13 October 2022
EMA/CHMP/251833/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Baxter

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/005848/0000

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List of abbreviations

BHT - Butylated Hydroxytoluene
BSA - body surface area
CEP - Certificate of Suitability of the EP
CQAs - Critical Quality Attributes
DHFR - dihydrofolate reductase
DNA - deoxyribonucleic acid
EDQM - European Directorate for the Quality of Medicines
ERA - Environmental Risk Assessment
EU - European Union
GARFT - glycinamide ribonucleotide formyltransferase
GC - Gas Chromatography
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
ICP-OES - Inductively coupled plasma - optical emission spectrometry
IR - Infrared
KF - Karl Fischer titration
LDPE - Low density polyethylene
MO - Major Objection
MPM - Malignant pleural mesothelioma
NSCLC - Non-small cell lung cancer
PDE - Permitted Daily Exposure
Ph. Eur. - European Pharmacopoeia
QbD - Quality by design
QTPP - quality target product profile
RNA - ribonucleic acid
SIM - Stability indicating method
SmPC - Summary of Product Characteristics
TAMC - Total Aerobic Microbial Count
TYMC - Total Combined Yeasts/Moulds Count
UV - Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Baxter Holding B.V. submitted on 29 July 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Pemetrexed Baxter, 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 29 January 2021.

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 indications:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Baxter 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 Baxter 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 Baxter 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).

1.2. Legal basis, dossier content

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, non-clinical and clinical data based on bibliographic literature substituting all non-clinical tests and clinical studies.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Alimta, 100 mg and 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: Union
- Union Marketing authorisation number: EU/1/04/290/001-002

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

- Product name, strength, pharmaceutical form: Alimta, 100 mg and 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: Union
- Union Marketing authorisation number: EU/1/04/290/001-002

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Elita Poplavska

The application was received by the EMA on	29 July 2021
The procedure started on	19 August 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 November 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 December 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 March 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	25 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	05 May 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	12 August 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	31 August 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	20 September 2022
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 Baxter on	13 October 2022

2. Scientific discussion

2.1. Introduction

This application concerns a generic version of pemetrexed 100 mg or 500 mg powder for concentrate for solution for infusion, Pemetrexed Baxter, which has the same active substance in comparable amounts to the centrally approved reference medicinal product Alimta (EU/1/04/290/001-002).

Pemetrexed is an antifolate antineoplastic agent that works by inhibiting multiple enzymes involved in folate metabolism, and pyrimidine and purine synthesis. Pemetrexed works primarily by inhibiting thymidylate synthase, but it also inhibits other folate-dependent enzymes: dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT). By inhibiting the biosynthesis of precursor purine and pyrimidine nucleotides, pemetrexed prevents the formation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which is required for the growth and survival of cancer cells.

Pemetrexed Baxter has applied for all indications of the reference product Alimta (EU/1/04/290/001-002):

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Baxter 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 Baxter 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 Baxter 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.

Posology

Pemetrexed Baxter must only be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

Pemetrexed Baxter in combination with cisplatin

The recommended dose of Pemetrexed Baxter 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. The recommended dose of cisplatin is 75 mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each 21-day cycle. Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin (see also cisplatin Summary of Product Characteristics for specific dosing advice).

Pemetrexed Baxter as single agent

In patients treated for non-small cell lung cancer after prior chemotherapy, the recommended dose of Pemetrexed Baxter is 500 mg/m^2 BSA administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are: mannitol, hydrochloric acid (pH adjustment), and sodium hydroxide (pH adjustment).

The product is available in type I glass vial with chlorobutyl rubber stopper as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of active substance is disodium N-{p-[2-(2-amino-4,7-dihydro-4-oxo-1H- pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamate heptahydrate corresponding to the molecular formula $C_{20}H_{19}N_5Na_2O_6 \cdot 7H_2O$. It has a relative molecular mass of 597.49 and the following structure:

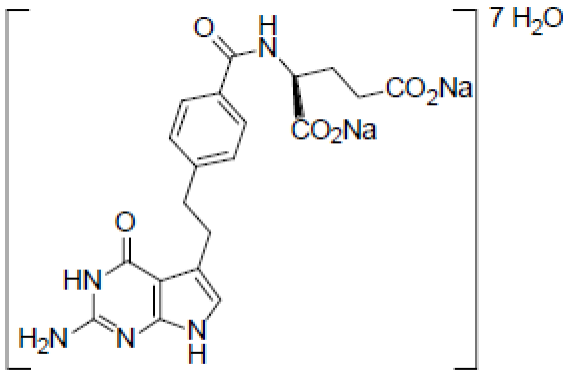

Figure 1: Active substance structure

As there is a monograph of pemetrexed disodium in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

Information on the elucidation of structure and other characteristics of the active substance provided by the CEP holder in the certification dossier has already been approved by the EDQM.

The active substance is a slightly hygroscopic white or almost white powder very slightly soluble in water at pH

1.2 at 37°C; freely soluble in water at pH 4.5-8.0 at 37°C; freely soluble in water at 25°C and 37°C.

The active substance exhibits stereoisomerism due to the presence of one chiral centre. The final obtained active substance corresponds to (L)-pemetrexed disodium. The chiral impurity (D)-pemetrexed disodium is controlled routinely in the active substance specification.

Polymorphism has been observed for the active substance. The crystal form (heptahydrate form) is consistently produced by the manufacturing process.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification from the finished product manufacturer includes tests for appearance (visual), identification (IR, sodium, HPLC), colour of solution after reconstitution (Ph. Eur.), clarity of solution after reconstitution (Ph. Eur.), pH (Ph. Eur.), assay (HPLC), impurities (HPLC), enantiomeric purity (HPLC), water content (KF), residual solvents (GC), elemental impurities (ICP-OES), microbial enumeration (TAMC, TCYMC) (Ph. Eur.), and bacterial endotoxins (Ph. Eur).

The acceptance criteria for impurities are based on Ph. Eur. Monograph. The acceptance criteria of specified impurities, any individual unspecified impurity and total impurities conform to ICH Q3A(R2), *Impurities in New Drug Substances*, and are based on data generated on batches of the pemetrexed active substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variability and the stability characteristics of the active substance.

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

Batch analysis data (n=9) commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph.

Stability

Pemetrexed stability is not covered by a CEP issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM).

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (30 ± 2°C/ 75 ± 5% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided.

The following parameters are tested*:* appearance, assay, impurities, water content, colour of solution, clarity of solution, bacterial endotoxins, TAMC and TCYMC.

All the results remained within specification for both long-term and accelerated conditions.

A forced degradation study was performed to investigate the stability under stress conditions and to evaluate the suitability of the analytical testing methods of HPLC for assay and impurity as stability indicating methods (SIM). The stress conditions for solution stability include hydrolysis, oxidation under acidic and alkalic , and photostability. Results showed that the active substance is labile in hydrolytic and oxidative conditions, and

sensitive to photolytic condition. The results also indicated the HPLC methods for assay and impurity are capable of using as SIMs.

A solid state stability study was also performed. The objective of the stress study was to investigate the photolytic and thermal stability on the solid-state in order to establish a preliminary storage condition. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

Description of the product and Pharmaceutical development

The finished product is presented as white to either light yellow or green-yellow lyophilized powder.

The goal of the development studies was to develop a generic version of ALIMTA, the reference medicinal product.

The finished product was developed using the QbD approach. A quality target product profile (QTPP) was established by reviewing compendial requirements, the properties of the active substance, and characterisation of the EU reference product. From the established QTPP the Critical Quality Attributes (CQAs) of the finished product were identified.

All excipients are well known pharmaceutical ingredients and their 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 of this report.

Stability data demonstrate that the proposed finished product is chemically and physically stable under long-term, intermediate, and accelerated storage; therefore, the stability data supports the compatibility of the active substance with the excipients.

The finished product is a single-use, sterile, lyophilised form. Formulation development is sufficiently described. The finished product is formulated to a target potency of 100% of label claim. The pemetrexed filling overage included to compensate vial and syringe retentions is suitable to allow withdrawal and delivery of the labeled dose.

As the generic product contains the same amount and concentration of the same active substance, and concerns the same pharmaceutical form as the reference medicinal product and is proposed for parenteral use, a bioequivalence study is not required.

