26 January 2017
EMA/78284/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jylamvo

International non-proprietary name: methotrexate

Procedure No. EMEA/H/C/003756/0000

Note

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

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List of abbreviations

ALL	acute lymphoblastic leukaemia
AUC	area under the plasma concentration versus time-curve
CEP	Certificate of Suitability of the EP
EDQM	European Directorate for the Quality of Medicines
GC	gas chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LDPE	low density polyethylene
MTX	methotrexate
7-OHMTX	7-hydroxymethotrexate
RA	rheumatoid arthritis
JIA	juvenile idiopathic arthritis
PEG	polyethylene glycol
Ph. Eur.	European Pharmacopoeia
RH	relative humidity
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TYMC	Total Combined Yeast and Mould Count
UPLC	ultra-high performance liquid chromatography
UV	ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Therakind Limited submitted on 4 December 2014 an application for Marketing authorisation to the European Medicines Agency (EMA) for Jylamvo, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 May 2013. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications.

Jylamvo is for use in adults, adolescents and children aged 3 years and over.

In rheumatological and dermatological diseases

- Active rheumatoid arthritis in adult patients.
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- Severe, treatment-refractory, disabling psoriasis, which does not respond sufficiently to other forms of treatment such as phototherapy, PUVA therapy and retinoids, and severe psoriatic arthritis in adult patients.

In malignant tumours and haemoblastosis

Malignant tumours and haemoblastosis as part of a polychemotherapy regimen insofar as oral treatment is indicated.

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, two bioequivalence studies and appropriate non-clinical and clinical data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

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: METHOTREXAT “Lederle” 25mg-vials
- Marketing authorisation holder: Pfizer Corporation Austria Ges.m.b.H
- Date of authorisation: 29-03-1984
- Marketing authorisation granted by:
  - Member State (EEA) : Austria
- Marketing authorisation number: 17.626

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

- Product name, strength, pharmaceutical form: METHOTREXAT “Lederle” 25mg- vials
- Marketing authorisation holder: Pfizer Corporation Austria Ges.m.b.H
- Date of authorisation: 29-03-1984
- Marketing authorisation granted by:
  - Member State (EEA) : Austria
- Marketing authorisation number: 17.626

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: METHOTREXAT “Lederle” 2.5mg tablets
- Marketing authorisation holder: Pfizer Corporation Austria Ges.m.b.H.
- Date of authorisation:15-01-1959
- Marketing authorisation granted by:
  - Member State (EEA): Austria
  - Marketing authorisation number(s): 10.496
- Bioavailability study number(s): MTX002

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Bruno Sepodes

- The application was received by the EMA on 4 December 2014.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2015. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 June 2015.
- During the meeting on 9 July 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.

- During the meeting on 23 July 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 12 September 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 October 2016.
- During the PRAC meeting on 27 October 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 10 November 2016, 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 22 December 2016.
- During the PRAC meeting on 3 January 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 January 2017.
- During the meeting on 26 January 2017, 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 Jylamvo on 26 January 2017.
- The CHMP adopted a report in similarity of Jylamvo with Atriance, Xaluprine, Blincyto and Iclusig on 26 January 2017.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Methotrexate (MTX) has been used extensively for the treatment of cancer (particularly acute lymphoblastic leukaemia [ALL]) since the mid-1950s following authorization by the US Food and Drug Administration (FDA) in 1953 and has been authorised in the EU since the 1960s. The authorised indications for MTX have since been extended beyond cancer to include treatment of autoimmune and inflammatory diseases: adult rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and psoriasis. All of these indications are chronic debilitating/ life-threatening illnesses requiring long-term treatment.

Thus, MTX is a well-established drug which has been used safely and effectively in humans for over 50 years in the European Union (EU). It is currently authorised for long-term use in children and adults by oral and parenteral routes of administration.

In addition to its use for adult RA and psoriasis, oral MTX plays a pivotal role in the treatment of children with ALL and JIA. However, the only oral presentations authorised and marketed in the community currently are tablets

available in 2.5mg, 5mg and 10mg strengths. The majority of children less than 12 years old (and many adolescents and adults) cannot swallow tablets. In addition, the authorised doses necessitate that MTX is administered to children at doses related to their body size. As a consequence tablets have to be split and/or crushed, exposing the carer and environment to cytotoxics and providing inaccurate dosing. Alternatively unlicensed liquid formulations, prepared extemporaneously or as ready-prepared 'specials', are prescribed and dispensed. This unlicensed use potentially exposes children to medication errors, inappropriate excipients and the consequential higher risk of adverse reactions or inadequate efficacy.

