

Specification

The active substance specification includes tests for: appearance (visual), pH (Ph. Eur.), water (Ph. Eur.), colour and clarity of solution (Ph. Eur.), identity (Ph. Eur.), sodium (Ph. Eur.), assay (Ph. Eur.), impurities (Ph. Eur.), D-isomer (Ph. Eur.), residual solvents (GC), water content (titration), heavy metals (Ph. Eur.), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). The active substance meets the requirements of the current edition of the Ph. Eur. monograph for pemetrexed disodium heptahydrate. Stricter acceptance criteria for microbiological quality than those requested in Ph. Eur. for non-sterile substances for pharmaceutical use are applied. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

Batch analysis results for five pemetrexed disodium heptahydrate batches manufactured at the proposed site at full-scale using the commercial process were presented. The results indicate compliance with Ph. Eur. monograph.

Stability

Stability data on five production scale batches of active substance manufactured at the commercial sites and stored in packaging intended for marketing for up to 36 months at 25 °C / 60% RH (long-term condition), for up to six months at 40 °C / 75% RH (accelerated condition), and for up to 36 months at 5°C (backup condition for long-term storage) were provided. Stability studies were conducted according to the ICH guidelines. The following parameters were tested: package characteristics, description, assay, related substances (total and individuals), water, colour and clarity. The analytical methods used were the same as for release and were stability indicating. No significant change in any of the tested parameters was observed over the time-points evaluated at long-term or accelerated conditions.

Supporting stability data on three production scale batches of active substance manufactured during development at a different site and stored in packaging intended for marketing for up to 36 months at 25 °C / 60% RH (long-term condition), for up to six months at 40 °C / 75% RH (accelerated condition), and for up to 36 months at 5°C were also provided. Stability studies were conducted according to the ICH guidelines. Samples were tested: package characteristics, description, assay, related substances (total and largest individual), D-isomer and water. The analytical methods used were the same as for release and were stability indicating. No significant change in any of the tested parameters was observed over the time-points evaluated at long-term or accelerated conditions.

The first three production batches manufactured at the proposed manufacturing site, at the commercial scale have been placed on stability studies.

Stress studies were performed on one commercial scale batch in solid state and unprotected (open-dish), exposed to heat (60 °C at uncontrolled humidity, 6 months), humidity (25 °C /90% RH, 6 months), and heat and humidity (40 °C / 75% RH, 6 months). Pemetrexed disodium showed no significant change in assay, related substances, D-isomer, or water content over 6 months for the 25 °C / 90% RH and 40 °C / 75% RH conditions. As anticipated, increased impurity levels were observed at the 60°C condition over 6 months.

A photostability study was conducted as per ICH Q1B requirements on one commercial scale batch. The photostability study did not show a significant change in assay, D-isomer, or related substances, or any other unexpected change.

In conclusion, the proposed re-test period of 3 years with no specific storage restrictions when the active substance is stored in the proposed packaging is adequately supported by the stability data provided and is acceptable.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The proposed generic medicinal product Pemetrexed Lilly and the centrally approved reference medicinal Alimta (EU/1/04/290/001-002) share the same qualitative and quantitative composition, same pharmaceutical form, same Marketing Authorisation Holder, Eli Lilly Nederland B.V. (The Netherlands). The quality documentation submitted for the current application is identical with the authorised dossier for Alimta. Since the generic and reference product are the same, there are no differences with regards to quality.

Pemetrexed Lilly powder for concentrate for solution for infusion is presented in two strengths: 100 mg/vial and 500 mg/vial. The product is a sterile lyophilised powder that must be reconstituted and then diluted with a suitable intravenous solution prior to administration. Each 100 mg vial and 500 mg vial are reconstituted respectively with 4.2 ml or 20 ml of commercially available 0.9% Sodium Chloride Injection, without preservatives. The reconstituted solution contains 25 mg/ml of pemetrexed. The required amount of the reconstituted pemetrexed solution is further diluted to 100 ml in 0.9% Sodium Chloride Injection prior to intravenous infusion.

