19 November 2015
EMA/819302/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pemetrexed Actavis

International non-proprietary name: pemetrexed

Procedure No. EMEA/H/C/004109/0000

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 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

API	Active pharmaceutical ingredient
ASMF	Active Substance Master File
AUC	Area Under the Curve
BSA	Body Surface Area
CCRF-CEM	Human T cell lymphoblast-like cell line
CHO	Chinese Hamster Ovary
DMSO	Dimethyl sulfoxide
GARFT	glycinamide ribonucleotide formyltransferase
GC3/C1	Human colon carcinoma cell line
GLP	Good Laboratory Practice
IV	Intravenous
HCT-8	Human colon carcinoma cell line
MAA	Marketing authorisation application
MDCK	Madin-Darby Canine Kidney
MXR/BCRP	breast cancer resistance protein/mitoxantrone resistance protein
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European pharmacopoeia
OAT	organic anion transporter
PCFT	Proton Coupled Folate Transporter
RFC	Reduced Folate Carrier
TLC	Thin Layer Chromatography
UV/VIS	Ultraviolet/Visible Absorption Spectrophotometer

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Actavis Group PTC ehf. submitted on 4 February 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pemetrexed Actavis, 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 23 October 2014.

The application concerns a hybrid 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 in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer

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

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

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

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

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

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Alimta 100 mg, powder for concentrate for solution for infusion
- Marketing authorisation holder: Eli Lilly Nederland B.V.
- Date of authorisation: 20-09-2004
- Marketing authorisation granted by:
  - Community

- Community Marketing authorisation number: EU/1/04/290/002

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

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

Information on paediatric requirements

Not applicable.

Scientific advice

Not applicable.

Licensing status

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

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alar Irs

- The application was received by the EMA on 4 February 2015
- The procedure started on 26 February 2015
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 15 May 2015
- PRAC Rapporteur assessment report circulated on 30 May 2015
- PRAC Rapporteur updated assessment report circulated on 18 June 2015
- PRAC assessment overview adopted by PRAC via written procedure on 23 June 2015
- During the meeting on 25 June 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 July 2015
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 September 2015
- PRAC Rapporteur assessment report circulated on 7 September 2015
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 7 October 2015
- PRAC Rapporteur assessment report circulated on 8 October 2015
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 12 October 2015
- During the CHMP meeting on 22 October 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the Second CHMP consolidated List of Outstanding Issues on 27 October 2015
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the Second List of Outstanding Issues to all CHMP members on 3 November 2015
- The Rapporteur circulated an updated Assessment to all CHMP members on 11 November 2015
- During the meeting on 19 November 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 Actavis

2. Scientific discussion

2.1. Introduction

This submission concerns a hybrid application for pemetrexed concentrate for solution for infusion. Pemetrexed Actavis 100 mg, 500 mg or 1000 mg Concentrate for Solution for Infusion has the same active substance and the same excipients in comparable amounts to the centrally approved reference medicinal product Alimta (EU/1/04/290/001-002). After reconstitution, each vial contains 25 mg/ml of pemetrexed.

The claimed indication for Pemetrexed Actavis is:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

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

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

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

As monotherapy or in combination with cisplatin, the recommended dose of pemetrexed is 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.

Pemetrexed Actavis must be diluted prior to use.

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) and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed gains entry to the cell via the reduced folate carrier (RFC) and proton coupled folate transporter (PCFT). In the cell, pemetrexed is rapidly converted to polyglutamate forms bynthe 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 concentrate for solution for infusion containing 25 mg/ml of pemetrexed (as pemetrexed diacid) as active substance.

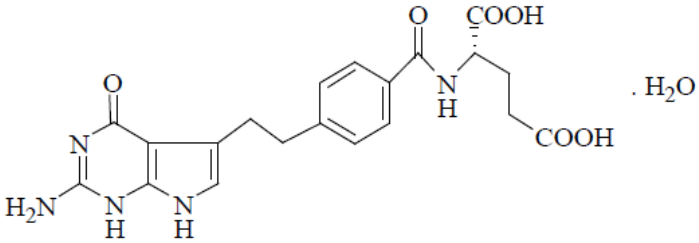
Other ingredients are: trometamol, anhydrous citric acid, cysteine hydrochloride monohydrate, and water for injection.

The product is available in colourless glass vial (type I) with type I rubber (bromobutyl) serum stopper and an aluminium cap with polypropylene disk as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

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



A series of analysis methods were applied to verify the structure: peak purity, elemental analysis (EA), ultraviolet/visible absorption spectrophotometry (UV/VIS) and molar absorptivity, infrared absorption spectrophotometry (IR), Nuclear Magnetic Resonance (NMR), Thin Layer Chromatography (TLC), and electrical conductivity.

The active substance is a white or almost white powder, practically insoluble in water, anhydrous ethanol, and methylene chloride, and is slightly hygroscopic. Pemetrexed contains a single chiral centre and is synthesised as the single L-isomer. The D-isomer (Impurity E) is limited in the active substance specification. Based on XRPD test results, the crystalline form of the active substance is Form B.

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

Manufacture, characterisation and process controls

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

The active substance is synthesised in one manufacturing site.

Pemetrexed is synthesized in nine main steps by 5 well defined starting materials. During evaluation, re-definition of the proposed starting material was requested by CHMP as a large part of the full synthesis including incorporation of structural elements and stereochemistry was outside the proposed

route falling under GMP requirements. The re-defined starting materials are controlled by acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
Potential and actual impurities were well discussed with regards to their origin and characterised.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Pemetrexed diacid is packed in two layers of pharmaceutical LDPE (Low-Density polyethylene) bags and then sealed in aluminium foil bag. The polymer used for the manufacturing of LDPE complies with the requirement for food contact material legislation. The polymer also complies with the requirement of Ph. Eur. and with EU Regulation 1183/2012. The specifications of the LDPE bag and aluminium foil bag are presented.

Specification

The active substance specification includes tests for appearance, solubility, identification (UV, IR, HPLC), clarity of solution (Ph Eur), color of solution (Ph Eur), water (Ph Eur), heavy metals, residue of ignition (Ph Eur), related substances (HPLC), residual solvents (GC), bacterial endotoxins (Ph Eur), microbial limit (Ph Eur), and assay (HPLC).
The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided.

Batch analysis data on 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 12 months under long term conditions at -20 ºC ± 5 ºC and for up to 6 months under accelerated conditions at 5 ºC ± 3 ºC according to the ICH guidelines were provided.

The following parameters are tested during stability study: appearance, identification by HPLC, clarity and colour of solution, water, related substances, enantiomer and assay. The analytical methods used were the same as for release and were shown to be stability indicating.

The batches meet the acceptance criteria in the specification and showed no change during the storage.

Photostability testing following the ICH guideline Q1B was performed on 3 batches. Photostability results of three batches meet the acceptance criteria in the specification thus it is concluded that no additional light protection packaging is needed for the active substance.