2.1.2. About the product

Methotrexate Oral Solution has been developed as an alternative oral presentation to the authorised tablet form. The formulation has been developed primarily for use in children (but can also be used in adolescents and adults unable to swallow tablets) and account has been taken of the EMA guideline on pharmaceutical development of medicines for paediatric use: EMA/CHMP/QWP/805880/2012 Rev. 1. The formulation contains the following excipients: Polyethylene Glycol (PEG) 400, Glycerol, Orange flavour, Sucralose, Ethyl parahydroxybenzoate (E214), Sodium methyl parahydroxybenzoate (E219), Citric acid, Tri-sodium citrate and Purified water. The liquid will be administered with an oral dosing syringe which will allow administration of accurate doses (based on body surface area).

The proposed indications were:

Jylamvo is for use in adults, adolescents and children aged 3 years and over.

In rheumatological and dermatological diseases

- Active rheumatoid arthritis in adult patients.
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- Severe, treatment-refractory, disabling psoriasis, which does not respond sufficiently to other forms of treatment such as phototherapy, PUVA therapy and retinoids, and severe psoriatic arthritis in adult patients.

In malignant tumours and haemoblastosis

Malignant tumours and haemoblastosis as part of a polychemotherapy regimen insofar as oral treatment is indicated.

The name of the medicinal product was changed during the procedure from Methotrexate Therakind 2 mg/ml Oral Solution to Jylamvo.

2.2. Quality aspects

2.2.1. Introduction

Jylamvo is presented as an oral solution containing 2 mg/ml of methotrexate as the active substance.

Other ingredients of the oral solution are polyethylene glycol (PEG) 400, glycerol, sucralose, ethyl parahydroxybenzoate (E214), sodium methyl parahydroxybenzoate (E219), orange flavour, citric acid monohydrate, tri-sodium citrate and purified water.

The product is available in amber type III glass bottles with tamper evident child-resistant closures. Each pack contains one bottle, an LDPE bottle adaptor and a white polypropylene dosing syringe, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of methotrexate is (*S*)-2-[4-[[(2,4-diaminopteridin-6-yl)methyl]methylamino]-benzoylamino]-pentanedioic acid corresponding to the molecular formula $C_{20}H_{22}N_8O_5$. It has a relative molecular mass of 454.4 g/mol and the following structure:

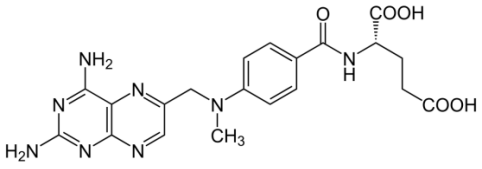

***Figure 1** Structure of methotrexate.*

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

The active substance appears as an orange or yellow, crystalline, hygroscopic powder, practically insoluble in water and alcohol, freely soluble in dilute solutions of alkali hydroxides and carbonates and slightly soluble in 6N hydrochloric acid. Its pKa was found to be 4.7 and its partition co-efficient -1.85.

Manufacture, characterisation and process controls

The information regarding manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation, manufacturing process development and packaging material is covered by the CEP. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification complies with the specifications and test methods of the Ph. Eur. monograph. The CEP includes an additional control for the residual solvent ethanol which is performed by GC. Satisfactory information regarding the reference standards used has been provided.

Batch analyses data for three batches were provided. The results are consistent from batch to batch and comply with the specification in all cases.

Stability

The proposed re-test period of 5 years and packaging material for methotrexate are covered by the CEP.

2.2.3. Finished medicinal product

Pharmaceutical development

The finished product is an oral solution containing 2 mg/ml of methotrexate as the active substance.
The aim of the pharmaceutical development programme was to design a palatable multi-dose oral liquid formulation of methotrexate, suitable for dosing to paediatric patients and bioequivalent to a currently licensed methotrexate product, Ebetrexat 10mg tablets. Jylamvo was developed as an orange flavoured, preserved, oral liquid in a 60 ml presentation with an oral dosing syringe 10 ml. The composition of the orange flavouring has been provided.

The initial pre-formulation studies aimed to establish a suitable pH for the formulated finished product, optimise the antibacterial preservative agents and identifying suitable solvents and buffer.

The subsequent formulation studies investigated a range of formulations that optimised the concentration of the buffer systems and solvents whilst investigating any compatibility issues with the flavourings and sweeteners. Satisfactory justifications regarding the inclusion of buffer components, co-solvents and preservatives in the formulation were provided. A further study was conducted, confirming the palatability of the formulation (bioequivalence clinical study [MTX001]. Sufficient information regarding the suitability and safety of the selected orange flavouring for use in pharmaceutical products, when administered via the oral route, was provided.

Jylamvo is an aqueous based multi-dose product and therefore a preservative was included in order to maintain the microbiological integrity of the product during its shelf life for both the unopened bottle and during use. The effectiveness of the preservatives has been demonstrated via the preservative efficacy test outlined by Ph. Eur. 5.1.3.

Jylamvo is packed in a 75 ml amber glass bottle (containing 60 ml extractable volume of solution) and closed with a child-resistant cap. The packaging materials comply with the current EU relevant regulations. The child resistance feature of the caps complies with EN ISO 8317. The bottle is presented in a carton containing a bottle neck adaptor and a 10 ml white polypropylene oral dosing CE marked syringe. The accuracy of withdrawn dose was studied with the proposed syringe. All results at each dose level, met the criteria of less than 10% variation. Therefore, the syringe is deemed suitable for use across the entire dosing range.

