26 May 2016
EMA/CHMP/407425/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Fresenius Kabi

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/003895/0000

Note

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

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List of abbreviations

AS active substance

ASMF Active substance master file

BET Bacterial endotoxin

CHMP Committee for medicinal products for human use

CQA Critical quality attribute

DSC Differential scanning calorimetry

EU European Union

FDM Freeze drying microscopy

FK Fresenius Kabi (Applicant)

GC Gas chromatography

GMP Good manufacturing practice

HDPE High-density polyethylene

HPLC High performance liquid chromatography

ICH International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use

ICP-MS Inductively coupled plasma mass spectrometry

IPC In-process control

IR Infrared

KF Karl Fisher titration

LCMS Liquid chromatography–mass spectrometry

LDPE Low-density polyethylene

MS Mass spectrometry

NMR Nuclear magnetic resonance

NMT Not more than

Ph. Eur. European Pharmacopoeia

PL Package Leaflet

QTPP Quality target product profile

SmPC Summary of product characteristics

TLAP Triple laminated aluminium pouch

USP United States Pharmacopeia

UV Ultraviolet

XRPD X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Oncology Plc submitted on 21 May 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pemetrexed Fresenius Kabi, 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 21 November 2013.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Fresenius Kabi in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).

Pemetrexed Fresenius Kabi is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy (see section 5.1).

Pemetrexed Fresenius Kabi is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology (see section 5.1).

The 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 instead of non-clinical and clinical unless justified otherwise. There is no requirement for bioequivalence testing according to CPMP/EWP/QWP/1401/98 Rev.1.

Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Alimta 100 mg/500 mg powder for concentrate for solution for infusion
- Marketing authorisation holder: Eli Lilly Nederland B.V.

- Date of authorisation: 20-09-2004
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/04/290/001-002

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

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

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Karsten Bruins Slot

CHMP Peer reviewer: Juris Pokrotnieks

- The application was received by the EMA on 21 May 2015.
- The procedure started on 25 June 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2015.
- The PRAC Rapporteur's first Assessment Report was circulated to all CHMP/PRAC members on 25 September.
- During the meeting on 22 October 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 27 January 2016.
- The CHMP/PRAC Rapporteurs' circulated their joint Assessment Report on the applicant's responses to the List of Questions to all CHMP/PRAC members on 8 March 2016
- PRAC RMP Advice and assessment overview, adopted by PRAC on 17 March 2016.
- The CHMP/PRAC Rapporteurs' circulated their updated joint Assessment Report on the applicant's

responses to the List of Questions to all CHMP/PRAC members on 23 March 2016.

- During the CHMP meeting on 1 April 2016, 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 26 April 2016.
- The CHMP/PRAC Rapporteurs' circulated their joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP/PRAC members on 11 May 2016.
- During the meeting on 26 May 2016, 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 Fresenius Kabi.

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion. Pemetrexed Fresenius Kabi 100 mg or 500 mg Powder for Concentrate for Solution for Infusion has the same active substance (different salt) and the same excipients in comparable amounts to the centrally approved reference medicinal product Alimta (EU/1/04/290/001-002).

The claimed indication for Pemetrexed Fresenius Kabi is:

"Malignant pleural mesothelioma

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

Non-small cell lung cancer

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

The difference in active substance salt form between the applied product and the reference product is therefore not relevant for the clinical efficacy and safety of the ready to use infusion.

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.

The active substance in Fresenius Kabi's Pemetrexed for Injection is pemetrexed diacid instead of pemetrexed disodium as in the originator product Alimta. Both products are intended for intravenous use and must be reconstituted and further diluted prior to use. When reconstituted and diluted for administration, the active moiety remains the same irrespective of the salt form.