Additional accelerate stability studies under conditions of 40 ºC ± 2 ºC / 75% ± 5% RH and long term study under conditions of 25 ºC ± 2 ºC / 60% ± 5% RH were performed on three validation batches manufactured from redefined starting materials. The test results up to 3 months meet the acceptance criteria and no significant changes were observed during the storage. Only 3 months results are available hence it is not possible to make extensive conclusions on the stability at these conditions. Therefore, the CHMP recommends that the manufacturer should continue the study and in case no changes are detected the manufacturer could take it into account to set the storage conditions to be less restrictive.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period of 12 months stored in a freezer (-20ºC±5ºC) and keep the container tightly closed to protect from moisture.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product has been developed as a concentrate for solution for intravenous infusion intended to be diluted with 5% glucose solution. There are no objections either form the quality or from the clinical point of view to accept glucose as diluent. The finished product is a sterile, clear and colourless to slightly yellowish or yellow-greenish solution.

A letter from the applicant dated 5 November 2015 was received requesting for the product only to be authorised for administration in 5% glucose solution on the basis of the existence of a relevant usage patent regarding administration of the product in saline.

The finished product Pemetrexed Actavis 25 mg/ml – Concentrate for solution for infusion (100 mg/4 ml; 500 mg/20 ml; 1000 mg/40 ml) was developed as a hybrid to the reference product Alimta powder for concentrate for solution for infusion (100 mg/vial; 500 mg/vial) authorized in the Community via the centralized procedure. Pemetrexed Actavis 25 mg/ml - Concentrate for solution for infusion contains the same active substance as the reference product Alimta,. It has an identical content of active substance per vial (as pemetrexed free base) as the reference product Alimta, for the presentation forms 100 mg pemetrexed/vial and 500 mg pemetrexed/vial. The pharmaceutical form (concentrate for solution for infusion) is different than the reference product Alimta (powder for concentrate for solution for infusion). Pemetrexed Actavis has the same concentration of active ingredient like Alimta (25 mg/ml of pemetrexed active moiety). In powder form, Alimta is a salt - pemetrexed disodium salt; once reconstituted/diluted for administration, the ions are dissociating in water.

The aim of the development of the product Pemetrexed 25 mg/mL concentrate for solution for infusion 100 mg/4 ml, 500 mg/20 ml and 1g/40 ml was:

- A finished product presented as concentrate for solution for infusion, simplifying the administration by eliminating the first reconstitution step;
- A finished product with three commercial presentation forms of Pemetrexed Actavis 25 mg/ml concentrate for solution for infusion: 100 mg/4 ml, 500 mg/20 ml and 1000 mg/40 ml;
- A finished product having an identical content of active substance per vial (100 mg of pemetrexed; 500 mg of pemetrexed) as the reference product Alimta;
- An additional 1000 mg strength of pemetrexed, which is proportional in quantitative composition to the other two presentations and which also results in a concentration of 25mg/ml.

The active substance used for the product development is pemetrexed diacid, which is insoluble in water. In order to obtain the pemetrexed solution, stabilising base compounds that provide counter ions to the pemetrexed diacid, forming water soluble base addition salts were proposed: diethanolamine, trometamol and meglumine. L-Cysteine and trisodium citrate were added as antioxidants and stabilizer.

The excipients used in the formulation of Pemetrexed Actavis25 mg/ml – Concentrate for solution for infusion are trometamol, anhydrous citric acid, cysteine hydrochloride monohydrate, water for injection

and nitrogen. The excipients are in compliance with current Ph Eur. Trometamol is a mildly alkaline chemical compound used in a wide variety of pharmaceutical preparations, where it serves as buffer (pH = 7.0 – 8.0), neutralizer, solubilizer and stabilizer. Citric acid anhydrous is used as antioxidant synergist. Cysteine hydrochloride monohydrate is aα-amino acid with a thiol side chain used as an antioxidant. Water for injection is used as solvent to obtain the pemetrexed solution. Nitrogen is used as a technological additive in the phases of pemetrexed solution preparation and filtrations and in the phase of vial closing in order to limit the oxidative degradation reactions.

The proposed product Pemetrexed Actavis 25 mg/ml concentrate for solution for infusion has three strengths (100 mg, 500 mg and 1000 mg), whereas the reference product has only two (100 mg and 500 mg). As dosing is performed on a mg/m^2 basis, the use of the proposed 1000 mg strength does not result in the administration of a higher dose to the patient. Taking an average adult body surface area of 1.6 m^2 (female) and 2.0 m^2 (male) and the maximum dosing regimen, a patient would need to receive between 800 mg and 1000 mg pemetrexed. Therefore commercialising a larger strength could be more convenient for healthcare professionals in some circumstances and will allow the pysician's choice in the vials selected to prepare an individual patient's dose. The bulk formulation and manufacturing process of the 1000 mg preparation are stated to be identical to those of the proposed 100 mg and 500 mg presentations. Consequently, no additional safety or efficacy studies are necessary to support the 1000 mg strength.

Physico-chemical studies demonstrated that both test and reference products contain pemetrexed active moiety dissociated in an ionic solution in a similar manner. When further diluted for intravenous administration, both Alimta and Pemetrexed Actavis have the same concentration of active ingredient. The extrapolated concentration of 1000 mg vial of Actavis is the same per unit (ml) as the one of smaller vials of Alimta. Therefore, adding the 1000 mg vial does not imply any changes in administration of the product, it just addresses the need of facilitating the product administration (average dosage per patient is 900 mg, so diluting from one vial is easier).

Given the change in formulation, the applicant analysed in depth the existing differences and performed comparative physicochemical and non-clinical studies to demonstrate equivalence between the proposed product and Alimta.

The comparative studies that have been conducted to demonstrate equivalence between the proposed product and Alimta are provided. Both in-vitro studies performed demonstrated the similar behaviour of reference and hybrid medicinal product on both intracellular uptake and renal elimination. The studies are detailed in the Nonclinical Overview and the full study reports are enclosed in Module 4.

At the time of the pharmaceutical development, after the formulation was defined, the finished product was stored in a normal and reversed position at 56°C in order to study the influence of the head space volume, the type of the gas bubbled in the solution and the compatibility of the solution with selected stoppers. It was showed that at higher head space, the degradation increased as it was indicated by the assay values and the purity profile. On the other hand, it was noticed that for the finished product bubbled with N_2, the degradation was not so advanced as in the case of air bubbling (for same solution volume and vial capacity) which justifies the use of N_2 bubbling.

A further study was performed on 1 batch to evaluate that the active substance in Pemetrexed 25 mg/ml concentrate for solution for infusion did not racemize under stress temperature conditions (60 °C after 4 and 7 days) and light exposure (22 hours at 1.32 million lux and integrated near ultraviolet energy of 495 watt/ m^2, at 25°C + 2°C, on vials placed in both upright and inverted positions; the vials rapped with aluminium foil have been used as dark control). The results showed that Pemetrexed active ingredient in Pemetrexed 25 mg/ml, concentrate for solution for infusion does not racemize after

both thermal and light stress: the enantiomeric purity in stressed samples does not change with respect to its content in the unstressed sample.