Manufacture of the product

The manufacturing process can be considered as a standard process which comprises the following main steps: dissolving the active substance and excipients in a buffer solution through successive steps of addition, dissolution and homogenization. Prior to filling the pH is adjusted and the solution is filtered before being filled into bottles which are then sealed with a cap.

The manufacturing process and equipment is satisfactorily described. Critical steps have been defined and the applied in-process controls are adequate and justified. The proposed holding time of bulk solution was justified.

The process has been validated with three pilot scale batches manufactured using the mixing principles intended for commercial production. All three batches have been monitored in the formal ICH stability programme and one of them has been used for the pivotal clinical study. The process has subsequently been optimised and scaled from the pilot scale to the intended commercial scale. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Production scale validation batches of Jylamvo will be manufactured and tested according to the proposed process validation protocol which is acceptable since the process is a standard one and the validation protocol is considered adequate.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (UPLC retention time and UV), assay (UPLC), related substances (UPLC), preservative identity (UPLC), sodium methyl parahydroxybenzoate assay (UPLC), ethyl parahydroxybenzoate assay (UPLC), pH (Ph. Eur.), preservative efficacy (at shelf life: Ph. Eur.), uniformity of mass of delivered dose from multi-dose container (Ph. Eur.), fill volume (weight), relative density (Ph. Eur.) and microbial purity (Ph. Eur.).

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

Batch analysis data on five pilot scale batches and two commercial scale batches were presented. All batches are representative of the commercial formula and process and meet the specification limits.

Stability of the product

Stability data from three pilot scale batch of finished product stored for up to 24 months at 5 ºC, 25 ºC / 60% RH, up to 12 months at 30 ºC / 60% RH and for 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Results on one smaller laboratory scale batch stored for 24 months at 5 ºC and 25 ºC / 60%RH and 6 months at 40 ºC / 75% RH were also provided. The stability batches were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, methotrexate assay, related substances, sodium methyl parahydroxybenzoate assay, ethyl parahydroxybenzoate assay, pH, microbial purity and preservative efficacy testing. The methods used were the same as for release testing and are stability indicating. The results indicate that the samples stored at 5 ºC and 25 ºC / 60% RH complied with specification at all time-points tested. No trends were observed. However, data from two batches showed out of specification results for an individual impurity at the 12 month time-point in samples stored at 30 ºC / 60% RH; all other parameters complied with the specification. In addition, all batches stored at 40 ºC / 75% RH gave out of specification results for assay, related substances and preservative assay at the 6 month time-point (two batches at 3 months). Based on these findings appropriate storage conditions have been proposed (SmPC section 6.4).

In-use stability testing was performed on two pilot-scale batches stored at 25 °C / 60% RH for 3 months. The protocol utilised is identical for both batches, one at the beginning of the proposed shelf life and a second towards the end of it. The following parameters were evaluated: appearance, pH, methotrexate assay, related substances, sodium methyl parahydroxybenzoate assay, ethyl parahydroxybenzoate assay and microbial purity. No significant changes were observed to any of the measured parameters over the 3 months' testing for the first batch.

The in-use stability study with the second batch was initiated following storage at ambient conditions for 20 months, the originally proposed shelf life being 24 months at the time. The results for appearance, pH, methotrexate assay, preservative assay and microbial purity all remained within specification throughout the duration of the study and support the proposed in-use shelf life of 3 months. However, the results for methotrexate assay, preservative assay and related substance were already close to the specification limit when this study was initiated. Although the data for methotrexate assay and preservative assay remained within specification, the data generated for an individual impurity and consequently total impurities was just above the proposed limits. Consequently the proposed shelf life was limited from 24 to 20 months. Although the in-use study has been conducted beyond the proposed shelf life of 20 months, the data continue to support the proposed in-use shelf life of 3 months as there is very little change in any of the parameters investigated over the period of the study.

The photostability studies were performed on one laboratory-scale batch of Jylamvo exposed to UV light for 3 months. The following parameters were evaluated: appearance, pH, assay and related substances. Results showed no change in the appearance or pH of the solution. However, there was a decrease in assay and a corresponding increase in related substances. After 3 months direct intense UV light, Jylamvo just fails the specification for an individual impurity. However, the data also demonstrate that the primary packaging provides sufficient protection from light. Photostability studies have also been conducted on one pilot scale batch in line with the guidance set out by ICH Q1B and demonstrated that the product is light sensitive but also that a type III amber glass bottle provides sufficient protection.

Based on the overall data presented, the revised shelf life of 20 months, the proposed in-use shelf life of 3 months and the proposed storage conditions “Do not store above 25ºC” and “Keep the bottle tightly closed”, as mentioned in the SmPC sections 6.3 and 6.4, are supported.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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

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

2.3.2. Pharmacology, Pharmacokinetics and Toxicology

The MTX oral solution has been developed as a hybrid generic presentation with reference to both an authorised injection (originator) and oral tablet formulation. The Applicant has not conducted any new non-clinical studies.

