22 March 2018
EMA/CHMP/225126/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Krka

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/003958/0000

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 KRKA d.d., Šmarješka cesta 6, 8501 Novo mesto, Slovenia submitted on 24 May 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Pemetrexed Krka, 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 17 December 2015.

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, as defined in Article 10 (2)(a) of Directive 2001/83/EC, 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 Krka in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

Pemetrexed Krka 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 Krka 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 Krka 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, complete quality data and a bioequivalence study with the reference medicinal product Alimta instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Alimta, 500 mg, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: (22-09-2004)
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/290/001

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, Powder for concentrate for solution for infusion
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: (22-09-2004)
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/290/002

Information on paediatric requirements

Not applicable

1.2. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Kolbeinn Gudmundsson Co-Rapporteur: N/A

- The application was received by the EMA on 24 May 2017.
- The procedure started on 15 June 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 31 August 2017.. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 12 September 2017.
- During the meeting on 12 October 2017, 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 November 2017.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 December 2017.
- During the PRAC meeting on 8-11 January 2018, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 25 January 2018, the CHMP agreed on a list of outstanding issues to be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 15 February 2018.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 6 March 2018.
- During the meeting on 19-22 March 2018, 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 Krka.

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion, Pemetrexed Krka 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 Pemetrexed Krka is:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Krka 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 Krka 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 Krka 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.

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

About the product

Pemetrexed is a multi-targeted anti-cancer antifolate agent that exerts its action by disrupting crucial folate-dependent metabolic processes essential for cell replication.

Mode of action

In vitro studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is transported into cells by both the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is rapidly and efficiently converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase.

The polyglutamate forms are retained in cells and are even more potent inhibitors of TS and GARFT.

Polyglutamation is a time- and concentration-dependent process that occurs in tumour cells and, to a lesser extent, in normal tissues. Polyglutamated metabolites have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 100 mg/vial or 500 mg/vial of pemetrexed (as disodium salt hemipentahydrate) as active substance. After reconstitution, the two presentations result in 25 mg/ml of pemetrexed.

Other ingredients are: mannitol, hydrochloric acid and sodium hydroxide.

The product is available in transparent Type I glass vials with bromobutyl rubber stopper and aluminium cap with tear off part made of polypropylene (embossed with sign “FLIP OFF”) as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

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

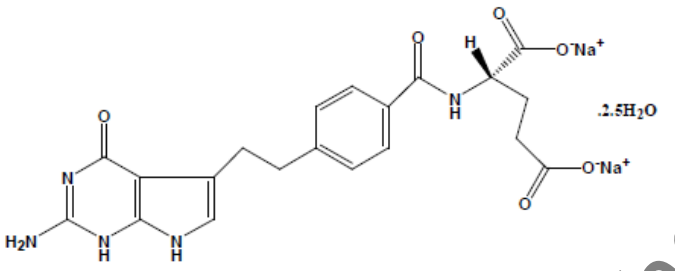

Figure 1: active substance structure

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

The active substance is white or almost white hygroscopic crystalline powder, soluble in water and methanol, slightly soluble in DMSO and practically insoluble in acetonitrile, ethyl acetate, DMF, THF, acetone, as well as methylene chloride. Its molecular weight is 516.4 gmol^{-1}, corresponding to the general molecular formula $C_{20}H_{19}N_5O_6Na_2.2.5H_2O$.

Pemetrexed disodium hemipentahydrate is an optically active compound due to the stereogenic centre of the glutaminic acid part which originates in one of the starting materials. The active form is the L-enantiomer. Enantiomeric purity is controlled routinely by chiral HPLC. Pemetrexed disodium can exist in an amorphous form or different hydrated forms (pseudo-polymorphs). The most relevant crystalline forms are the hemipentahydrate and the heptahydrate (which has a Ph. Eur. monograph). The form routinely produced by the proposed manufacturing process is the hemipentahydrate form, as supported by XRPD data. The polymorphic form remains stable during storage of the active substance.

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

Manufacture

The synthesis of pemetrexed disodium hemipentahydrate is documented in one ASMF supporting this procedure.

There are two manufacturers employing different synthetic routes to make the intermediate . A third manufacturing site performs the remaining four stages to convert this intermediate to the final active substance. All starting materials used throughout both synthetic routes have been well defined and acceptable specifications have been set (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 well discussed with regards to their origin and characterised. The potential elemental impurities likely to be introduced from the various sources such as starting materials/raw materials/reagents, equipment have been evaluated in pemetrexed disodium

drug substance as per the requirements of ICH Q3D. Potentially genotoxic impurities were demonstrated not to be detected in the active substance and are thus not routinely tested for.