The hemipentahydrate form was used in early development formulations but there were handling issues observed because it is hygroscopic. The heptahydrate form was determined to be more stable with respect to relative humidity and was therefore selected. Since the manufacture of pemetrexed powder for concentrate for solution for infusion involves dissolution of the active substance, the solubility of the drug substance is an important physicochemical property. Considering that the active substance is sensitive to degradation by hydrolysis and oxidation (presence of oxygen) pH range was selected to minimise hydrolysis. Oxidation is controlled in the commercial formulation by minimising exposure to oxygen using a nitrogen overlay.

In addition the effect of headspace oxygen was evaluated; it was demonstrated that the product stability is acceptable when the headspace oxygen is controlled within specific limits. The impact of light on the stability of the drug product solution during manufacturing was studied and it was concluded that no additional protection from light is required during manufacturing.

The excipients used in the formulation of the product are the same as those used in the reference product Alimta. Both the 100 mg/vial and the 500 mg/vial are filled from a common 25 mg/ml bulk solution.

Formulation development efforts were initially directed toward developing a terminally sterilised solution formulation. This was changed to a lyophilised terminally sterilised formulation because of stability issues with the solution formulation. Potential terminal sterilisation was evaluated using the "Decision Tree for Sterilisation Choices for non-Aqueous Liquid, Semi-Solid or Dry Powder Products" in regulatory guidance CPMP/QWP/054/98. Sterilisation by dry heat or by ionizing radiation (e-beam) was shown to be not acceptable for this lyophilised product. Therefore, the product is sterilised by filtration of the manufactured solution using a validated process followed by aseptic processing. Bioburden levels in the active substance are controlled and monitored. The lyophilisation cycle of has been optimised during development. The XRPD data of the commercial cycle and development cycle show that solid-state characteristics are similar, with amorphous pemetrexed and crystalline mannitol.

A microbial challenge study was performed on pemetrexed manufactured solution and demonstrated that the solution is neither growth promoting or inhibiting up to 96 hours. Based on the results a processing time limit has been established from the start of solution manufacture until the end of pre-filtration.

The compatibility studies were designed to assure that the drug product is compatible with the diluent and the container closure system. Based on these studies, compatibility has been demonstrated when the product is reconstituted and diluted with the media and administered with the materials as described in the SmPC (section 6.6). However Pemetrexed Lilly powder for concentrate for solution for infusion is not compatible with Ringer's Injection or Lactated Ringer's Injection due to the calcium chloride component of the Ringer's solutions.

The product packaging components for the 100 mg/vial and 500 mg/vial configurations are 10ml and 50 ml type I clear glass vial with bromobutyl rubber stopper and an aluminium seal with a polypropylene flip top.

The glass containers as well as rubber stoppers comply with the requirements of the relevant monographs of Ph. Eur. Compatibility of the stopper to the reconstituted solution has been tested. The results for the inverted vials indicate the stopper has no impact on the reconstituted product stability. The container closure system has been demonstrated to maintain integrity using a microbial ingress method.

Manufacture of the product and process controls

The product is manufactured in six main steps: preparation of solution, pre-filtration, sterile filtration-filling-stoppering, lyophilisation, sealing, and secondary packaging-labelling. The critical steps have been identified and adequate in-process controls, including solution pH and bioburden, tank purging with nitrogen, temperature of solution, filter integrity and processing times, are in place for this type of manufacturing process.

In accordance with Annex II to the guideline on process validation the aseptic manufacturing process by sterile filtration in combination with a lyophilisation process is considered a non-standard manufacturing process. Process validation has been performed on three consecutive production scale batches for both 100 ml and 500 ml vial. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this kind of dosage form including description (visual), reconstitution time, clarity, colour and pH of solution (Ph. Eur.), identification (TLC-HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), impurities (HPLC), particulate matter (Ph. Eur.), water content (KF or NIR), headspace oxygen (electrochemical), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). Endotoxins are not tested at the end of shelf life, because it is not considered a stability-indicating parameter. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analysis results are provided for seven production scale batches of 100 mg/vial presentation and eight production scale batches of the 500 mg/vial strength manufactured at the proposed site. All results comply with the proposed specifications. The presented results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on four batches of the 100 mg/vial strength, four batches of the 500 mg/vial strength, all manufactured at production scale and stored for up to 36 months under long term conditions (25 °C / 60% RH), for up to 36 months under intermediate conditions (30 °C / 75% RH) were provided. There were some deviations from the ICH guidelines in that product has not been studied under accelerated conditions (40 °C / 75% RH) and also with regards to the frequency of testing. The stability study results at the accelerated conditions are available for Alimta. Taking into account the fact that the proposed generic medicinal product Pemetrexed Lilly 100mg and 500mg and the centrally approved reference medicinal product Alimta 100 mg and 500 mg are the same product, this was considered acceptable. Also the deviation in the frequency of testing was accepted on the basis of the well established stability profile of the product (the proposed MAH has approximately 11 years of experience with the product).