Methotrexate, a folic acid antagonist, is an established antineoplastic agent and immunosuppressant drug that has been used safely and effectively in humans for over 50 years in the European Union (EU) and USA. The pharmacology, toxicity, kinetics and clinical adverse effects of methotrexate following oral and systemic administration are well known.

For the nonclinical overview of methotrexate and the excipients in the oral solution, reference has been made to relevant published scientific literature and pharmacological monographs, to provide an integrated and critical assessment.

The non-clinical overview provided by the applicant was consistent with the known pharmacological, pharmacokinetic and toxicological profile of methotrexate. The toxicological documentation on the active ingredient and formulation excipients is considered to be satisfactory and does not raise any new concerns.

2.3.3. Ecotoxicity / environmental risk assessment

Summary of environmental fate / effects for

Substance (INN / Invented Name):			
PBT screening	Method	Results	**Conclusion**
Bioaccumulation potential- log K_{ow}	EPI* (EPA) – expkow database	log K_{ow} = -**1.85** (≤ 4.5)	Potential PBT (**N**)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log K_{ow} BCF (EPI* - EPA – BCFBAF v3.01)	(≤ 3) 3.162 L/KG wet-wt	B **(N)**
Persistence	EPI* (EPA) – BIOWIN v4.10	Not readily biodegradable	**P**
Toxicity (fish)			**Not available**
PBT-statement :	The compound is not considered as vP and vB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$	0.021	µg/L	≥0.01 threshold
Refined $PEC_{surfacewater}$	Assuming the different indications: 0.0059 0.0086 0.0051 0.00019	µg/L	≤0.01 threshold
Other concerns (e.g. chemical class)			**N**

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	EPI* (EPA) – KOCWIN v2.00 MCI method	*Log* K_{oc} = 3.167 K_{oc} = 1 468 L/Kg	K_{oc}≤10 000 L/Kg Low adsorption potential
Ready Biodegradability Test	EPI* (EPA) – BIOWIN v4.10	Not readily biodegradable	

Phase II-A Effect studies					
Study type	**Test protocol**	**End point**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition	Bioluminescence inhibition	Growth rate and survival	10	mg/L	

		EC 50			
Daphnia sp. Mobilisation Test	Bioluminescence inhibition	EC 50	>1000	mg/L	
Fish, Early Life Stage Toxicity					**Not available**

The Phase I $PEC_{surfacewater}$ of Methotrexate was calculated according the EMA guideline formula. It exceeds the action limit of 0.01 µg/L (PEC=0.021 µg/L for a DOSEai of 4.29 mg/day). A standard Phase II fate and effects assessment was not performed by the applicant.

The ERA results inserted in this application demonstrated an adsorption coefficient K_{oc}≤10 000 L/Kg, a not readily biodegradable capacity, a BCF of 3.162, a log Kow ≤3 and ≤4.5 and acute toxicological values of EC50 ≥10 mg / L.

A refined $PEC_{surfacewater}$ was performed by the applicant for the following indications: rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and acute lymphoblastic leukaemia (ALL). Different Fpen were calculated for each indication, assuming the highest prevalence values of different diseases.

The refined PEC for the different indications was calculated for the different indications: A) Rheumatoid Arthritis = 0.0059 µg/L; B) Juvenile Idiopathic Arthritis = 0.0086 µg/L; C) Psoriasis = 0.0051 µg/L; D) Acute Lymphoblastic Leukaemia (ALL) = 0.00019 µg/L, resulting in a total refined PEC of 0.01979 = 0.02 µg/L, well above the action limit of 0.01 µg/L. Despite the substance has a Log Kow of -1.28 not being PBT, it could reach the surface water and be toxic for the water species.

The Applicant did not carry out a Phase II environmental fate and chronic effect analysis based on relevant published scientific literature. This was justified by the applicant as the introduction of Jylamvo manufactured by Therakind Limited is considered unlikely to result in any significant increase in the combined sales volumes for all methotrexate containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

However, as Methotrexate is a cytotoxic substance the applicant followed the request of the CHMP to include the following sentence into SmPC (point 6.6) and package leaflet (point 5): “Any unused product or waste should be disposed of in accordance with local requirements for cytotoxic products”.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Methotrexate was provided and was accepted by the CHMP. No additional non clinical studies are considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Jylamvo containing methotrexate. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design. These studies were the pivotal studies.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

The MTX has been developed as a hybrid generic product with reference to Methotrexat "Lederle" 25 mg/ml i.v. – Stechampulle, (Pfizer Corporation Austria Ges.m.b.H., 1210 Wien). Demonstration of bioequivalence against the reference product was not feasible due to the differences in formulation (injection vs oral solution). Thus the applicant provided two bioequivalence (BE) studies to bridge to the clinical data and Product Information. MTX002 compared Jylamvo against Methotrexate “Lederle” 2.5 mg tablets, which belongs to the same global marketing authorisation as the originator injectable product (Methotrexat “Lederle" 25 mg/ml – Stechampulle) and MTX001 compared the oral bioavailability of the 2 mg/mL oral solution with the hybrid product Ebetrexat® 10 mg tablets to provide additional data in support of the oncological indication claimed.