The active substance is packaged in double heat-sealed LDPE bags with an intermediate silica gel pouch, packed inside a triple laminated sunlight barrier bag and stored inside an HDPE drum. All materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

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

Specification

The active substance specification is based on the Ph. Eur. monograph for pemetrexed heptahydrate salt and includes tests for appearance, solubility, identity (IR, HPLC, sodium test (Ph. Eur.)), water content (Ph. Eur.), clarity, appearance and pH of solution (Ph. Eur.), enantiomeric purity (HPLC), assay (HPLC),related substances (HPLC), residual solvents (GC), bacterial endotoxins (Ph. Eur.) and microbial contamination (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

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

Stability

Stability data on three production scale batches of active substance stored in the packaging simulating the proposed commercial package for up to 36 months under long term conditions (5±3 ºC), for up to 12 months under intermediate conditions (15 ºC / 60% RH), and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided.

Samples were tested for appearance, identification (IR), water content, clarity and appearance of solution, pH, D-Isomer content, related substances, assay, bacterial endotoxin and microbial limits.

The analytical methods used were the same as for release and were stability indicating. Out of specification results were observed for impurities under accelerated conditions, but no significant trends were observed under intermediate or long term conditions. Forced degradation studies including photostability studies following the ICH guideline Q1B were performed showing the active substance is sensitive to acid, base, light and oxidation but stable to thermal degradation. No racemisation occurred under any condition.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months at 2-8ºC in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of the pharmaceutical development was to develop a finished product equivalent to Alimta powder for concentrate for solution for infusion, in two strengths: 100 and 500 mg.

Pemetrexed Krka powder for concentrate for solution for infusion is a white to either light yellow or green-yellow lyophilized cake or powder. The formulation is packed in clear glass vials (10 mL / 50mL) made of transparent glass type I (Ph.Eur.). The rubber stoppers are made of grey bromobutyl rubber (Ph. Eur.). The cap for fixation of the stopper on the vial is made of aluminium and the tear off part of the cap is made of polypropylene ivory colour. The tear off part is embossed sign “FLIP OFF”. As secondary packaging, the labelled vial is packed with the PIL into a printed folding box. After reconstitution, each vial contains 25 mg/ml of pemetrexed.

The qualitative composition of the finished product pemetrexed Krka 100 mg and 500 mg is provided in the following table:

Table 1: Qualitative composition of the drug product 100 mg

Name of substance	Function
Pemetrexed disodium hemipentahydrate	Active substance
Mannitol	Tonicity agent vehicle Bulking agent
Hydrocloric acid concentrated	pH adjuster
Sodium hydroxide	pH adjuster
Water for injection**	Solvent

**eliminated during lyophilization process

Nitrogen is used as process aid for inertisation during preparation of bulk solution and for purging during filling of vials and just before stoppering in lyophilization process. Nitrogen complies to Ph.Eur. standard.

As mentioned above, the formulation contains the active substance pemetrexed disodium hemipentahydrate, whereas the reference product contains pemetrexed disodium heptahydrate. Since the active substance is fully solubilised during the manufacture of the finished product, the initial polymorphic form of the active substance does not influence the performance of the product.

Critical attributes of the active substance that can affect product performance or manufacturability have been discussed. The excipients used in the formulation of pemetrexed powder for concentrate for solution for infusion are mannitol as tonicity agent; sodium hydroxide and hydrochloric acid, which are used in small amounts for pH adjustment, and water for injection which is used as a vehicle during formulation. Water for injection is removed during the lyophilization step and is not included in the finished product. The excipients are the same as those used in the reference product. No alternative formulations were investigated.

The manufacturing process development comprised evaluation and optimization of the different steps of the process.

The data presented confirm the robustness and reproducibility of the formulation and the chosen manufacturing process.

The choice of the sterilisation method was justified on the basis the reference product is known to be sensitive to terminal sterilisation and it is sterilized by filtration. This is considered acceptable.

The applicant performed a number of comparability studies to demonstrate that Pemetrexed Krka is equivalent to the reference product.

Adventitious agents

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

Manufacture of the product

The manufacturing process is a non-standard process which involves five steps:

1. solution preparation/compounding
2. pre-filtration
3. final sterile filtration
4. aseptic filling
5. lyophilisation.

Since the bulk solution is sensitive to oxygen, the whole manufacturing process is conducted in the presence of nitrogen. Terminal sterilisation was not appropriate for the formulation as it affected the quality of the product thus sterilisation by filtration (through bacterial retentive filter) followed by aseptic processing was developed.

Compatibility studies with process components and equipment were conducted and were satisfactory.

Before filtration samples are taken to test the bioburden (microbiological quality of prepared solution). Two sterile filtrations are conducted. The in-process controls have been described and are considered sufficient.

Holding time studies for bulk solution of Pemetrexed 100 mg and 500 mg powder for concentrate for solution for infusion were performed.Based on the results from these studies, a holding time for the non-filtered bulk-solution and a holding time for the filtered bulk-solution were defined and are considered acceptable.

In addition, in order to study the effect of temperature variation on the product, likely to be encountered by the drug product during distribution, a cyclization test was performed for both product strengths. All results were within the specification limits and practically no differences were observed when compared to initial values.