Compatibility with 5% glucose solution, ie stability of the finished product after dilution have been studied under experimental conditions which simulate the recommendations for preparing and storing the product prior to administration, as indicated in the product information. The study covered all aspects known in medical practice and the results demonstrated the physicochemical and microbiological stability of the diluted solution is satisfactory.

In order to select the sterilisation method, the requirements of the guide CPMP/QWP/054/98 – "*Decision trees for the selection of sterilization methods*" (Annex to Note for Guidance on Development Pharmaceutics) were considered. The results obtained during the preformulation tests showed that the aqueous solution of 25 mg/ml pemetrexed diacid is not chemically stable under autoclaving conditions. The results obtained for one batch at the end of one and two autoclaving cycles (15 minutes at 121°C) were presented. After autoclaving the colour of the solution changed from colourless to dark green-yellow (more intensely coloured than reference solution and the level of impurities increased). Also, the level of the unknown impurity increased. Since sterilisation by moist heat is not applicable, according to the decision tree for sterilisation choices for aqueous products (CPMP/QWP/054/98) the use of a combination of aseptic filtration and aseptic processing (filling) was selected.

The choice of filter type was based on the solution type designated to be processed, the solution compatibility with the component material of the filter, its porosity, as well as on the efficiency of sterilization by filtration. The Pall filter with polyvinyliden fluoride membranes, 0.45 µm and 0.2 µm pore size were proposed for experimental and production scale processing of the product, in order to validate the industrial manufacturing process.

The packaging materials used as primary package (clear glass vials type I, bromobutylic rubber closures type I) are considered as standard for this type of pharmaceutical dosage form Teflon coated bromobutylic rubber stoppers were selected knowing that FluroTec® coated stoppers provide an effective barrier against most organic/inorganic extractable/leachables to minimize interaction between the drug and the stopper. Type I colourless glass vials meet the requirements of Ph.Eur. <3.2.1>.The closure complies with the Type I requirements for rubber closures as defined in monograph <3.2.9> of the current Ph. Eur. Tests and specifications together with certificates of analysis from the suppliers and manufacturers of the finished product have been provided. The suitability of the proposed closure system with the proposed formulation was investigated by studying their compatibility of the product. The integrity of the container closure system is ascertained by the results obtained for the microbiological parameters "Sterility" and "Bacterial endotoxins" at product release., and should be reconfirmedby the results of the stability study. The integrity of the container closure system is also demonstrated by the qualification of performances tests for the vial filling and closing machine, tests performed by using 1 ‰ methylene blue solution and 10^5 cfu/ ml microorganisms suspension. Compatibility studies with the rubber stopper have been performed, the stopper is compatible with the finished product formulation.

Manufacture of the product and process controls

The finished product is manufactured in one manufacturing site.

The manufacturing process involves the following steps: preparation of bulk solution, pre-filtration, first and second sterilising filtration, filling and stoppering, filled vial washing and labelling and packaging. All the manufacturing operations are conducted under nitrogen blanketing or bubbling until stoppering.

Critical steps and process parameters that are considered critical for the quality of the product were identified and are controlled by in-process controls adequate for this type of manufacturing process.

The process is considered to be a non-standard manufacturing process. As a non-standard manufacturing process is used, the validation was performed on three consecutive commercial scale batches of each concentration. Major steps of the manufacturing process (hold time, media fill, filtration and container closure integrity) have been validated by a number of studies. 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 specifications include appropriate tests for this kind of dosage form: appearance, colour (Ph Eur), clarity (Ph Eur), pH (PH Eur), visible particles (Ph Eur), visible particles (Ph Eur), sub-visible particles (Ph Eur), extractable volume (Ph Eur), osmolality and osmolarity (Ph Eur), identification (HPLC, TLC), assay (HPLC), degradation products (HPLC), bacterial endotoxins (Ph Eur) and sterility (Ph Eur).

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

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

During evaluation, the applicant agreed to tighten the limits for impurities according to the presented stability results. Most of the limits are set according to the qualification threshold of 0.2% except for Impurity RRT 0.43. A limit of NMT 0.4% is proposed based on the stability results and toxicological study. The CHMP agreed that this can be accepted at the moment but recommended that the limit should be re-revaluated once the stability studies have been completed up to 36 month period as foreseen by the applicant. The limit for total impurities can be accepted on the same grounds.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Three production scale batches (1 per concentration) were subjected to stability studies as per the ICH guidelines under refrigerated (2 to 8 °C), long-term (25 ± 2°C/60 ± 5% RH), intermediate (30 ± 2°C/75 ± 5% RH) for up twelve months and accelerated (40 ± 1°C/75 ± 5% RH) conditions for up to six months. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Testing was performed on appearance, clarity and colour, visible particles, sub-visible particles, pH, assay and degradation products, bacterial endotoxins, and sterility. The analytical methods used for testing of the stability samples are the same as the methods used for release testing.

The solution remained clear during stability studies, but intensifications in the solutions colour were observed, especially for some batches of the presentation form of 100 mg/ml, with results out of the specification. The obtained results for the assay show a very slight decrease, but remain around the theoretical value of 25 mg/ml. Some results for degradation products show an increase from the initial moment.

Pemetrexed Actavis is presented as concentrate for solution for infusion stored in glass vials. The product however is not stable at higher temperatures and the storage conditions 5 ± 3°C are proposed

for the shelf life of the product. The tests for visible and sub-visible particles are included in the shelf life specifications as an additional assurance if any delamination issues may occur.

Photostability studies were also performed on production scale batch by exposure to light in a Xenon lamp to a total light energy of minimum 1.2 million lux hour for 14 hours considered as the worse scenario of photostability study condition, covering the exposure to an integrated near ultraviolet energy of minimum 200 Watt hour/m2 (exposure for 3.4 hours). An accelerated photochemical degradation study was performed by exposure to light in a Xenon lamp to a total light energy of minimum 1.2 million lux for 22 hours on an R&D batch. Based on the photostability tests performed by the active substance manufacturer and cumulated with finished product manufacturer, it was demonstrated that both active substance and finished product are light sensitive, therefore the finished product should be protected from light in an outer carton.

The finished product was also subjected to various forced degradation studies in order to obtain information about the degradation pathways and potential degradation products. These studies were performed during the manufacturing development phase, and also as part of the photostability studies and analytical method validation. Stress-testing was conducted by exposing the finished product to thermos (80°C for 7 hours), photo (6 hours at photo light (1.2 million lux hours/200 Watts/m2)), acidic (0.1N HCl for 36 hours at 56 °C), alkaline (1 N NaOH for 16 hours at 56 °C) and oxidative degradation (1 % H_2O_2 for 7 hours at 56 °C). Based on the results, it can be concluded that the finished product is sensible to alkaline degradation, oxidative stress and thermal degradation and it was shown that the proposed analytical methods are stability indicating.

In use stability studies were performed in order to evaluate the physicochemical stability of the diluted solutions (10 mg/mL and 4 mg/mL) for Pemetrexed Actavis 25 mg/mL – concentrate for solution for infusion. The concentrations of the diluted solutions, 4 mg/ml and 10 mg/ml, were established based on the therapeutic indications of minimum and maximum recommended daily dose.