Table 1 Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	MTX001	To compare the to-be-marketed product (Jylamvo), and the reference product (Ebetrexat® 10 mg tablets)	Single-dose, open-label, laboratory blinded, randomised, two-period, two-sequence, cross-over	Oral solution (5 mL of 2mg/mL) OR 10 mg tablet; 10 mg dose; Oral	24	Healthy subjects	Single dose	Complete; full
BE	MTX002	To compare the to-be-marketed product (Jylamvo), and the reference product (Methotrexate “Lederle” 2.5 mg tablets)	Single-dose, open-label, laboratory blinded, randomised, two-period, two-sequence, cross-over	Oral solution (1.25 mL of 2mg/mL) OR 2.5 mg tablet; 2.5 mg dose; Oral	24	Healthy subjects	Single dose	Complete; full

2.4.2. Pharmacokinetics

MTX001

Methods

Study design

The bioequivalence study [**MTX001**] was conducted to compare plasma concentrations of, methotrexate 2 mg/ml oral solution with the hybrid product, Ebetrexat® 10 mg tablets. The study design was a single-dose, randomised, two-period crossover study with a wash-out period of 7 days between doses of methotrexate.

The study comprised:

- Screening period of maximum 21 days;
- Two treatment periods (each of which included a profile period of 72 hours) separated by a wash-out period of 7 calendar days between consecutive administrations of the Investigational Medicinal Product (IMP);
- A post-study visit within 14 to 21 calendar days after the last administration of IMP.

Participants were randomly assigned to treatment sequence, prior to the first administration of IMP.

Each treatment period included a profile period of 72 hours, which commenced with morning dosing of IMP on a 24 hour clinic stay at the study centre.

Participants were admitted to the study centre approximately 11.5 hours before dosing to ensure an overnight fast of at least 10 hours. Participants received either the test or reference product per treatment period, according to the randomisation schedule, under fasting conditions. Participants received each product once and were asked to comment on the taste of the test oral solution. Participants were allowed to leave the study centre 24 hours after administration of IMP, providing they returned for the subsequent blood sample collections.

Pharmacokinetic blood samples were collected at the following times: pre dose and post dose at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours (total number of samples per treatment period: 23). Safety assessments included adverse events (AEs), vital signs, haematology, clinical chemistry and urinalysis.

24 healthy volunteers were planned for inclusion to complete the study with 20 evaluable subjects. Since no drop-outs occurred, all 24 subjects were analysed. Inclusion criteria and details on the test and reference products were also provided.

All subjects received a single 10 mg oral dose of methotrexate (either as 5 ml of 2 mg/ml oral solution or 1 tablet) in each of the two treatment periods, separated by a wash-out period of 7 calendar days.

Test and reference products

Methotrexate 2 mg/mL oral solution (Batch no. THE/13/0103, 100.1%) has been compared to Ebetrexat 10mg tablets (Batch no. DL6270, 99.5%).

Population studied

Twenty-four (24) adult healthy volunteers were screened and entered into the study. All subjects completed

both treatment phases.

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method for methotrexate. The procedures provided in the standard operating procedures of the Bioanalytical Services Division (BASD) were followed during the performance of the method validation and study sample analysis. Independent quality assurance audits (i.e. facility-, process- and study-based) were performed.

Analytical method, VAL 258/01, was validated in accordance with internationally accepted standards as outlined in the FDA and EMA guidelines on bioanalytical method validation, as well as the procedures provided in the standard operating procedures of the Bioanalytical Services Division (BASD).

At the time of validation, the analytical method was shown to provide an acceptable degree of accuracy and precision over the concentration range 1.563 – 800.0 ng/ml based on peak area ratios with a linear calibration curve (y = mx + b) weighted by 1/concentration.

Pharmacokinetic variables

Primary PK Parameters

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration versus time curve (AUC) from time zero to t, where t is the time of the last quantifiable concentration ($AUC_{(0-t)}$)

Secondary PK Parameters

- AUC with extrapolation to infinity ($AUC_{(0-\infty)}$)
- Time to C_{max} (t_{max})
- Percentage of the $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{ex}$)
- Terminal elimination rate constant (λ_z)
- Apparent terminal elimination half-life ($t_{½}$).

Safety Variables:

Medical history, demographic and anthropometric data, haematology, clinical chemistry, serology, urinalysis, AEs, concomitant medication, drugs of abuse and tobacco screen, alcohol breath test, vital signs, ECGs, physical examination.

