23 July 2015
EMA/CHMP/467935/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Sandoz

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/004011/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

API	Active pharmaceutical ingredient
ASMF	Active Substance Master File
BSA	Body Surface Area
CHMP	Committee for Human Medicinal Products
DMF	Drug master File
EC	European Commission
EMA	European Medicines Agency
EU	European Union
GC	Gas chromatography
GI	Gastrointestinal
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
LoD	Limit of Detection
LoQ	Limit of Quantification
MAA	Marketing authorisation application
NfG	Note for Guidance
NIR	Near infrared spectroscopy
Ph. Eur.	European pharmacopoeia
PRAC	Pharmacovigilance risk assessment committee
RH	Relative humidity
RMP	Risk Management Plan
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
TEN	Toxic epidermal necrolysis
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SANDOZ GmbH submitted on 23 September 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pemetrexed Sandoz, 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 April 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 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 Sandoz in combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer:

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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information and complete quality data. There is no requirement for bioequivalence testing according to (cf.CPMP/QWP/EWP/1401/98 Rev. 1).

Information on paediatric requirements

Not applicable

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Alimta 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, 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/1/04/290/001-002

Licensing status

Pemetrexed Sandoz was given a Marketing Authorisation in Chile on 10 June 2014 (100 mg) and on 11 June 2014 (500 mg).

An application was filed in the following countries: South Korea and USA.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP:

Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 23 September 2014.
- The procedure started on 29 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 January 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 February 2015.
- During the meeting on 26 February 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 February 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 April 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 June 2015.

- PRAC RMP Advice and assessment overview, adopted by PRAC on 11 June 2015.
- During the CHMP meeting on 25 June 2015, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 30 June 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 July 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 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 Sandoz.

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed powder for concentrate for solution for infusion. Pemetrexed Sandoz 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 in combination with cisplatin is indicated for the treatment of chemotherapy naive 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 Lilly 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.

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

About the product

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

Mode of action

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

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

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

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 100 mg/vial, 500 mg/vial and 1000 mg/vial of pemetrexed (as disodium salt hemipentahydrate) as active substance.

Other ingredients are mannitol, hydrochloric acid and sodium hydroxide.

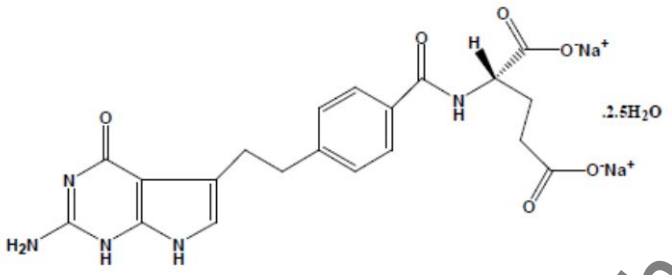
The product is available in clear, colourless, type I glass vials with chlorobutyl rubber stoppers and aluminium crimp caps with flip-off caps as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

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

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 salt hemipentahydrate and has the following structure and properties:



Molecular formula: $C_{19}H_{21}N_5Na_2O_6.[H_2O]_{2.5}$ - Relative molecular mass: 516.4 $gmol^{-1}$

The active substance is a white to off-white hygroscopic crystalline solid, freely soluble in water but practically insoluble in organic solvents. It has one chiral centre which originates in one of the starting materials and which is tested in the active substance by specific optical rotation and chiral HPLC.

Two polymorphs of pemetrexed disodium are known. The heptahydrate has a Ph. Eur. monograph whilst the hemipentahydrate used in this product is routinely produced by the given manufacturing processes.

Manufacture, characterisation and process controls

The synthesis of pemetrexed disodium hemipentahydrate is documented in two ASMFs supporting this procedure. Each uses a different manufacturing route. One employs one manufacturer to make an intermediate and another to convert this to the active substance. The second has two manufacturers employing different routes to make an intermediate and a third which converts it to the active substance. All manufacturing routes start from well-defined starting materials with acceptable specifications.

Starting materials in both ASMFs were re-defined during the procedure as a result of major objections, thus ensuring that steps critical to the quality of the active substance are described in the dossier. Active substance from both sources is released against the same set of specifications. Batch data indicates that active substance from both sources performs equivalently in secondary manufacture and produces finished product of equivalent quality.