Excipients of Pemetrexed Fresenius Kabi differ from Alimta. The excipients used are well known and commonly used in aqueous intravenous solution available on the European market, and the differences are not expected to have any significant impact in properties with regards to bioavailability, pharmacokinetics, safety and efficacy between these products.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 100 mg/vial and 500 mg/vial of pemetrexed (as pemetrexed diacid) as active substance. After reconstitution, both presentations result in 25 mg/ml of pemetrexed.

The powder has to be reconstituted with 5% glucose intravenous infusion before administration.

As described in section 6.1 of the SmPC, other ingredients are: mannitol (E421), hydrochloric acid concentrated (E507) (pH adjustment) and trometamol (pH adjustment).

The finished product is presented in Type I glass vial with chlorobutyl rubber stopper and green or blue flip-off seal respectively, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of the active substance is N-{4-[2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d] pyrimidin-5-yl) ethyl] benzoyl}-L-glutamic acid, corresponding to the molecular formula $C_{20}H_{21}N_5O_6$ and has a molecular mass of 427.41 g/mol. Pemetrexed diacid has the following structure (Figure 1):

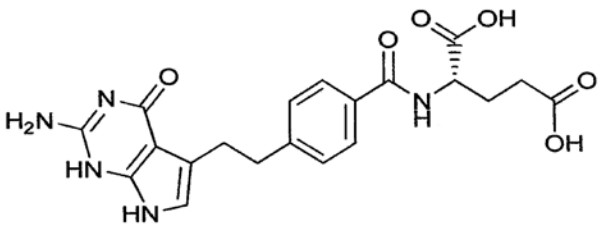

Figure 1. Molecular structure of Pemetrexed diacid.

The structure of pemetrexed diacid has been confirmed by mass spectrometry, infrared spectroscopy, proton nuclear magnetic resonance spectroscopy (1H-NMR), ^{13}C-NMR and X-ray Powder Diffraction (XRPD).

Pemetrexed diacid is a white to off-white coloured crystalline and highly hygroscopic powder that is soluble in dimethylformamide, dimethylsulphoxide and sodium hydroxide solution and insoluble in water.
Pemetrexed diacid possesses one chiral centre in the structure. There are two optically active isomers: the *R* (or D) isomer is inactive and the *S* (or L) isomer is the active isomer. Pemetrexed diacid is manufactured as the single *S* (or L) isomer. Enantiomeric purity is controlled routinely by chiral HPLC.

Several polymorphic forms of pemetrexed diacid are reported in literature. Pemetrexed diacid produced by the active substance manufacturer is the crystalline form. As requested by the CHMP, a test to control polymorphism was included in the active substance specifications as a non-routine test.

Pemetrexed as diacid is not described in Ph. Eur. A monograph exists however for pemetrexed as a disodium salt (heptahydrate).

Manufacture, characterisation and process controls

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

Pemetrexed diacid is manufactured in a nine stage process using five well defined starting materials. As requested by the CHMP, the Applicant has redefined the initially proposed starting material as an intermediate to ensure that all critical steps of the synthetic process are described in the dossier. Starting materials and intermediates are controlled by acceptable specifications. Adequate in-process controls are applied during the synthesis.

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 including related substances, residual solvents, inorganic impurities and genotoxic impurities were appropriately discussed in the ASMF. In particular, possible carry-over of potential genotoxic impurities in pemetrexed diacid samples have been determined by LCMS scan. It has been demonstrated that these impurities are absent in pemetrexed diacid final active substance. In addition, since pemetrexed diacid is indicated for treatment of advanced cancer, the absence of a full discussion on genotoxic impurities is accepted in accordance with ICH-M7.

The active substance is packed into a double polyethylene zipped bag (LDPE). It is further put into another polyethylene bag, heat sealed and then introduced into a triple laminated aluminium pouch (TLAP) and heat sealed. The TLAP is placed in a high density polyethylene (HDPE) opaque drum/ fibre board drum. The container closure system is in compliance with the Ph. Eur. monographs 3.2.2 and 3.1.3 and with the EU Regulation no 1183/2012 (amending and correcting the Regulation (EU) No 10/2011).