The in-use stability study of diluted solutions has been a concern; therefore it was performed from the beginning of finished product pharmaceutical development in order to study the behaviour of the diluted solutions.

Diluted solution stability studies were performed under different conditions of temperature and container available at different time points during this application (6 months shelf life at submission, 9 and 12 months shelf life at the time of this response preparation). The diluted solution stability studies protocols and results conducted on finished products having 12 months shelf life were provided and are considered satisfactory.

Based on the in-use stability results chemical and physical in-use stability of infusion solution of pemetrexed was demonstrated for 24 hours at refrigerated 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 as stated in the SmPC (section 6.3).

Based on available stability data, the proposed shelf-life for the unopened vial of 18 months, and the proposed storage conditions "Store and transport refrigerated (2°C to 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of the finished product

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.

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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

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:

- The manufacturer of the active substance should continue the accelerated stability studies and in case no changes are detected the manufacturer could take it into account to set the storage conditions to be less restrictive.

- The limits for Impurity RRT 0.43 and total impurities in the finished product specifications should be re-revaluated and if necessary tightened once the stability studies have been completed up to 36 month period as foreseen by the applicant.

2.3. Non-clinical aspects

2.3.1. Introduction

In vitro and in vivo studies have shown that pemetrexed had activity against a variety of tumour types, including non-small cell lung, breast, bladder, head and neck, and ovarian cancers, as well as mesothelioma.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. In addition, in order to further support the application, Actavis has conducted comparative pharmaceutical studies designed to demonstrate that the change in formulation and existing difference in excipients and the use of tromethamine salt do not impact the safety and efficacy of the product. The Applicant further investigated the degree of similarity between the test and reference product in two *in vitro* studies.

2.3.2. Pharmacology

No new pharmacodynamic studies were submitted.

2.3.3. Pharmacokinetics

The pharmacokinetic data on the pemetrexed have been adequately presented in review articles, monographs, and standard drug manuals (Eli Lilly Product Information Alimta 2004, 2011, 2012; Eli Lilly Product Monograph Canada, 2012; NDA-21-462, EMA Scientific Discussion Alitma, 2004; Alimta Eli Lilly SPC, 2012, etc.).

Pemetrexed was administered intravenously by the route intended for use in man. After single intravenous doses administered to mice, dogs, and human, plasma concentration of pemetrexed declined in a biphasic manner, a rapid distribution phase followed by a longer terminal elimination phase.

The AUC increased in a dose-dependent manner over the tested dosages (20-100 mg/kg). Approximately 90% of the active drug is excreted unchanged in urine. The elimination half-life was short in dogs compared to mice. The PK of pemetrexed in mice, dogs and man after single doses were similar.

The Applicant has conducted a comparative study to evaluate the Pemetrexed Actavis and Alimta as substrates of human OAT3 mediated transport in vitro. The products were studied in the concentration range of 10 – 500 µM. The studies demonstrated the similarity of transport through OAT3 of both tested products.

Study OPT-2014-136: "Assessment of Pemetrexed Actavis and Alimta as substrates of human RFC and PCFT mediated transport."

The purpose of the study is to determine whether Pemetrexed Actavis and Alimta are transported by human PCFT (proton-coupled folate transporter) and RFC (reduced folate carrier).

The uptake test systems for PCFT and RFC consisted of a polarized monolayer of MDCK-II cells grown on permeable supports. The MDCK-II cells were treated to express the transporter of interest or treated with a control vector. Experiments were performed under the same conditions for the cells expressing the transporter and for those treated with the control vector. Cells were seeded on 96-well plates approximately 24 hours before transfection. Transport assays were carried out approximately 48 hours after transfection.

The transport of the probe substrate was determined by radiometric detection. The transport of Pemetrexed Actavis and Alimta was determined by LC/MS/MS.

Pemetrexed Actavis and Alimta 100 mg dosage form was used for this experiment.

Data Analysis

1. PCFT and RFC Transporter: Net transporter mediated uptake of substrate by the PCFT or RFC is calculated by subtracting uptake in the control system, which does not express the transporter of interest, from uptake in the test system which does express the transporter of interest.

Net Transporter Mediated Substrate Uptake = (Cellular accumulation in the presence of the transporter) - (Mean cellular accumulation in the absence of the transporter)

2. Kinetic Analysis: The Km and Vmax are calculated by non-linear regression using the Michaelis-Menten equation.

Criteria for acceptable control values for transport:

- PCFT-mediated methotrexate uptake: ≥ 0.558 pmol/min/cm^2
- RFC-mediated methotrexate uptake: ≥ 0.095 pmol/min/cm^2

PCFT Results

Pemetrexed Actavis and Alimta were studied in the concentration range of 0.03 - 30 µM (7 total) in Ca2+ and Mg2+ free buffer for PCFT mediated transport. A dose dependent increase in uptake of both Pemetrexed Actavis and Alimta was observed (Table 2, Table 3). The Km values for Pemetrexed Actavis and Alimta are 0.0995 µM ± 0.0238 µM and 0.212 µM ± 0.0354 µM, respectively (Figure 1). The Vmax values for Pemetrexed Actavis and Alimta are 2.83 ± 0.103 pmol/min/cm^2 and 3.12 ± 0.0990 pmol/min/cm^2.

RFC Results

Pemetrexed Actavis and Alimta were studied in the concentration range of 0.1 - 100 µM (7 total) in Ca^{2+} and Mg^{2+} free buffer for RFC mediated transport. A dose dependent increase in uptake of both Pemetrexed Actavis and Alimta was observed (Table 4, Table 5). The Km values for Pemetrexed Actavis and Alimta are 1.95 µM ± 0.436 µM and 3.15 µM ± 1.47 µM, respectively (Figure 2). The V_{max} values for Pemetrexed Actavis and Alimta are 0.410 ± 0.0240 pmol/min/cm^2 and 0.524 ± 0.0743 pmol/min/cm^2.

Table 2. *In vitro* assay data for the assessment of PCFT mediated transport of Pemetrexed Actavis.

Pemetrexed Actavis (µM)	Cellular Accumulation (transporter) (pmol/min/cm^2)	Cellular Accumulation (control) (pmol/min/cm^2)	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)
0.03	*3.43 ± 0.645	*0.0664 ± 0.0216	*3.36 ± 0.645
0.1	1.67 ± 0.205	BQL	1.67 ± 0.205
0.3	1.76 ± 0.0387	BQL	1.76 ± 0.0387
1	2.65 ± 0.122	0.0601 ± 0.0121	2.59 ± 0.122
3	3.08 ± 0.139	0.151 ± 0.0457	2.93 ± 0.139
10	3.10 ± 0.169	0.438 ± 0.0508	2.66 ± 0.169
30	3.79 ± 0.549	0.867 ± 0.230	2.92 ± 0.549
0.1 µM methotrexate	1.55 ± 0.0642	0.0199 ± 0.00374	1.53 ± 0.0642

All results were presented as Mean ± SD.
BQL: below quantification limit of LC/MS/MS of 1 nM (equivalent 0.0444 pmol/min/cm^2), and treated as zero in further calculations.
**; outlier and excluded from kinetic analysis*

Table 3. *In vitro* assay data for the assessment of PCFT mediated transport of Alimta.