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. 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 either double heat-sealed polyethylene bags sealed inside a heat-sealed aluminium bag or doubly heat-sealed LDPE bags with an intermediate silica gel pouch, packed inside a triple laminated sunlight barrier bag and stored inside an HDPE drum, depending on the source. 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 ASMF and it was considered satisfactory.

Specification

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

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

Stability

Stability data on three production scale batches of active substance from one ASMF holder stored in 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. The analytical methods used were the same as for release and are 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 active substance from this source has a re-test period of 36 months when stored at 5±3 ºC in the original packaging.

Stability data on three production scale batches of active substance from the other ASMF holder stored in packaging simulating the proposed commercial package for up to 24 months under long term conditions (5±3 ºC) and 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Samples were tested for appearance, identity, clarity and colour of solution, specific optical rotation and optical isomer, impurities, water content, bacterial endotoxins and microbial limits. In addition, supportive stability data was provided on an additional seven batches of active substance for up to 24 months under long term conditions and for four of these, for up to 36 months at -20 ºC (a further long term condition). An out of specification result was observed for one impurity at 5±3 ºC and for several impurities under accelerated conditions. Forced degradation studies show the active substance is sensitive to oxidation. Active substance from this source has a re-test period of 24 months when stored at -20 ºC and 12 months when stored at 5±3 ºC in the original packaging.

Although the amount of stability data generated is different for each supplier, the trends are aligned. Stability commitments have been provided by each ASMF holder in order to generate additional data from one batch per year according to GMP and to continue the on-going studies until their planned conclusion. The finished product manufacturer stores the active substance in the original packaging at 5±3 ºC for up to the prescribed time from each supplier.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest periods at 5±3 ºC in the proposed containers.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of development was to produce a finished product equivalent to Alimta which is a lyophilised powder containing only the active substance, mannitol, and the pH adjusting agents HCl or NaOH. Pemetrexed Sandoz uses a different hydrate form to the reference medicinal product, but since it is fully solubilised during formulation, this has no impact. It is however more unstable and thus needs to be stored under controlled conditions. The excipients used are the same as for the reference medicinal product and are well known pharmaceutical ingredients whose quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. An over-fill of vials is used in order to ensure the claimed amount can be withdrawn from vials following reconstitution. The reconstitution method is adequately described in section 6.6 of the SmPC.

Since the finished product is administered as an aqueous intravenous solution in the same concentration as Alimta, the excipients are qualitatively and quantitatively equivalent, and the active substance is freely soluble in aqueous media, no bioequivalence study was required.

The active substance is unstable to oxygen and heat once in solution. Thus, all manufacture is carried out under a nitrogen atmosphere and temperature is limited to 2-8 ºC for processing times beyond four hours at 25 ºC. Terminal sterilisation by heat or radiation was demonstrated to be unsuitable due to instability of the finished product. Thus, the finished product is manufactured sterile filtration followed by aseptic processing. The lyophilisation was optimised during development to afford a stable and elegant cake. This had to be re-optimised following scale-up in commercial equipment and the manufacturing process subsequently underwent further refinement to ensure proper control of headspace oxygen content.

The primary packaging is clear, colourless type I glass vials with chlorobutyl rubber stoppers. The vials are sealed with aluminium crimp caps with a flip-off caps. The materials comply 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 four main steps: compounding and pre-filtration; sterile filtration and filling; lyophilisation; stoppering and further packaging. The process is considered to be a non-standard manufacturing process. The in-process controls are adequate for this type of manufacturing process. Of note, the pH, clarity, bioburden and oxygen content of solutions are checked during compounding, filters are checked for integrity before and after use, and the headspace of the sealed vials is checked by NIR for oxygen content.