Specification

The active substance in-house release specification include: description, solubility, identity (HPLC and IR), water content (KF), residue on ignition (USP), heavy metals (USP), colour (Ph. Eur.), clarity (Ph. Eur.), residual solvents (GC and HPLC), related substances (HPLC), chiral purity (HPLC), assay (HPLC), bacterial endotoxins (Ph. Eur.), microbial limit test (Ph. Eur.), elemental impurities (ICP-MS) and polymorphism (XRPD).

The purity requirements as defined in the active substance specification are sufficiently justified and considered acceptable. The absence of control of the active substance particle size in the specification was adequately justified based on the demonstration that it did not affect the dissolution rate of the drug substance. Studies showed that increased water content did not impact the quality of the active substance, so no test for water content is required. All analytical methods have been properly described and the in-house analytical methods have been adequately validated in line with the ICH guidelines. Satisfactory information regarding the reference standards used for the analytical validation of related substances and assay has been provided.

The results of three validation (production scale) batches demonstrate compliance to the proposed active substance specifications and batch to batch consistency.

Stability

Stability studies on the first three commercial scale validation batches of active substance from the proposed manufacturer stored in the intended commercial packaging over a period of 36 months at long-term storage conditions (30°C ± 2°C / 65% RH ± 5% RH) and over a period of 6 months at accelerated storage conditions (40°C ± 2°C / 75% RH ± 5% RH) were provided. The stability studies were performed according to the ICH Q1A(R2).

The following parameters were tested: description, identification, colour and clarity (2.5% w/v solution in 1N NaOH), water content, assay, bacterial endotoxins, microbial limit test, related substances and chiral purity.

The analytical test methods used for stability studies are those followed at the time of release and were stability indicating. No trends were observed and all parameters remained within the proposed specification.

Forced degradation studies were also conducted on one batch. The results showed that Pemetrexed diacid degrades in acid, base and oxidative stress conditions. The analytical test methods used for stability studies are those followed at the time of release and were stability indicating. Photostability testing following the ICH guideline Q1B was performed. Results did not show any significant change in the parameters studied.

Based on the submitted stability data, the active substance manufactured by the proposed supplier is stable for 36 months at long term conditions (30°C ± 2°C / 65% RH ± 5% RH) when packed in the intended container closure (see section “Manufacture, characterisation and process controls”). The retest period of 36 months when stored at controlled room temperature in the proposed container is acceptable.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of the pharmaceutical development was to develop a finished product generic to the reference medicinal product, Alimta (Eli Lilly Nederland B.V). The active substance in Pemetrexed Fresenius Kabi is pemetrexed diacid instead of pemetrexed disodium (Alimta). Since the active moiety in the solution for infusion remains the same irrespective of the salt form used for manufacture it has no impact.

The finished product Pemetrexed Fresenius Kabi has the same pharmaceutical form as the reference product, powder for concentrate for solution for infusion containing 100 mg or 500 mg of pemetrexed per vial. It is presented in 10 ml (100 mg/vial) or 50 ml (500 mg/vial) glass vials sealed with rubber stoppers and flip off caps. The powder is described as white to off-white lyophilized powder or solid. Before administration, the finished product should be reconstituted with 5 % glucose intravenous infusion and further diluted with 5 % glucose intravenous infusion according to the instructions given in the product information. Further information on this diluent is provided in the clinical part of this report. No reconstitution solution is supplied with the finished product.

Based on public information and characterisation studies on the reference product, as well as general requirements for the product type, a quality target product profile (QTPP) for the finished product was defined as a powder for concentrate for solution for infusion containing 100 mg or 500 mg pemetrexed per vial, meeting pharmacopoeial requirements for parenteral dosage forms, to be 100% bioavailable, with acceptable packaging that ensures an adequate shelf-life as packaged and an appropriate in-use shelf life following reconstitution and dilution.