Major steps of the manufacturing process have been validated by a number of studies. Process validation data on three commercial scale batches of each strength have been presented. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), pH (Ph. Eur.), water content (Ph. Eur.), assay (HPLC), uniformity of dosage units (by mass variation) (Ph. Eur.), reconsititution time, clarity and degree ofopalescence of the solution (Ph.

Eur.), colour of the solution (Ph. Eur.), particulate matter (Ph. Eur), related substances (HPLC), bacterial endotoxins (Ph. Eur), sterility (Ph. Eur.) and head space oxygen content (GC).

As mentioned above, pemetrexed has one chiral center, therefore two enantiomers are possible. Pemetrexed active substance is L-enantiomer while D-enantiomer of pemetrexed is controlled.Analyses for elemental impurities were performed to evaluate all possible sources e.g. active substance, excipients, equipment, primary packaging material, process, purified water of inorganic impurities in the final product. Based on the results obtained there is no need to specify any elemental impurities in final active substance or finished product specification.

Overall, the proposed specification is acceptable. The methods in the specifications for Pemetrexed KrKa powder for concentrate for solution for infusion are all compliant with the Ph.Eur. and in-house methods have all been adequately described and validated.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from seven commercial scale batches of finished product (four batches of the 100 mg strength, and three batches of the 500 mg strength) manufactured at the proposed manufacturing site were included in the stability study. The batches stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Pemetrexed Krka are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Vials were stored in upright position under long-term conditions and, to mimic worst case scenario, vials were also stored in inverted position under accelerated condition.

Samples were tested for appearance, assay, clarity and degree of opalescence of the solution, colour of the solution, pH, reconstitution time, related substances (impurities and degradation products), water, LAL test (tested at the beginning and at the end of stability testing), sterility (tested at the beginning and at the end of stability testing. The analytical procedures used are stability indicating.

All results of the samples stored at long term and accelerated storage conditions were well within the specifications and no general trends or signs of degradation were observed.

A photostability test was performed on one batch of each strength, according to the ICH Guideline Q1B. The product did not show signs of degradation after exposure to light without the protection of the primary and secondary packaging materials. Therefore it was concluded that the finished product is not photo-sensitive.

In addition, a stability study on the reconstituted solution in the inverted original vial at concentration 25mg/ml of pemetrexed and diluted solution at concentration 0.25mg/ml of pemetrexed was performed on one batch of Pemetrexed powder for concentrate for solution for infusion 100mg, 500mg.

Samples were stored for 24 hours at 2-8°C and 25°C.

For the reconstituted and diluted solution appearance, assay, clarity and degree of opalescence of the solution, colour of the solution, pH, related substances (impurities and degradation products), LAL test

(tested at the beginning and at the end of stability testing), sterility (tested at the beginning and at the end of stability testing) were monitored.

The compatibility of the diluted solution of Pemetrexed powder for concentrate for solution for infusion 100 mg, 500 mg was demonstrated with polyolefin-lined infusion bags. . Based on these results and additional justification provided it was concluded that polyvinyl chloride infusion bags can be used for Krka's Pemetrexed powder for concentrate for solution for infusion 100 mg, 500 mg.

No significant changes of the stability indicating parameters were observed in these studies.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions, as stated in the SmPC (section 6.3), is acceptable. Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at 2-8°C (and 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 not be longer than 24 hours at 2°C to 8°C.

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 results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pemetrexed Krka manufactured by KRKA, d.d. 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. Published literature has been reviewed and is considered of suitable quality.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for powder for concentrate for solution for infusion containing pemetrexed.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of pemetrexed based on published literature. The SmPC is in line with the SmPC of the reference product.

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

Relevant for the clinical assessment is the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98)

Exemption

The active substance contained in Alimta is pemetrexed disodium heptahydrate whereas the active substance contained in Pemetrexed Krka 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. Once dissolved in water and lyophilized, the final drug product is identical to the reference product Alimta.

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

Pemetrexed Krka 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

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

There are no concerns with Pemetrexed Krka 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 Krka and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and is deemed acceptable and sufficiently up-to-date. This is in accordance with the relevant guideline and additional clinical/bioequivalence studies were not considered necessary. The CHMP

considers that there are no objections to approval of Pemetrexed Krka 100 mg and 500 mg powder for concentrate for solution for infusion from a clinical point of view.

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 Bone marrow suppression Gastrointestinal disorders Renal disorders Sepsis Bullous skin reaction including SJS and TEN Interstitial pneumonitis Radiation pneumonitis Radiation recall
Important Potential Risks	None
Missing Information	None

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to identify and characterise the risks of the product.

Risk minimisation measures

The safety information in the product information is aligned to the reference medicinal product. Routine risk minimisation measures are considered sufficient to reduce the risks associated with the above safety concerns.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.2 is acceptable.

2.6. 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.

Periodic Safety Update Reports submission requirements

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. Product information

2.7.1. 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; 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 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 Krka is favourable in the following indication:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Krka 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 Krka 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 Krka 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 CHMP 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.

Other 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.