The applicant stated that the presented formulation studies support the pharmaceutical equivalence of the generic product to the reference medicinal product. Comparability of test product with EU reference product was based on insufficient analytical data for quality critical attributes that did not allow for a definitive conclusion on the pharmaceutical equivalence of the proposed medicinal product to the reference medicinal product. Therefore, the CHMP requested as Major Objection (MO) that additional data demonstrating pharmaceutical equivalence of the generic to the EU reference product should be provided. As a response, the applicant provided three new batches for each finished product strength to examine the pharmaceutical equivalence with the EU reference product. Results demonstrated physico-chemical similarity of both products for those tested parameters. The response was considered satisfactory.

The development of the manufacturing process was described. The rationale for a sterile filtration followed by an aseptic process has been satisfactorily discussed; the product is sensitive to terminal sterilisation methods.

The manufacturing process was developed to minimise oxidative degradation by reducing exposure of pemetrexed solution to oxygen.. The lyophilisation cycle development experiments were described, and finalised results were provided. The scale up to validation batches was also described and considered satisfactory.

According to the product information of the reference medicinal product, each 100 mg vial is reconstituted with 4.2 mL of 0.9% sodium chloride, and each 500 mg vial is reconstituted with 20 mL of 0.9% sodium chloride. An appropriate quantity of the reconstituted solution must be further diluted into a solution of 0.9% sodium chloride (preservative free), so that the total volume of solution is 100 mL. The reconstituted and further diluted finished product is stable for 24 hours from the time of reconstitution under refrigerated conditions (2-8 °C). A stability study of the generic medicinal product reconstituted solution was performed. The results showed that the impurity levels are comparable between reference medicinal product and the generic medicinal product when the vials are reconstituted with 0.9% sodium chloride and stored for 24 hours as recommended by the product information.

The primary packaging is 10 mL or 50 mL colourless borosilicate type I glass vial with grey chlorobutyl rubber stopper . 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. Container leachables were evaluated and discussed indicating that there is no appreciable risk in reconstituted finished product solution. The evaluation supports the use of the container closure system for the finished product.

Manufacture of the product and process controls

The manufacturing process consists of 7 main steps: weighing and compounding, bioburden reducing filtration and sterile filtration, aseptic filling and semi-stoppering, lyophilization and capping, and packing. The process is considered to be a non-standard manufacturing process as it is an aseptic process by sterile filtration in combination with a lyophilisation process.

The critical process parameters (CPP), process parameters (PP), and in-process parameters (IPC) and their control criteria have been specified and indicated according to each stage of production.

Major steps of the manufacturing process have been validated by a number of studies on 4 production scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UV, HPLC), reconstitution testing (Ph. Eur.), impurities (HPLC), water content (KF), assay (HPLC), uniformity of dosage units (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), container closure sterility test (Ph. Eur.), injections and implanted finished products (Parenterals)-Product Quality Tests (Ph. Eur.)

The finished product specifications cover appropriate parameters for this dosage form and follows general recommendations provided in the *Note for Guidance and Specifications: Test Procedures and Acceptance Criteria for New Drug Substances* and *New Drug Products: Chemical Substances (CPMP/ICH/367/96); Note for Guidance on manufacture of the finished dosage form (CPMP/QWP/486/95); Impurities in new drug products (CPMP/ICH/2738/99)* and the European Pharmacopoeia. Acceptance criteria are justified based on ICH guidelines, requirements of pharmacopoeia, testing results of reference product and on batch analysis data of test product.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results are provided for 7 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 4 commercial scale batches per strength of the finished product stored for up to 18 months for the 100 mg strength and 24 months for the 500 mg strength under long term conditions (30°C ± 2°C / 65% ± 5% RH) and for up to 6 months under accelerated conditions (40°C ± 2°C / 75% RH ± 5% RH) according to the ICH guidelines were provided. Vials were stored in upright and inverted orientations. The stability batches are identical to those proposed for marketing and were packaged in the primary packaging proposed for marketing.