Alimta (µM)	Cellular Accumulation (transporter) (pmol/min/cm^2)	Cellular Accumulation (control) (pmol/min/cm^2)	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)
0.03	0.307 ± 0.0149	BQL	0.307 ± 0.0149
0.1	0.745 ± 0.0156	BQL	0.745 ± 0.0156
0.3	1.84 ± 0.108	BQL	1.84 ± 0.108
1	3.12 ± 0.0536	0.0761 ± 0.00645	3.05 ± 0.0536
3	2.96 ± 0.140	0.164 ± 0.0107	2.79 ± 0.140
10	3.42 ± 0.274	0.405 ± 0.0167	3.01 ± 0.274
30	3.98 ± 0.362	1.05 ± 0.127	2.93 ± 0.362
0.1 µM methotrexate	1.55 ± 0.0642	0.0199 ± 0.00374	1.53 ± 0.0642

All results were presented as Mean ± SD.
BQL: below quantification limit of LC/MS/MS of 1 nM (equivalent 0.0444 pmol/min/cm^2), and treated as zero in further calculations.

Table 4. *In vitro* assay data for the assessment of RFC mediated transport of Pemetrexed Actavis.

Pemetrexed Actavis (µM)	Cellular Accumulation (transporter) (pmol/min/cm^2)	Cellular Accumulation (control) (pmol/min/cm^2)	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)
0.03	BQL	BQL	BQL
0.1	0.0841 ± 0.0249	0.0510 ± 0.00658	0.0331 ± 0.0249
0.3	0.200 ± 0.0312	0.0634 ± 0.0103	0.136 ± 0.0312
1	0.379 ± 0.0294	0.131 ± 0.0100	0.248 ± 0.0294
3	0.641 ± 0.0526	0.264 ± 0.0140	0.377 ± 0.0526
10	0.812 ± 0.0420	0.453 ± 0.0385	0.358 ± 0.0420
30	*1.47 ± 0.212	*1.44 ± 0.2080	*0.0370 ± 0.212
0.5 µM methotrexate	0.492 ± 0.0388	0.220 ± 0.0221	0.273 ± 0.0388

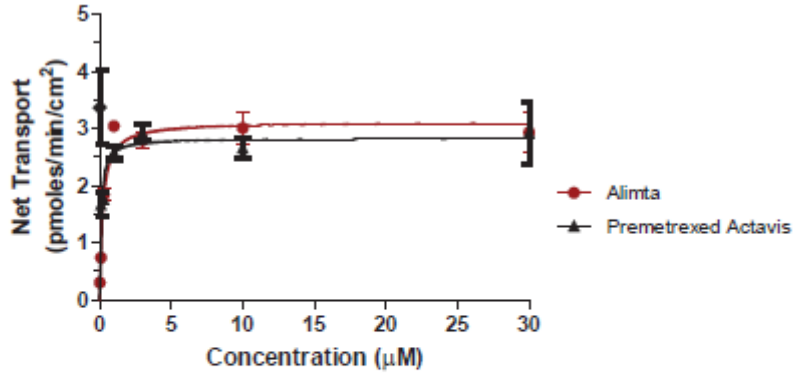
All results were presented as Mean ± SD.
BQL: below quantification limit of LC/MS/MS of 1 nM (equivalent 0.0444 pmol/min/cm^2), and treated as zero in further calculations.
**; saturated and excluded from kinetic analysis*

Table 5. *In vitro* assay data for the assessment of PCFT mediated transport of Alimta.

Alimta (µM)	Cellular Accumulation (transporter) (pmol/min/cm^2)	Cellular Accumulation (control) (pmol/min/cm^2)	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)
0.03	BQL	BQL	BQL
0.1	0.119 ± 0.0369	0.0482 ± NA	0.0703 ± 0.0369
0.3	0.218 ± NA	0.0761 ± 0.00798	0.142 ± NA
1	0.401 ± 0.0197	0.212 ± NA	0.189 ± 0.0197
3	0.750 ± 0.114	0.258 ± 0.0123	0.492 ± 0.114
10	0.882 ± NA	0.479 ± NA	0.404 ± NA
30	*1.91 ± 0.298	*1.42 ± NA	*0.490 ± 0.298
0.5 µM methotrexate	0.492 ± 0.0388	0.220 ± 0.0221	0.273 ± 0.0388

All results were presented as Mean ± SD.
BQL: below quantification limit of LC/MS/MS of 1 nM (equivalent 0.0444 pmol/min/cm^2), and treated as zero in further calculations.
NA: not available, one of the triplicates was excluded by Grubb Test.
**; saturated and excluded from kinetic analysis*

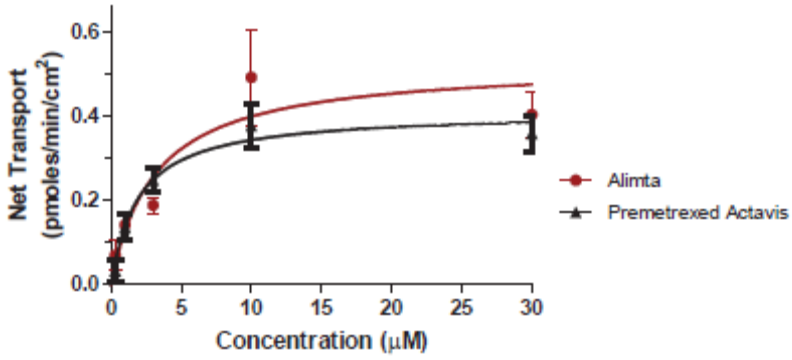
Figure 1. Transport of Pemetrexed Actavis and Alimta by PCFT.



	Alimta	Premetrexed Actavis
Best-fit values		
Vmax	3.117	2.832
Km	0.2122	0.09945
Std. Error		
Vmax	0.09898	0.1030
Km	0.03543	0.02378

Pemetrexed Actavis and Alimta were studied in the concentration range of 0.03 - 30 µM. The 0.03 µM pemetrexed Actavis uptake was treated as an outlier and excluded from kinetic analysis. Data represent the mean and standard deviation of triplicate samples.

Figure 2. Transport of Pemetrexed Actavis and Alimta by RFC.



	Alimta	Premetrexed Actavis
Best-fit values		
Vmax	0.5240	0.4097
Km	3.147	1.946
Std. Error		
Vmax	0.07426	0.02397
Km	1.473	0.4355

Pemetrexed Actavis and Alimta were studied in the concentration range of 0.1 - 100 µM. The 0.03 µM pemetrexed Actavis uptake was treated as an outlier and excluded from kinetic analysis. Data represent the mean and standard deviation of triplicate samples.

In conclusion

PCFT: Pemetrexed Actavis and Alimta were studied in the concentration range of 0.03 - 30 µM. A dose dependent increase in uptake of both Pemetrexed Actavis and Alimta was observed. The Km values for Pemetrexed Actavis and Alimta are 0.0995 µM and 0.212 µM, respectively.