Process validation was carried out on four batches of the 100 mg/ml strength, seven batches of the 500 mg/ml strength, and three batches of the 1000 mg/ml strength. The process was subsequently re-validated on two batches of each strength due to changes implemented late in development. The combination of data provided demonstrates that the major steps of the manufacturing process have been validated. It has been

demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description of cake, reconstitution time, description of solution, clarity, colour and pH of solution (Ph. Eur.), visible and sub-visible particles (Ph. Eur.), identification (UV, HPLC), uniformity of dosage units (Ph. Eur.), water content (KF), optical isomer content (chiral HPLC), assay (HPLC), impurities (HPLC), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.) and headspace oxygen (NIR). Limits are set in line with the relevant ICH guidelines and batch data. Tests are designed to ensure the product is equivalent to the innovator product.

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

Batch analysis results are provided for four production scale batches of 100 mg/vial presentation, seven production scale batches of the 500 mg/vial strength, and three production scale batches of the 1000 mg/vial presentation confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. These batches were manufactured before the introduction of the revised vial closure process. Batch analysis data on an additional two production scale batches of each strength were provided, meeting all specifications including the newly added test for headspace oxygen.

Stability of the product

Stability data on four production scale batches of the 100 mg/vial strength, seven batches of the 500 mg/vial strength and three batches of the 1000 mg/vial strength, all manufactured at production scale stored for up to 36 months under refrigerated conditions (5±3 ºC), for up to 36 months under long term conditions (25 ºC / 60% RH), for up to 36 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Other than the subsequent change in vial stoppering process, the batches of Pemetrexed Sandoz were identical and were packed in the primary packaging proposed for marketing. Vials were stored in both upright and inverted positions. Batches of each strength were manufactured using active substance from both suppliers. Samples were tested according to the release specifications with the omission of the test for headspace oxygen. No significant changes were observed to any of the measured parameters other than an increase in impurities under intermediate and accelerated conditions in some samples. These studies were instigated before the revision of the vial stoppering process and a correlation between oxygen ingress and an increase in impurities has been demonstrated. New stability studies on two batches of each strength manufactured using the new process are underway under all conditions. After six months, all measured parameters remained well within their specifications and no trends were observed.

In addition, the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed to appearance of the solid or solutions thereof, nor to assay and impurity levels. It can be concluded that the finished product is not photosensitive.

Forced degradation studies were carried out with reconstituted samples treated with heat, acid, base, light and or an oxidant. The product is unstable under each condition. The analytical procedures used are stability indicating.

Thermal cycling studies were also carried out in order to assess the impact of brief temperature excursions. Samples were stored at -20 ºC and 40 ºC for 3 x 48 hours at each extreme, then stored under long term conditions for up to 6 months. No significant changes to any of the measured parameters were observed, indicating the low impact of brief temperature excursions.

Finally, in use stability studies were carried out as reconstituted and in infusion solutions in either 5% glucose or 0.9% sodium chloride at concentrations of 4 and 10 mg/ml. Samples were stable for up to 4 days at 5±3 ºC without light protection.

Based on available stability data, the shelf-life of 24 months with no special storage conditions and as stated in the SmPC is acceptable.

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. 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 Sandoz manufactured by Sandoz is considered unlikely to result in any significant increase in the combined sales volumes for all pemetrexed containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion and conclusion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of pemetrexed are well known. No non-clinical data are submitted with this application. Published literature has been reviewed and is considered of suitable quality.

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

2.4. Clinical aspects

2.4.1. Introduction

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

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

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

Exemption

Pemetrexed Sandoz has the same active substance,excipients, indications, route of administration, 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 Sandoz are: 100 mg/vial, 500 mg/vial and 1000 mg/vial.

The composition of Pemetrexed Sandoz 100 mg and 500 mg vial and Alimta 100 mg and 500 mg vial is qualitatively identical, with small quantitative differences only. A quantitative composition comparison of the applied and the reference product is provided below.

Component	Function	Sandoz Proposed Formulation		Alimta ® Formulation (as per Package Insert)	
		100 mg/vial	500 mg/vial	100 mg/vial	500 mg/vial
Pemetrexed	Active	107.5 mg	515.0 mg	100 mg	500 mg
Mannitol	Bulking agent	107.5 mg	515.0 mg	106 mg	500 mg
Hydrochloric Acid [1]	pH adjustment	q.s.	q.s.	As needed	As needed
Sodium Hydroxide	pH adjustment	q.s.	q.s.	As needed	As needed
---	pH	7.2		6.6 – 7.8	

The qualitative composition of the new presentation, 1000 mg/vial, is comparable to the composition of the 100 mg and 500 mg vials.