Statistical methods

The test product was compared to the reference product by means of statistical analysis with respect to the primary PK parameters (Cmax and AUC0-t) using an analysis of variance with *sequence*, *subject(sequence)*, *product* and *period* effects after logarithmic transformation of the data.

Conventional bioequivalence limits (80.00% to 125.00%) were pre-defined in the study protocol.

Results

Data from 24 evaluable subjects were analysed. There was no carry-over effect of methotrexate between the two treatment periods with all pre-dose values in Treatment-period 2 recorded as zero.

Table 2 Summary of plasma methotrexate primary pharmacokinetic parameters (n = 24)

Statistics	**Methotrexate oral solution (Test product)**		***Ebetrexat*® tablets (Reference product)**	
	C_{max} (ng/mL)	**$AUC_{(0-t)}$ (h*ng/mL)**	**C_{max} (ng/mL)**	**$AUC_{(0-t)}$ (h*ng/mL)**
Mean	262.1	882.643	257.0	908.601
(SD)	(53.81)	(170.398)	(56.50)	(174.821)
CV%	20.53	19.31	21.98	19.24

Table 3 Summary of plasma methotrexate secondary pharmacokinetic parameters (n = 24)

Statistics	**T_{max} (h)**	**$AUC_{(0-\infty)}$ (h*ng/mL)**	**λ_z (1/h)**	**$t_{½}$ (h)**	**AUC_{ext} (%)**
Ebetrexat® tablets (Reference product)					
Mean	1.076	926.237	0.194	3.778	1.978
SD	0.305	174.131	0.044	1.071	1.123
Median	1.125	956.263	0.192	3.602	1.774
CV%	28.40	18.80	22.53	28.34	56.79
Methotrexate oral solution (Test product)					
Mean	0.872	900.316	0.195	3.623	2.026
SD	0.197	170.040	0.027	0.515	0.988
Median	0.750	905.850	0.192	3.610	1.898
CV%	22.58	18.89	13.70	14.22	48.78

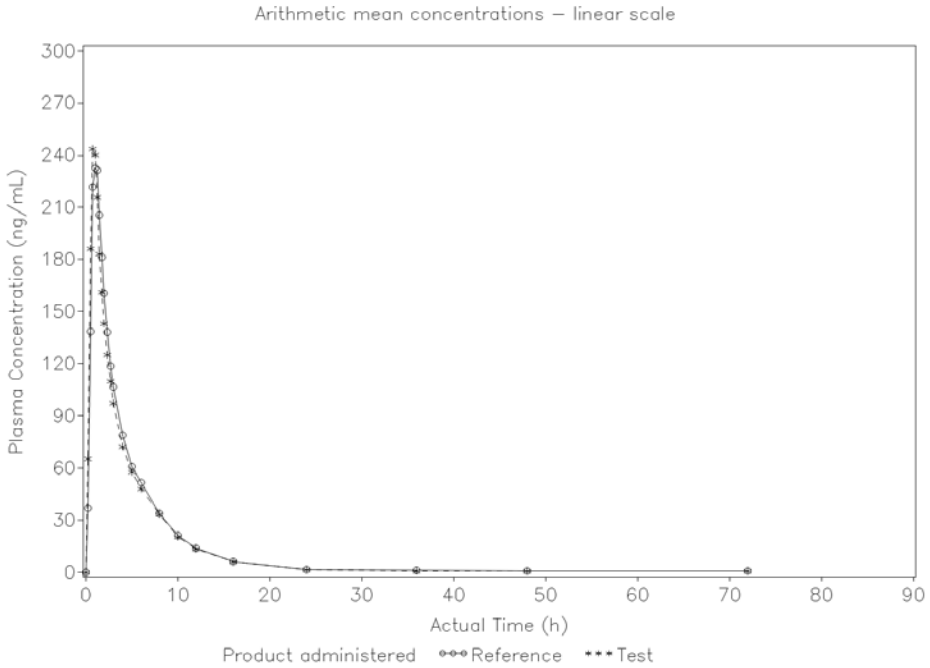

Figure 2 *- Graphical Representation of Methotrexate Concentrations – Arithmetic Mean – Linear Scale*

Bioequivalence was based on the primary PK parameters of methotrexate. For C_{max} the mean ratio was 102.55% with the 90% confidence interval between 95.46% and 110.17%. The mean ratio of the $AUC_{(0-t)}$ was 97.2% with confidence interval between 89.68% and 105.35% (Table below). The median t_{max} was 1.125 hours and 0.750 hours for the reference and the test products, respectively.

Table 4 ***Summary of statistical analyses of plasma methotrexate primary pharmacokinetic parameters (n = 24)***

PK Parameter (unit)	LS Mean (Geometric Mean)		Mean Ratio (%)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Ebetrexat® (Reference product)	Methotrexate (Test product)			
C_{max} (ng/mL)	250.757	257.158	102.55	95.46; 110.17	14.53
$AUC_{(0-t)}$ (h*ng/mL)	891.716	866.728	97.2	89.68; 105.35	16.35

The 90% confidence intervals for all primary PK parameters were within the pre-defined bioequivalence limits of 80.00% to 125.00%.