RFC: Pemetrexed Actavis and Alimta were studied in the concentration range of 0.1 - 100 µM. A dose dependent increase in uptake of both Pemetrexed Actavis and Alimta was observed. The Km values for Pemetrexed Actavis and Alimta are 1.95 µM and 3.15 µM, respectively.

Study OPT-2014-058: "Assessment of Pemetrexed Actavis and Alimta as substrates of human OAT3 mediated transport

The purpose of the study is to determine whether Pemetrexed Actavis and Alimta are transported by human OAT3.

The uptake test system for OAT3 consisted of a polarized monolayer of MDCK-II cells grown on permeable supports. The MDCK-II cells were treated to express the transporter of interest or treated with a control vector. Experiments were performed under the same conditions for the cells expressing the transporter and for those treated with the control vector. Cells were seeded on 96-well plates approximately 24 h before transfection. Transport assays were carried out approximately 48 h after transfection. Positive control was 10 µM [H^3]-p-aminohippurate.

The transport of the probe substrate was determined by radiometric detection. The transport of Pemetrexed Actavis and Alimta was determined by LC/MS/MS.

Data Analysis

1. OAT3 Transporter: Net transporter mediated uptake of substrate by the OAT3 is calculated by subtracting uptake in the control system, which does not express the transporter of interest, from uptake in the test system which does express the transporter of interest.

Net Transporter Mediated Substrate Uptake = (Cellular accumulation in the presence of the transporter) - (Mean cellular accumulation in the absence of the transporter)

2. Kinetic Analysis: The Km and V_{max} are calculated by non-linear regression using the Michaelis-Menten equation.

Criteria for acceptable control values for transport:

- OAT3-mediated p-aminohippurate uptake: ≥0.287 pmol/min/cm^2

Criteria for acceptable control values for reference inhibition:

- Percent inhibition of human OAT3 mediated aminohippurate uptake by 100 µM probenecid: ≥80.7%

Results

Pemetrexed Actavis and Alimta were studied in the concentration range of 10 - 500 µM (7 total) in Ca^{2+} and Mg^{2+} free buffer. A dose dependent increase in uptake of both Pemetrexed Actavis and Alimta was observed (Table 6, Table 7). The Km values for Pemetrexed Actavis and Alimta are 11.7 µM ± 2.99 µM and 11.6 µM ± 3.25 µM, respectively (Figure 3). The Vmax values for Pemetrexed Actavis and Alimta are 8.12 ± 0.389 pmol/min/cm2 and 8.77 ± 0.444 pmol/min/cm^2. Km and Vmax determined experimentally are similar for Pemetrexed Actavis and Alimta.

Table 6. *In vitro* assay data for the assessment of OAT3 mediated transport of Pemetrexed Actavis.

Pemetrexed Actavis (µM)	Cellular Accumulation (transporter) (pmol/min/cm^2)	Cellular Accumulation (control) (pmol/min/cm^2)	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)
10	4.11 ± 0.507	0.371 ± 0.00713	3.74 ± 0.507
20	6.00 ± 0.464	0.492 ± 0.0563	5.51 ± 0.464
50	7.19 ± 0.592	0.778 ± 0.0539	6.41 ± 0.592
100	8.41 ± 0.521	1.13 ± 0.0966	7.28 ± 0.521
150	8.22 ± 1.06	1.68 ± 0.314	6.54 ± 1.06
200	9.39 ± 0.979	2.17 ± 0.0949	7.22 ± 0.979
500	12.6 ± 1.52	3.65 ± 2.18	8.97 ± 1.52
10 µM p-aminohippurate	0.458 ± 0.0685	0.114 ± 0.00872	0.344 ± 0.0685

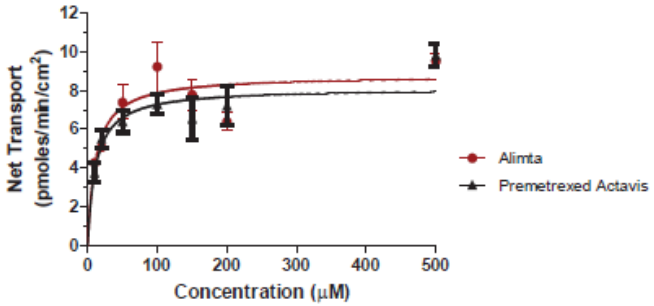
All results were presented as Mean ± SD.

Table 7. *In vitro* assay data for the assessment of OAT3 mediated transport of Alimta.

Alimta (µM)	Cellular Accumulation (transporter) (pmol/min/cm^2)	Cellular Accumulation (control) (pmol/min/cm^2)	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)
10	4.80 ± 0.118	0.530 ± 0.0112	4.27 ± 0.118
20	5.73 ± 0.204	0.665 ± 0.0339	5.07 ± 0.204
50	9.01 ± 0.883	1.620 ± 0.634	7.39 ± 0.883
100	10.5 ± 1.30	1.31 ± 0.278	9.23 ± 1.30
150	10.2 ± 0.795	2.42 ± 1.26	7.79 ± 0.795
200	11.0 ± 0.450	4.61 ± 3.02	6.39 ± 0.450
500	15.7 ± 0.401	6.21 ± 0.899	9.51 ± 0.401
10 µM p-aminohippurate	0.458 ± 0.0685	0.114 ± 0.00872	0.344 ± 0.0685

All results were presented as Mean ± SD.

Figure 3. Transport of Pemetrexed Actavis and Alimta by OAT3.



	Alimta	Premetrexed Actavis
Best-fit values		
Vmax	8.772	8.117
Km	11.55	11.66
Std. Error		
Vmax	0.4436	0.3892
Km	3.246	2.993

Pemetrexed Actavis and Alimta were studied in the concentration range of 10 - 500 µM. Data represent the mean and standard deviation of triplicate samples.

In conclusion

Pemetrexed Actavis and Alimta were studied in the concentration range of 10 - 500 µM. A dose dependent increase in uptake of both Pemetrexed Actavis and Alimta was observed. The Km values for Pemetrexed Actavis and Alimta are 11.7 and 11.6 µM, respectively.

2.3.4. Toxicology

No new toxicology studies were submitted.

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Pemetrexed Actavis manufactured by Actavis Group PTC ehf 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.

2.3.6. Discussion on non-clinical aspects

The Applicant presented in vitro studies and literature data. The scientific literature submitted is relevant for the pemetrexed and excipients (trometamol, citric acid and L-cysteine). There is a lack of the safety pharmacology published studies but these are not critical for this type of Application.

According to the EPAR of Alimta, because of better transport efficiency, RFC is likely to be the main carrier for pemetrexed, as in the case for natural folates. PCFT has been more recently described and its physiological role is not entirely clear. It is well established that pemetrexed is actively secreted by OAT3. Both studies used standard experimental conditions in respect to cell system (MDCK-II cells), positive controls (methotrexate and p-aminohippurate, respectively), over a wide range of pemetrexed concentrations. According to the EPAR of Alimta, peak circulating levels of pemetrexed approach 200

µg/ml (468 µM) in humans. For OAT3 study pemetrexed concentration tested ranged from 10-500 µM, and is appropriate. For folate transporter studies, pemetrexed concentration ranged from 0.03-30 µM and 0.1-100 µM. No justification was provided on the selected range of concentrations.