Samples were tested for appearance, reconstitution time, pH after reconstitution, appearance after reconstitution, visible particles after reconstitution, sub-visible particles (particulate matter) after reconstitution, assay, impurities, water content, bacterial endotoxins, sterility, and container closure integrity. No significant changes have been observed under long term and accelerated stability conditions. During the

evaluation, the CHMP considered that oxygen content is a critical finished product quality attribute as test for oxygen is considered early indicative test with subsequent increase of impurities during storage, therefore, the CHMP recommended to incorporate a new specification parameter with an appropriate test method for oxygen content into the post-approval stability program [REC 001].

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. All results met the acceptance criteria with minimal change observed for the light exposed vials, indicating the proposed drug product does not require protection from light.

A thermal cycle study was conducted on one batch per strength of the finished product. All test results met the study's acceptance criteria indicating the finished product can tolerate short-term exposures to temperatures ranging from -20°C to 60°C.

The stability of the product after reconstitution with 0.9% sodium chloride to a concentration of 25 mg/ml, as described in the SmPC has been tested for 3 batches of each presentation. The reconstituted solution was found to be stable up to 24 hours when stored at 2 – 8°C.

The stability/compatibility of the diluted product (ready for use) for concentration of 9 mg/ml and 1 mg/ml n polyolefin bags has been tested. The diluted solution was found to be stable and compatible with polyolefin bags up to 24 hours when stored at 2 – 8°C for concentration of 9 mg/ml.

The CHMP recommended to perform in-use stability testing for diluted product at a concentration of 1 mg/mL for all essential quality parameters including appearance, visible and sub-visible particles for 100 mg batch and to repeat in-use stability study for diluted product at the end of shelf-life for both strengths and proposed concentrations (9 mg/ml and 1 mg/ml) in accordance with specifications [REC 003].

A microbial challenge study was conducted on one batch of each strength. The results confirm the microbiological acceptability of the reconstituted product after 48 hours of refrigerated temperature storage. This study supports the label recommendation that reconstituted, preservative-free product should be stored under refrigerated conditions (2-8 °C) for no longer than 24 hours from the time of reconstitution.

Based on available stability data, the proposed shelf-life of 18 months for the 100 mg unopen vials and 2 years for the 500 mg unopen vials without storage conditions as stated in the SmPC (section 6.3 and 6.4) are acceptable.

For the reconstituted and infusion solutions, chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated (2 °C to 8 °C) temperature. 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.

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.

One MO had been raised about demonstrating pharmaceutical equivalence of the generic to the EU reference product, which was resolved by provision of sufficient additional data. Overall, during the procedure, the information of the dossier has been updated and improved as requested.

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.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product which pertain to include oxygen testing with appropriate analytical method in the shelf-life specification of the finished product and stability protocol, to perform in-use stability testing for diluted product at a concentration of 1mg/mL essential quality parameters including appearance, visible and sub-visible particles for 100 mg batch and to repeat in-use stability study for diluted product at the end of shelf-life for both strengths and proposed concentrations (9 mg/ml and 1 mg/ml) in accordance with specifications. These points are put forward and agreed as recommendations for future quality development.

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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- [REC 001] To include oxygen testing with appropriate analytical method in the shelf-life specification of the finished product and stability protocol.
- [REC 002] To perform in-use stability testing for diluted product at a concentration of 1 mg/mL for all essential quality parameters including appearance, visible and sub-visible particles for 100 mg batch.
- [REC 003] To repeat in-use stability study for diluted product at the end of shelf-life for both strengths and proposed concentrations (9 mg/ml and 1 mg/ml) in accordance with specifications.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Pemetrexed Baxter manufactured by Baxter Holding B.V. 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.

2.3.3. Discussion and conclusion on non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of pemetrexed are well known. The non-clinical overview is based on an up-to-date and adequate review of the relevant literature available in the public domain. 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.

Based on the toxicological assessment of impurities, it can be concluded that related substances are not relevant.

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

As per Environmental Risk Assessment Phase I (Pre-screening), PEC (Predicted Environmental Concentration) and logKow (octanol-water partition coefficient) values are below action limits, and further assessment is not deemed necessary. Pemetrexed Baxter is not predicted to increase the environmental risk.

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.