Safety data

Nine (9) subjects had a total of 13 AEs during the study. Three of the events (nausea, pre-syncope and diarrhoea) were considered by the investigator to be possibly related to the study drug (reference tablet) and 10 as not related to the study drug. All AEs were of mild intensity. No SAEs were reported during this study and none of the AEs were of severe intensity. No AEs related to laboratory variables were reported. No subjects withdrew or were withdrawn from the study.

None of the laboratory findings found to be marginally outside the reference ranges was reported as AEs. Pulse rate and blood pressure remained essentially unchanged throughout the study. Body temperature before dosing on clinic days ranged between 35.8°C and 37.6°C, and no subjects were withdrawn due to pathologically raised body temperature. No clinically relevant abnormal 12-lead ECG results were reported for any of the subjects. No abnormalities were observed in any of the subjects during physical examination. The test product (oral solution) is palatable.

Conclusions

This study met the bioequivalence criteria as all 90% geometric confidence intervals were within the predefined acceptance range.

Both formulations were well tolerated, with no major side effects and no important differences in safety profiles were observed between the treatments, particularly with respect to the number and pattern of adverse events.

Based on the presented bioequivalence study Jylamvo is considered bioequivalent with Ebetrexat® 10 mg tablets.

MTX002

Methods

Study design

The bioequivalence study MTX002 was a single center, single-dose, open-label, laboratory-blind, randomized, two-period, two-sequence crossover study to determine the bioequivalence of an oral solution (2 mg/ml) and tablet formulation containing 2.5 mg methotrexate in at least 20 healthy male subjects under fasting conditions.

Each treatment period included a profile period of 72 hours. Subjects were admitted to the study center approximately 11.5 hours before dosing to ensure an overnight fast of at least 10 hours. Subjects received either the test or reference product per treatment period, according to the randomization schedule, under fasting conditions. The two treatment periods were separated by a wash-out period of 8 calendar days.

Pharmacokinetic blood samples were collected at the following times: pre-dose (0 hours) and at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, 1 hour 45 minutes, 2 hours, 2 hours 20 minutes, 2 hours 40 minutes, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours, 24 hours, 36 hours, 48 hours and 72 hours post-dose (total samples: 23).

Test and reference products

Methotrexate 2 mg/mL oral solution (Batch no. THE/13/0103, 100.1%) has been compared to Methotrexate “Lederle” 2.5 mg tablets (Batch no. C750B, 99.4%).

Population(s) studied

Twenty-four (24) healthy male subjects were enrolled to ensure completion of at least 20 evaluable subjects. All 24 subjects completed the study as per protocol.

Analytical methods

Quantitative analysis of methotrexate in the collected plasma samples were performed by the Bioanalytical Services Division (BASD) using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

The analytical laboratories of BASD have been inspected for their compliance with GLP, based on the OECD guidelines ENV/MC/CHEM (98)17 revised 1997. These inspections have confirmed that the laboratory was able to successfully apply GLP principles in studies that were performed at BASD. Analytical methods had been validated according to internationally accepted standards (as per EMA guidelines for Bioanalytical Method Validation).

Pharmacokinetic variables

Pharmacokinetic Parameters:

Primary Parameters for Methotrexate

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration versus time curve (AUC) from time zero to t, where t is the time of the last quantifiable concentration ($AUC_{(0-t)}$)

Secondary Parameters for Methotrexate

- C_{max}, syringe weight adjusted
- $AUC_{(0-t)}$, syringe weight adjusted
- Time to maximum observed plasma concentration (t_{max})
- Area under the plasma concentration versus time curve, with extrapolation to infinity ($AUC_{(0-\infty)}$)
- Percentage of $AUC_{0-\infty}$ obtained by extrapolation (%AUCex)
- Terminal elimination rate constant (λz)
- Apparent terminal elimination half-life ($t_{½}$)

Safety Variables:

- Hematology
- Clinical chemistry
- Urinalysis
- Adverse events (AEs)
- Concomitant medication
- Electrocardiogram (ECG)
- Vital signs

Statistical methods

The test product was compared to the reference product by means of statistical analysis with respect to the primary PK parameters using an analysis of variance with sequence, subject (sequence), treatment and period

effects after logarithmic transformation of the data. Point estimates and 90% confidence intervals for the "test/reference" geometric mean ratios of these primary PK parameters were tabulated.

Bioequivalence of the test and reference products was assessed on the basis of the 90% confidence intervals for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products using an analysis of variance (ANOVA) in relation to the conventional bioequivalence range of 80.00% to 125.00%.

Results

The data listings, descriptive statistics, statistical analysis and graphs of this study were generated using SAS/STAT® and SAS/GRAPH® software.