No apparent differences in the observed Km and V_{max} values were seen for Pemetrexed Actavis and Alimta. However, from a clinical point of view it is difficult to define maximum allowed difference in the Km and V_{max} values to result in clinically significant differences in PK or PD. On these grounds, these studies are considered supportive.

Physico-chemical characterisation in comparative pharmaceutical studies is considered pivotal for this application. Data provided demonstrate saturation of transporters at very low pemetrexed concentrations. Raw data provided supportive internal validity of the results.

The toxicity profile of pemetrexed remains unchanged. The safety profile of excipients in parenteral drug products administered IV is well known, and relatively large doses are currently administered to humans in various drug products; therefore, no safety concern regarding their dosage is expected. No new toxicology studies are required for this application.

The bulk formulation and manufacturing process 1000 mg/vial preparation of the Pemetrexed Actavis is identical to those of the Alimta (100 and 500 mg/vial) presentations. Consequently, no additional safety or efficacy studies are necessary to support the Pemetrexed Actavis 1000 mg/vial strength.

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.

2.3.7. Conclusion on the non-clinical aspects

The in vitro pharmacodynamic and pharmacokinetic studies demonstrated that Pemetrexed Actavis has the same similar intracellular uptake and renal elimination profiles as the reference product Alimta. Given the fact that the products are administered intravenously, and their transport and elimination mechanisms are comparable, the CHMP agrees that no further non-clinical studies are required.

2.4. Clinical aspects

2.4.1. Introduction

This is an application 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.

2.4.2. Clinical Pharmacology

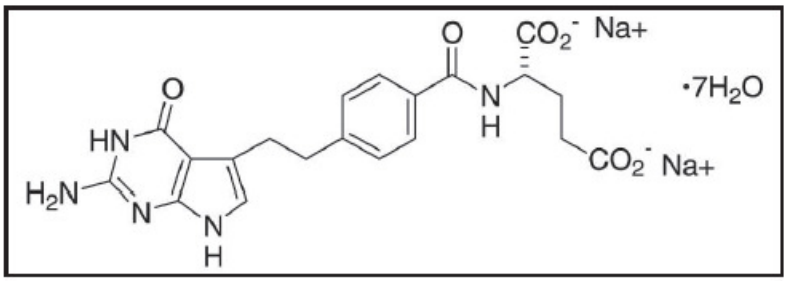
Exemption

The application has been submitted under Article 10.3 of Directive 2001/83/EC (i.e. hybrid application), due to the differences in terms of pharmaceutical form (concentrate for solution for

infusion instead of powder for concentrate for solution for infusion) and addition of 1000 mg/vial strength. No bioequivalence studies have been conducted.

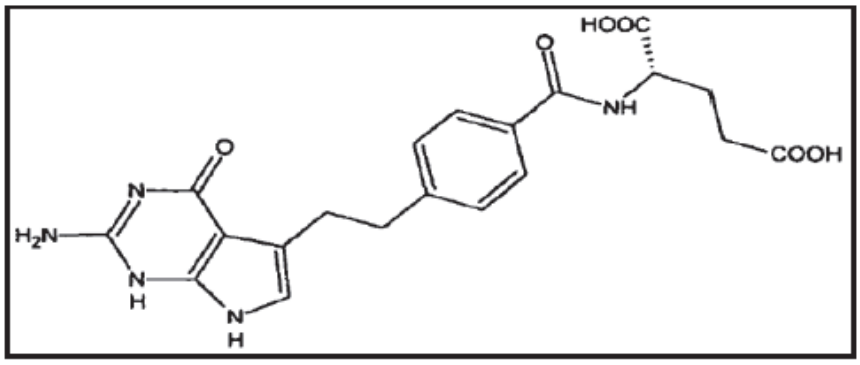
Reference product disodium pemetrexed is chemically synthesized and purified. Its molecular formula is C20H19N5O6Na2 and its molecular weight is 597.49 Da.

The structural formula is as follows:

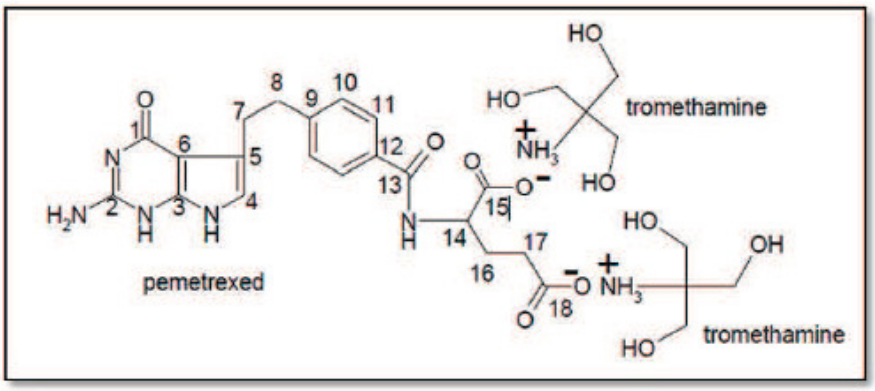


Disodium pemetrexed is an ionic compound being able to dissociate in plasma to release the ionic molecule active drug. Supporting evidence is provided by Li Li et al, 2011 study, demonstrating that pemetrexed molecule is mostly dissociated at physiological pH. The authors correlated the pH with the antifolates binding capacity to cell receptors, the polar molecule of pemetrexed is described as having 2 negative charges at pH 7.0. Pemetrexed (PMX) is a polyelectrolyte carrying two carboxyl groups, with pKa of 3.46 (α-carboxyl) and 4.77 (γ-carboxyl), and the guanidinic N-1 on the pterine ring (pKa 5.27). At physiological pH, PMX exists in a predominantly negatively charged form because of the deprotonation of the two carboxyl groups.

Pemetrexed Actavis contains diacid pemetrexed which has a chemical formula of C20H21N5O6 and a molecular mass of 427.5g/mol. Its chemical name is N-[4-[2-(2-Amino-4, 7-dihydro-4-oxo-1H-pyrrolo [2, 3-d]pyrimidin-5-yl) ethyl] benzoyl]-L-glutamic acid and it has the following chemical structure:



Pemetrexed diacid is practically insoluble in water, ethanol anhydrous and methylene chloride. Pemetrexed is white or almost white powder, slightly hygroscopic. The structural formula or pemetrexed-ditromethamine is shown below, as demonstrated by NMR characterization studies performed by the Applicant:



This compound is formed in-situ, in the watery solution, from diacid pemetrexed and tromethamine (molar report 1:2), as salt, resulted from the interaction between an acid and a base. The structure was elucidated by the Applicant by physico-chemical studies (detailed in the Pharmaceutical Development section).