For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 in its current version is of particular relevance.

Exemption

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 Corr **) for parenteral solutions, "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. However, if any excipients interact with the drug substance (e.g. complex formation), or otherwise affect the disposition of the drug substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance".

The active substance contained in Alimta is pemetrexed disodium heptahydrate, and the active substance contained in Pemetrexed Baxter is also pemetrexed disodium heptahydrate, i.e., the composition is qualitatively and quantitatively the same.

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.

Alimta and Pemetrexed Baxter are medicinal products for parenteral administration as an aqueous intravenous solution and as such are anticipated to be immediately bioavailable.

Furthermore, none of the excipients interact with the drug substance (e.g., complex formation); none of the excipients affect the disposition of the drug substance.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

No new pharmacokinetic studies were conducted however pharmacokinetic data from scientific publications were presented.

In a population pharmacokinetic analysis by Latz et al. (2006), presented by the applicant, data on 287 patients (441 cycles collectively) from 10 phase II clinical trials of pemetrexed in cancer patients was evaluated using NONMEM. The patients were dosed based on BSA and were initially assigned to receive a 10-minute IV infusion of 500 or 600 mg/m2 of pemetrexed every 21 days (without folic acid or vitamin B12 supplementation). A population pharmacokinetic model was developed using an index dataset from 8 of the 10 studies and predictive performance was evaluated using data from the other 2 studies. This analysis showed that pemetrexed demonstrated a relatively small volume of distribution (Vss=16.3), suggesting that the compound has limited tissue distribution.

Ouellet et al. (2000) found that the typical value for clearance is dependent on the body weight, alanine transferase, clearance of creatinine and folate deficiency.

A phase I study by Mita et al., (2006) was conducted to assess the impact of renal dysfunction in 47 patients with solid tumours. The patients received a 10-minute infusion of 150 to 600 mg/m2 of pemetrexed every 21 days and during the first cycle, plasma and urine pharmacokinetics were evaluated. Pemetrexed plasma clearance positively correlated with glomerular filtration rate, resulting in increased drug exposure in patients with impaired renal function. This was also evident in the population pharmacokinetic analysis by Latz et al. (2006) where by the range of systemic clearance estimates that represents approximately 95% of all patients in the study population (i.e., population pharmacokinetic evaluations on 287 patients) was 53.2 to 146 mL/min. These results suggest, according to the authors, that dose adjustments based on renal function, rather than BSA, might be considered for pemetrexed.

A later pharmacokinetic analysis by de Rouw et al. (2021) on pemetrexed in a population that included patients with impaired renal function on (i.e., 47 patients, with a total of 548 paired observations of time and plasma concentrations after pemetrexed administration) found that renal clearance accounts for up to 84% of total pemetrexed clearance.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.3. Post marketing experience

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

2.4.3. Discussion on clinical aspects

No studies have been conducted and presented by the applicant. The justification for waiving bioequivalence studies is acceptable from the clinical point of view.

The application contains an adequate review of published clinical data concerning the clinical use of pemetrexed for the proposed indications.

Pemetrexed has been in use as an anticancer medication for more than 10 years and the safety profile and tolerability of the medicinal product have become well established.

All data regarding safety and efficacy available for the reference medicinal product also apply for this application.

Clinical parts of the proposed Summary of Product Characteristics are in line with those of reference product Alimta.

The Clinical overview on the efficacy and safety is considered adequate. The Applicant has complemented the clinical pharmacology section of the Clinical Overview with new pharmacokinetic data from the scientific publications.

2.4.4. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Pemetrexed Baxter and justifications that the active substance does not differ significantly, in properties with regard 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

2.5.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

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

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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

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.

2.7.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The request was accepted by the QRD Group based on the space constraints argued by the applicant, and also because the same request has been previously agreed for the originator product and other generics (same presentations/size vials).

3. Benefit-risk balance

This application concerns a generic version of pemetrexed 100 and 500 mg 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.

The pharmaceutical equivalence has been demonstrated and the justification for waiving bioequivalence studies is acceptable.

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.

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

4. Recommendations

Outcome

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

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Baxter 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 Baxter 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 Baxter 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 marketing authorisation holder (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.