Based on the QTPP, compendial requirements, available information on the reference product and additional characterization studies, physicochemical properties of the drug substance and developmental studies conducted by Fresenius Kabi, critical quality attributes (CQAs) of the finished product were identified. These CQAs are description/appearance, identification, water content, uniformity of dosage units, reconstitution time, description of reconstituted solution, completeness and clarity of solution after reconstitution, particulate matter (visible and sub-visible particles), pH, related substances, assay, bacterial endotoxins and sterility.

Risk assessment was conducted on these CQAs to form the basis for product development studies in order to mitigate the risk through formulation and process design and control. The potential attributes affecting these CQAs were identified and their potential to impact any of the finished product CQAs was classified as low, medium or high risk. Based on the identified QTPP, CQAs and initial risk assessment, product development studies were conducted to identify a stable formulation and a manufacturing process to consistently produce a product of the intended quality.

The suitability of all the excipients and their compatibility with the active substance was verified by stability studies. The excipients used in the formulation of Pemetrexed Fresenius Kabi are the same used in the reference product except sodium hydroxide, which is replaced by trometamol. Trometamol is a known buffering agent/pH adjuster and solubilizer. In addition, hydrochloric acid has been added as a pH adjusting agent. Mannitol is the main excipient used as a bulking agent during lyophilization process. The list of excipients is included in section 6.1 of the SmPC and in paragraph 1.1.1 of this report. All excipient are of Ph. Eur. quality and suitable for parenteral formulations.

The effects of temperature, pH, light and dissolved oxygen on the bulk solution stability during the manufacturing process were evaluated. Light protection of the liquid product and nitrogen purging and flushing to control oxygen level during manufacturing were then identified as critical process controls. Drug dissolution was also considered a critical step of the process. Complete dissolution was ensured by applying appropriate in-process controls.

As the active substance is sensitive to oxidation and vulnerable to hydrolysis in aqueous environment it is formulated as a lyophilised powder, and stored under nitrogen in type I glass vials as the reference medicinal product. The finished product is manufactured by sterile filtration followed by aseptic processing. Sterile filtration was considered a critical step. This resulted in the performance of a test for filter integrity with the filters tested before and after filtration. In addition, a pre-filtration bio-burden test before sterile filtration was

conducted to ensure that the bio-burden load was within acceptable limits. The lyophilisation process was developed based on the product's critical temperatures as characterised by differential scanning calorimeter (DSC) and freeze drying microscopy (FDM).

No bioequivalence study was deemed required as the finished product is to be administered as an aqueous solution containing the same active substance in the same concentration as the reference product.

The primary packaging is Ph. Eur. Type-I, tubular glass vials (100 mg in 10 ml and 500 mg in 50 ml) closed with 20 mm chlorobutyl rubber stopper and sealed with green or blue, respectively, aluminium flip-off over seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of three stages: bulk solution, aseptic filtration and filling/lyophilisation. The critical steps of the manufacturing process were properly described. The in-process controls are adequate for this type of manufacturing process.

The manufacturing process is considered to be non-standard as the finished product is sterilised by sterile filtration followed by aseptic processing.

Major steps of the manufacturing process (bulk solution, filtration, filling and lyophilisation and sealing) have been validated by a number of studies. Process validation has been performed with three commercial scale batches of each of the presentations (100 mg/ vial and 500 mg/ vial). 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 specification includes appropriate tests for this kind of dosage form description (visual), identification (UV and HPLC), water (KF, Ph.Eur.), uniformity of dosage units (Ph.Eur.), reconstituted solution including reconstitution time, description of reconstituted solution(visual), completeness and clarity of solution (visual) and particulate contamination (visual), colour (Ph.Eur.), particulate contamination (sub-visible particle, Ph.Eur.), pH (Ph.Eur.), related substances (HPLC), assay (HPLC), bacterial endotoxins (Ph.Eur.), sterility (Ph.Eur.) and seal integrity test(vacuum decay or Dye intrusion).The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards used for analytical validation, method transfer and release testing of the finished product has been provided.