Pemetrexed Actavis has the same concentration of active ingredient as Alimta. In powder form, Alimta is a salt – pemetrexed disodium; once reconstituted/diluted for administration, the ions are dissociating in water. Actavis' studies demonstrated that both test and reference products contain pemetrexed active moiety dissociated in a ionic solution in a similar manner. When further diluted for intravenous administration, both Alimta and Pemetrexed Actavis have the same concentration of active ingredient.

The proposed Actavis product contains the following excipients: trometamol, L-Cysteine and citric acid and has no mannitol (which is present in Alimta; mannitol is very frequently used excipient in powder drugs).

2.4.3. Pharmacokinetics

No pharmacokinetic studies have been submitted.

According to the SmPC of Alimta, pemetrexed has a steady-state volume of distribution of 9 l/m^2. In vitro studies indicate that pemetrexed is approximately 81 % bound to plasma proteins. Pemetrexed undergoes limited hepatic metabolism. Pemetrexed is primarily eliminated in the urine, with 70 % to 90 % of the administered dose being recovered unchanged in urine within the first 24 hours following administration. In vitro studies indicate that pemetrexed is actively secreted by OAT3 (organic anion transporter). Pemetrexed total systemic clearance is 91.8 ml/min and the elimination half-life from plasma is 3.5 hours in patients with normal renal function (creatinine clearance of 90 ml/min). Between patient variability in clearance is moderate at 19.3 %. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed are consistent over multiple treatment cycles.

As the originator and hybrid product are administered as IV solution, the bioavailability is considered to be 100%. The safety and efficacy of Pemetrexed Actavis based on a different salt is not expected to differ from Alimta.

2.4.4. Pharmacodynamics

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

2.4.5. Post marketing experience

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

2.4.6. Discussion on clinical aspects

This application is based on quality, non-clinical studies and literature data.

Pemetrexed 25 mg/mL concentrate for solution for infusion contains the same active substance as the reference product Alimta, but conjugated to a different salt (tromethamine salt instead of sodium salt).

In order to support the application, Actavis has conducted comparative pharmaceutical studies designed to demonstrate that the change in formulation and existing difference in excipients and the tromethamine salt used do not impact in any way the safety and efficacy of the product.

When diluted for administration, both products contain the same amount of pemetrexed as free base. In a watery environment, both products release the free Pemetrexed ions from the sodium and trometamol salts respectively.

The Applicant investigated further the degree of similarity between the test and reference product in two in-vitro studies.

Alimta and Pemetrexed Actavis were comparatively tested in an in vitro study OPT-2014-058, assessing the affinity of pemetrexed at renal level by OAT3 transporters. The study demonstrated the similarity of pemetrexed affinity to the OAT3 transporter from both Alimta and Pemetrexed Actavis formulations. Pemetrexed Actavis and Alimta were studied in the concentration range of 10 - 500 µM. A dose dependent increase in uptake of both Pemetrexed Actavis and Alimta was observed. The Km values for Pemetrexed Actavis and Alimta are 11.7 and 11.6 µM, respectively.

Furthermore, in order to assess the similarity of drug transport inside the cell, the Applicant performed another in-vitro comparative study OPT-2014-136. The study was designed to evaluate the degree of similarity of Pemetrexed Actavis and Alimta through human RFC (reduced folate carrier) and PCFT (proton coupled folate transporter) receptors. For PCFT, Pemetrexed Actavis and Alimta were studied in the concentration range of 0.03 - 30 µM. The Km values for Pemetrexed Actavis and Alimta are 0.0995 µM and 0.212 µM, respectively. For RFC, Pemetrexed Actavis and Alimta were studied in the concentration range of 0.1 - 100 µM. The Km values for Pemetrexed Actavis and Alimta are 1.95 µM and 3.15 µM, respectively.

In vitro studies with folate and OAT3 transporters demonstrated similar affinity of Pemetrexed Actavis and Alimta. However, from clinical point of view it is difficult to define maximum allowed difference in the Km and Vmax values to result in clinically significant differences in PK or PD. On these grounds, these studies are considered supportive. Physico-chemical characterisation in comparative pharmaceutical studies is considered pivotal for this application.

As the active substance pemetrexed is widely used and well- known, the applicant has not provided additional clinical studies but a justification that further studies are not needed. The CHMP agrees with the justification.

Appropriate data from published literature on pemetrexed were provided supporting the safe and effective use of Pemetrexed Actavis in the intended indications.

Pemetrexed Actavis contains trometamol as an excipient. Trometamol is incompatible with cisplatin resulting in degradation of cisplatin. This medicinal product must not be mixed with other medicinal

products. Intravenous lines should be flushed after administration of Pemetrexed Actavis (see section 6.6 of the SmPC).

Pemetrexed Actavis is proposed to be diluted in 5% glucose solution. More rigorous post treatment serum glucose monitoring may be needed in patients with diabetes mellitus. It is expected that the physician will take the general health status of the patient into account before treating patients with Pemetrexed Actavis.

2.4.7. Conclusions on clinical aspects

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

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.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 3.0 (dated 28 September 2015) is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the RMP version 3.0 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 toxicities Renal disorders Gastrointestinal disorders Interstitial pneumonitis Radiation pneumonitis Radiation recall Sepsis Bullous skin reaction including Stevens-Johnson syndrome and toxic epidermal necrolysis

Summary of safety concerns	
	Bone marrow suppression
Important potential risks	None
Missing information	None

Pharmacovigilance plan

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

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

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Non-compliance with folic acid and vitamin B12 regimens, manifested mainly as haematological and gastrointestinal toxicities	Text in SmPC sections 4.2, 4.4, 4.8, 5.1, 5.2, and PIL section 3. Prescription only medicine.	None
Renal disorders	Text in SmPC sections 4.2, 4.4, 4.5, 4.8, and PIL sections 2, and 4. Prescription only medicine.	None
Gastrointestinal disorders	Text in SmPC sections 4.4, 4.5, 4.8 and PIL sections 2, and 4. Prescription only medicine.	None
Interstitial pneumonitis	Text in SmPC section 4.8 and PIL section 4. Prescription only medicine.	None
Radiation pneumonitis	Text in SmPC sections 4.4, 4.8, and PIL sections 2, and 4. Prescription only medicine.	None
Radiation recall	Text in SmPC sections 4.4, 4.8, and PIL sections 2, and 4. Prescription only medicine.	None
Sepsis	Text in SmPC section 4.8 and PIL section 4. Prescription only medicine.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bullous skin reactions including SJS and TEN	Text in SmPC sections 4.2, 4.4, 4.8, and PIL sections 3, and 4. Prescription only medicine.	None
Bone marrow suppression	Text in SmPC sections 4.2, 4.4, 4.8, 4.9, and PIL sections 2, 3, and 4. Prescription only medicine.	None

PSUR submission

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

2.6. Product information

2.6.1. User consultation

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

3. Benefit-risk balance

This application concerns a hybrid version of Pemetrexed Actavis 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.

Nonclinical studies have been provided for this application 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.

This application contains a different salt of the active substance and additional non clinical studies in accordance with the relevant guideline were submitted and were considered sufficient.

A positive benefit/risk balance 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 Actavis in the following indications:

Malignant pleural mesothelioma

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

Non-small cell lung cancer

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

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

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

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.