitution study was performed with one strength (500 mg /vial). Pemetrexed Accord was reconstituted with 0.9% Sodium Chloride as per the SmPC instructions in section 6.6. The reconstituted solutions were observed at 25 °C and 2-8 °C temperature for signs of discoloration and/or precipitation at suitable intervals for a period of initial, 24, 48 and 72 hrs. The solutions were analysed for assay, related substances, particulate matter and pH. The results showed that the reconstituted product is well stable up-to recommended time points when reconstituted as indicated in the SmPC. Dilution: Pemetrexed Accord concentrate was further diluted as per the SmPC instruction in section 6.6. The diluted solution was stored at 20-30 °C (immediately and after 24 hrs) & 2-8 °C (immediately and after 24, 48 and 72 hrs) and analysed respectively. The data showed that the product upon further dilution of the reconstituted solution with recommended dilution procedure is well stable up to recommended time points when diluted as indicated in the SmPC.
Considering that Pemetrexed Accord is identical in qualitative composition to the reference product and the solution to be used for reconstitution / dilution is the same one used for the reference product, the in-use / compatibility study performed is considered sufficient.

On the basis of the overall available stability data, the shelf life of 36 months without any special storage conditions 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. The proposed starting materials as they have been redefined and the overall control strategy of the active substance are acceptable. Pemetrexed Accord 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 to the intended quality in a reproducible manner. The choice of the sterilisation 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. 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.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pemetrexed Accord manufactured by Accord Healthcare Limited, UK comprises of 100 mg powder for concentrate for solution for infusion; 500 mg powder for concentrate for solution for infusion and 1000 mg powder for concentrate for solution for infusion which are substitutable versions of the previously approved reference products Alimta; Eli Lilly Nederland B.V.. Therefore, it is considered unlikely to result in any significant increase in the combined sales volumes for all pemetrexed containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion and conclusion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of pemetrexed are well known. No non-clinical data were submitted with this application. Published literature has been reviewed and is considered of suitable quality. Therefore, the CHMP agreed that no further non-clinical studies are required.

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

The composition of Pemetrexed Accord 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. A quantitative composition comparison of the applied and the reference product is provided below.

Ingredients	**Proposed Generic Pemetrexed for Injection (mg/vial)**			**Innovator ALIMTA Eli Lilly Nederland B.V. (mg/vial)**	
	100 mg/vial	**500 mg/vial**	**1000 mg/vial**	**100 mg/vial**	**500 mg/vial**
Pemetrexed (as Pemetrexed disodium)	100.0 mg	500.0 mg	1000.0 mg	100.0 mg	500.0 mg
Mannitol	100.0 mg	500.0 mg	1000.0 mg	Not specified	Not specified
Hydrochloric acid	q.s. to pH	q.s. to pH	q.s. to pH	q.s. to pH	q.s. to pH
Sodium hydroxide	q.s. to pH	q.s. to pH	q.s. to pH	q.s. to pH	q.s. to pH

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 chloride 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 submitted.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were submitted..

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

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

There are no concerns with Pemetrexed Accord 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 Accord 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 the clinical information provided is adequate to support the approval of Pemetrexed Accord 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion.

2.5. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 1.0 (dated 03 November 2014) could be acceptable if the applicant

implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report dated 12 March 2015.

The CHMP endorsed this advice without changes.

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

The CHMP endorsed the RMP version 3.0 (dated 15 October 2015) with the following content:

Safety concerns

Important identified risks	• Bullous skin reactions including SJS and TEN • Gastrointestinal disorders • Interstitial pneumonitis • Noncompliance with folic acid and vitamin B12 regimens, manifested mainly as haematological and gastrointestinal toxicities • Radiation pneumonitis • Radiation recall • Sepsis • Renal disorders • Bone marrow suppression
Important potential risks	N/A
Missing information	N/A

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 Accord, 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 pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Bullous skin reaction including SJS and TEN	Text in SmPC section 4.8, and PIL. Prescription only medicine.	None
Gastrointestinal disorders	Text in SmPC sections 4.4, 4.5, 4.8, and PIL. Prescription only medicine.	None
Interstitial pneumonitis	Text in SmPC section 4.8, and PIL. Prescription only medicine.	None
Noncompliance with folic acid and vitamin B12 regimens, manifested mainly as hematological and gastrointestinal toxicities	Text in SmPC sections 4.2, 4.4, 5.2, and PIL. Prescription only medicine.	None
Radiation pneumonitis	Text in SmPC sections 4.4, 4.8, and PIL. Prescription only medicine.	None
Radiation recall	Text in SmPC sections 4.4, 4.8, and PIL. Prescription only medicine.	None
Sepsis	Text in SmPC section 4.8, and PIL. Prescription only medicine.	None
Renal disorders	Text in SmPC sections 4.4, 4.5, 4.8, and PIL. Prescription only medicine.	None
Bone marrow suppression	Text in SmPC sections 4.4, 4.8, 4.9, and PIL. Prescription only medicine.	None
Important potential risks	N/A	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Missing information	N/A	N/A

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, Zoledronic Acid Accord and Levetiracetam Accord. 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.

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

A positive 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 that the benefit-risk balance of Pemetrexed Accord in the following indication:
Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Accord 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 Accord 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 Accord 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.