Samples were tested for appearance of the powder, particulate matter of the reconstituted solution, colour and clarity of the reconstituted solution, water content, reconstitution time, pH of the reconstituted solution, assay, purity tests and sterility with the methods used for release. The stability data for both strengths is within the shelf-life specifications and there are no trends present in the data generated for both storage conditions.

In-use stability studies on the reconstituted product with sodium chloride 0.9% were provided. Compatibility of the stopper to the reconstituted solution has been tested during development studies when vials were stored upright and inverted positions. The results for the inverted vials were acceptable. The proposed in-use storage statement of the SmPC (section 6.3) "Chemical and physical in-use stability after reconstitution and further dilution in 0.9 % Sodium Chloride solution has been demonstrated for 24 hours at 2 °C to 8 °C" is acceptable.

Photostability studies in accordance with the ICH conditions were conducted on the finished product. Photostability studies were also conducted on product reconstituted with 0.9% Sodium Chloride Injection (preservative free), and the product reconstituted and further diluted in IV bags with 0.9% Sodium Chloride Injection (preservative free). Based on the results protection from light is not required under the typical in-use conditions.

The proposed shelf life and storage condition are considered justified as they are the same as currently approved for Alimta.

Based on the data and justification provided the proposed shelf-life of 36 months and storage conditions "This medicinal product does not require any special storage conditions" as stated in the SmPC (section 6.3 and 6.4) are accepted.

Adventitious agents

No excipients of human or animal origin are used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

The proposed generic medicinal product Pemetrexed Lilly and the centrally approved reference medicinal Alimta (EU/1/04/290/001-002) share the same qualitative and quantitative composition, same pharmaceutical form, same Marketing Authorisation Holder, Eli Lilly Nederland B.V. (The Netherlands). The quality documentation submitted for the current application is identical with the authorised dossier for Alimta. Since the generic and reference product are the same, there are no differences with regards to quality.

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.

2.4.5. 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.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. 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.

2.5.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pemetrexed Lilly manufactured by Eli Lilly 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.

2.5.3. 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 (EMA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.6. Clinical aspects

2.6.1. 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

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 Lilly 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.

2.6.2. Pharmacokinetics

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

2.6.3. Pharmacodynamics

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

2.6.4. Post marketing experience

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

2.6.5. Discussion on clinical aspects

There are no concerns with Pemetrexed Lilly 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*".

2.6.6. Conclusion on clinical aspects

The CHMP considers that there are no objections to approval of Pemetrexed Lilly powder for concentrate for solution for infusion from a clinical point of view.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. 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 1.0 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 1.0 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 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 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	Appropriate wording in the SmPC	N/A
GI disorders	Appropriate wording in the SmPC	N/A
Serious renal events	Appropriate wording in the SmPC	N/A
Interstitial pneumonitis	Appropriate wording in the SmPC	N/A
Radiation pneumonitis	Appropriate wording in the SmPC	N/A
Radiation recall	Appropriate wording in the SmPC	N/A
Sepsis	Appropriate wording in the SmPC	N/A
Bullous skin reaction including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Appropriate wording in the SmPC	N/A
Cardiovascular events	Appropriate wording in the SmPC	N/A
Peripheral vascular disease	Appropriate wording in the SmPC	N/A
Hearing loss/hypoacusis	Routine pharmacovigilance activities	N/A

2.9. 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.

2.10. Product information

2.10.1. 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 Lilly is a generic product of the centrally approved medicinal product Alimta (EU/1/04/290/001-002) of the same marketing authorisation holder (Eli Lilly Nederland B.V).

The proposed product information (PI) for Pemetrexed Lilly 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 Lilly in the following indications:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

Pemetrexed Lilly 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 Lilly 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 Lilly 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 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• **Additional risk minimisation measures**

Not applicable.

• **Obligation to conduct post-authorisation measures**

Not applicable.