Batch analyses results for three full scale batches (process validation batches) for all the strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification have been provided.

Stability of the product

Stability data of three commercial scale batches of each strength of the finished product packed in the primary packaging proposed for marketing were provided. The batches of Pemetrexed Fresenius Kabi are identical to those proposed for marketing. The conditions applied were in line with the ICH guidelines and were the

following: accelerated conditions (40°C/75 % RH) for up to 6 months, intermediate conditions (30°C/65 % RH) and long term conditions (25°C/60 % RH) for 12 months.

Samples were tested for: description, water, pH, assay (by HPLC), particulate contamination (sub-visible particles), reconstituted solution tests (reconstitution time, description of reconstituted solution, completeness and clarity of solution after reconstitution, particulate contamination – visible particles, pH, colour) bacterial endotoxins, sterility, related substances (by HPLC) and seal integrity test.

The analytical methods used were the same as for the release and they are stability indicating.

The results showed that Pemetrexed for Injection 100 mg/vial and 500 mg/vial, are chemically, physically and microbiologically stable. No significant changes were observed during the stability studies at any of the conditions tested and all parameters remained within the proposed specification.

In addition, a photostability study was also performed according to ICH Q1B on one batch of each of the presentations. Samples were analyzed for description, assay, pH and related substances. All results remained within the specifications and no significant trends were observed, demonstrating that that the finished product is not light sensitive. Therefore, it can be concluded that no special protection from light is required for the drug product in the proposed primary packaging.

A reconstitution stability study was also conducted on one batch of the 100 mg presentation after reconstitution with the prescribed volume of diluent (5% glucose). Samples were stored at room temperature (25°C±2°C) and at 2°C-8°C for up to 48 hrs. EU and US reference product was also studied for reconstitution stability for up to 24 hrs. The reconstituted samples were analyzed for: description, assay, pH and related substances. No significant change in assay and impurity profile was observed on the reconstituted test product at any of the conditions studied. The reconstituted stability of the test product was found to be comparable to that of reference product. It is recommended to use reconstituted Fresenius Kabi's Pemetrexed for Injection within 24 hours at refrigerated temperature with the recommended diluent 5% Glucose intravenous infusion.

Since reconstituted Pemetrexed for Injection is intended to be diluted before administration in 5% Glucose intravenous infusion, a dilution study was also conducted. Samples of 1 mg/ml and 9 mg/ml of Pemetrexed were stored for up to 48 hours at room temperature (25°C±2°C) and at 2°C-8°C. The samples were withdrawn at pre-defined time points and were analyzed for description, assay, related substances, pH and osmolality (initial time point only). The study demonstrated that the product developed is compatible with both diluents at the conditions tested. In light of the results it is recommended to use reconstituted Fresenius Kabi's Pemetrexed for Injection within 24 hours at refrigerated temperature with the recommended diluent 5% Glucose intravenous infusion.

Furthermore, in order to study the impact of extreme low temperature conditions, outside the labelled storage conditions, that may occur during finished product shipment, a thermal excursion study was performed. The results showed that short exposure of the product at -20 °C for 14 days and 60°C for 2 days does not have any deleterious effect on product stability.

Finally, the impact of fluctuating environmental conditions that may occur during finished product distribution, thermal cycling study was also evaluated. Samples were stored at -20°C or 2°-8°C for 2 days, followed by 40±2°C/75±5%RH for other 2 days. The results showed that short exposure of product to these conditions does not have any adverse effect on the product.

Based on the available stability data, the proposed shelf life of 24 months without any special storage conditions as stated in the SmPC (section 6.3) is acceptable. Specific instructions for use have also been included in this section of the SmPC.

Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. As requested by the CHMP, the applicant re-defined the proposed starting materials to ensure that all critical steps of the synthetic process are described in the dossier. The active substance in Pemetrexed Fresenius Kabi is pemetrexed diacid instead of pemetrexed disodium (Alimta). Since the active moiety in the solution for infusion remains the same irrespective of the salt form used for manufacture it has no impact. 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 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

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The overview refers to 15 publications up to 2013. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data, and that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product which is in accordance with relevant guidelines. The excipients, mannitol, hydrochloric acid and trometamol are widely used in parenteral products and have well-known safety profiles

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

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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pemetrexed Fresenius Kabi manufactured by Fresenius Kabi 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 environmental risk 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

Biowaiver

No bioequivalence studies have been submitted.

Referring to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), the applicant claims that a bioequivalence study is not required for this application since Pemetrexed 100 mg and 500 mg powder for concentrate for solution for infusion is to be administered as an aqueous intravenous solution containing the same active substance as the reference product Alimta powder for concentrate for solution for infusion. Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

The active substance in Fresenius Kabi's Pemetrexed for Injection is Pemetrexed diacid instead of Pemetrexed disodium as in Alimta 100 mg/500 mg powder for concentrate for solution for infusion. Before use, the powder is reconstituted with 5 % Glucose solution to achieve a concentration of 25 mg/ml of pemetrexed. The concentrate is further diluted before intravenous infusion. In the solution for intravenous infusion the active moiety remains same irrespective of the salt form.

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 were submitted. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

According to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), 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. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

The active substance in Fresenius Kabi's Pemetrexed for Injection is Pemetrexed diacid instead of Pemetrexed disodium as in Alimta 100 mg/500 mg powder for concentrate for solution for infusion. When reconstituted and diluted for administration, the active moiety remains the same irrespective of the salt form. Accordingly, both medicinal products are considered to contain the same active substances.

Trometamol is a known buffering agent/pH adjuster used in formulations available in Europe and US. It is agreed that the quantity used in Fresenius Kabi's formulation is less than the required quantity to produce pharmacological action and would not be expected to cause any adverse effects of its own. The other excipients are well known and commonly used in aqueous intravenous solution available on the European market. The existing differences in the excipients of the applied product as compared to the reference product are not expected to have any significant impact in properties with regards to bioavailability, pharmacokinetics, safety and efficacy between these products.

Taking into account all aforementioned, the requirements set out in the bioequivalence guideline are considered met, and a waiver of bioequivalence study is considered acceptable from a clinical point of view, provided the product is deemed to be essentially similar to the reference product based on the pharmaceutical assessment.

The clinical overview supports the indications and covers adequately the clinical pharmacology, efficacy and safety of the product.

The proposed SmPC of the applied product is in line with the SmPC of Alimta.

2.4.6. Conclusions on clinical aspects

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

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	Non-compliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities Renal disorders Gastrointestinal disorders Interstitial pneumonitis Radiation pneumonitis Radiation recall Sepsis Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) Bone marrow suppression
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

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

Risk minimisation measures

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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities	Proposed text in SmPC sections 4.2, 4.4 and 4.8	None
Renal disorders	Proposed text in SmPC sections 4.2, 4.4 and 4.8	None
Gastrointestinal disorders	Proposed text in SmPC sections 4.4 and 4.8	None
Interstitial pneumonitis	Proposed text in SmPC sections	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.2, 4.4 and 4.8	
Radiation pneumonitis	Proposed text in SmPC sections 4.4 and 4.8	None
Radiation recall	Proposed text in SmPC sections 4.4 and 4.8	None
Sepsis	Proposed text in SmPC section 4.8	None
Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Proposed text in SmPC section 4.8	None
Bone marrow suppression	Proposed text in SmPC sections 4.2, 4.4 and 4.8	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. PSUR submission

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

2.7. Pharmacovigilance

Pharmacovigilance system

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

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

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

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Alimta in combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

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

Alimta is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

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

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

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 that the benefit-risk balance of Pemetrexed Fresenius Kabi in the following indication:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Fresenius Kabi 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 Fresenius Kabi 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 Fresenius Kabi 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.

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.