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 intravenous solution containing the same active drug substance in the same concentration as the currently authorised product. Pemetrexed Sandoz is to be administered as an intravenous aqueous solution and contains the same active drug substance at the same concentration as the reference product (25 mg/mL) 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

The two lowest strengths (100 mg and 500 mg) of the medicinal product have been authorised in Chile since June 2014. No post-marketing data were submitted for this application, and the applicant has confirmed that no such data are available.

2.4.5. Discussion on clinical aspects

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

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

There are no concerns with Pemetrexed Sandoz 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

The CHMP considers that there are no objections to approval of Pemetrexed Sandoz 100 mg, 500 mg and 1000 mg powder for concentrate for solution for infusion from a clinical point of view.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The CHMP endorsed this advice without changes.

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

The CHMP endorsed the Risk Management Plan version 1.4 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Non-compliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities Serious renal events

Summary of safety concerns	
	Gastrointestinal disorders Interstitial pneumonitis Radiation pneumonitis Radiation recall Sepsis Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
Important potential risks	Cardiovascular events Peripheral vascular disorders Hearing loss/hypoacusis
Missing information	None

Pharmacovigilance plan

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

The 1000 mg strength does not exist for the reference originator Alimta. Therefore, PRAC and CHMP estimate that, even if not listed as a specific risk in the RMP of Pemetrexed Sandoz, the risk of medication error should be under specific surveillance by the MAH. Should a significant increase in the frequency of reported medication errors be detected, the MAH should report this as a signal.

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

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Noncompliance with folic acid and vitamin B12 regimens manifested mainly as haematological and gastrointestinal (GI) toxicities	Guidance is given in sections 4.2 “Posology and method of administration”, and 4.4 “Special warnings and precautions for use” of the SmPC.	N/A
Gastrointestinal disorders	Guidance is given in sections 4.2 “Posology and method of administration”, 4.4 “Special warnings and precautions for use”, 4.5 “Interaction with other medicinal products and other forms of interaction” and 4.8 “Undesirable effects” of the SmPC.	N/A
Serious renal events	Guidance is given in sections 4.2 “Posology and method of	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	administration", 4.4 "Special warnings and precautions for use", 4.5 "Interaction with other medicinal products and other forms of interaction" and 4.8 "Undesirable effects" of the SmPC.	
Interstitial pneumonitis	Guidance is given in sections 4.4 "Special warnings and precautions for use", and 4.8 "Undesirable effects" of the SmPC.	N/A
Radiation pneumonitis	Guidance is given in sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use", and 4.8 "Undesirable effects" of the SmPC.	N/A
Radiation recall	Guidance is given in sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use", and 4.8 "Undesirable effects" of the SmPC.	N/A
Sepsis	Guidance is given in section 4.8 "Undesirable effects" of the SmPC.	N/A
Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Guidance is given in sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use", and 4.8 "Undesirable effects" of the SmPC.	N/A
Cardiovascular events	Guidance is given in sections 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use", and 4.8 "Undesirable effects" of the SmPC.	N/A
Peripheral vascular disease	Guidance is given in section 4.8 "Undesirable effects" of the SmPC.	N/A
Hearing loss/hypoacusis	Currently available data do not support the need for risk minimization measures.	N/A

2.7. 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.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

Pemetrexed Sandoz is a generic product of the centrally approved medicinal product Alimta (EU/1/04/290/001-002).

The proposed product information (PI) for Pemetrexed Sandoz is almost identical to the PI of the reference product. There are minor differences due to the adaptation of the PL to the last version of the QRD template. However, these changes do not affect the results of the previous readability test, therefore the bridging statement to the Alimta PI is considered acceptable

3. Benefit-risk balance

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

Malignant pleural mesothelioma

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

Non-small cell lung cancer

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

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

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

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

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

A benefit/risk ratio comparable to the reference product Alimta can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference

medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pemetrexed Sandoz in the following indications:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Sandoz 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 Sandoz 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 Sandoz 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.