Table 5 Summary of Statistical Analyses of Plasma Methotrexate Primary Pharmacokinetic Parameters (n=24)

PK Parameter (unit)	LS Mean (Geometric)		Mean Ratio (%) (Test/Reference)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Methotrexate "Lederle" (Reference product)	Methotrexate (Test product)			
C_{max} (ng/mL)	86.469	89.679	103.71	98.97 ; 108.68	9.5
$AUC_{(0-t)}$ (h•ng/mL)	253.248	250.349	98.86	93.96 ; 104.00	10.3

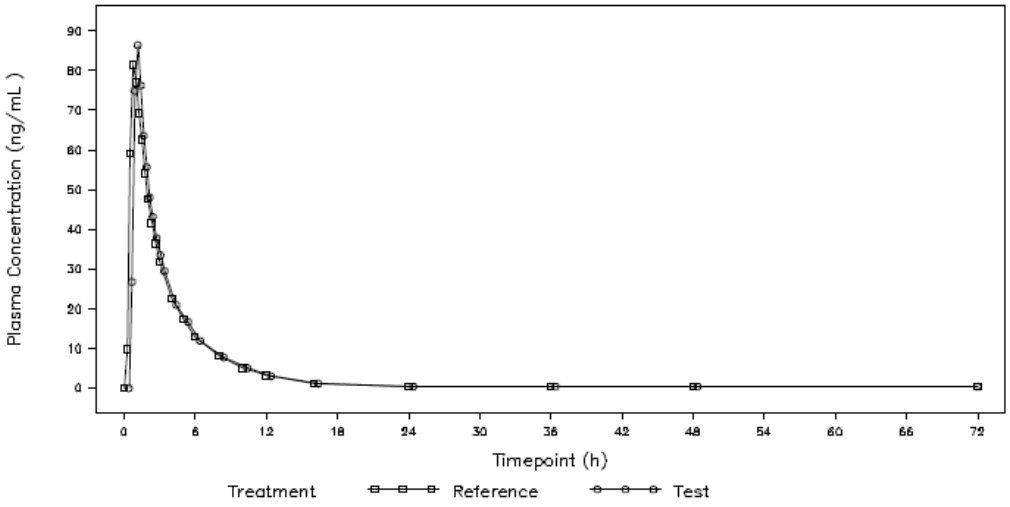

Figure 3 ***Graphical Representation of Methotrexate Concentrations – Arithmetic Mean – Linear Scale***

The median t_{max} was 0.76 hours and 0.75 hours for the reference and the test products, respectively, and was not statistically significantly different between the two products.

Safety data

Study medication was well tolerated by all subjects in this study. No AEs, deaths or SAEs were reported and no subjects were withdrawn due to AEs. Electrocardiogram evaluations performed at screening and at post-study,

were compatible with expectations for a healthy male population. There was no clinically significant and/or consistent drug-related change in vital signs, physical findings or safety laboratory values after oral administration of 2.5 mg methotrexate per treatment period. Laboratory tests found to be marginally outside the reference ranges were considered not to be of clinical relevance.

Conclusions

Based on the presented bioequivalence study Jylamvo is considered bioequivalent with Methotrexate “Lederle” 2.5 mg tablets.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented. The applicant has provided a detailed discussion of the mechanism of action of methotrexate in the treatment of neoplastic diseases, RA, JIA and psoriasis, based on data from the literature.

Methotrexate is a folic acid antagonist that, as an antimetabolite, belongs to the class of cytotoxic active substances. It acts by competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis.

It has not yet been possible to date to clarify whether the efficacy of methotrexate in the management of psoriasis, psoriatic arthritis and chronic polyarthritis is due either to an anti-inflammatory or immunosuppressive effect, or to what extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to this effect.

Highly proliferating tissue such as malignant cells, bone marrow, foetal cells, skin epithelium and mucosa is generally more sensitive to this effect of methotrexate. Cell proliferation is usually greater in malignant tumours than in normal tissue and methotrexate can therefore exert a sustained effect on malignant growth without causing irreversible damage to normal tissue.

In psoriasis, cell proliferation of the epithelium is markedly increased compared with normal skin. This difference in cell proliferation rate is the starting point for the use of methotrexate in particularly severe, generalised, treatment-resistant psoriasis and psoriatic arthritis.

2.4.4. Post marketing experience

No post-marketing data are available. At time of the submission the medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The Jylamvo has been developed as a hybrid generic product with reference to an authorised injection (originator: Methotrexat "Lederle" 25 mg – Stechampulle, of Pfizer Corporation Austria Ges.m.b.H., 1210 Wien); reference was also made to an oral tablet (hybrid) formulation (Ebetrexat® 10 mg tablets, EBEWE Pharma Ges.m.b.H. Nfg. KG, 4866 Unterach, Austria).

The Applicant has not conducted any new clinical efficacy/safety study. To support this application, two bioequivalence studies were conducted using two different products. MTX001 compared the oral bioavailability

of the 2 mg/mL oral solution with the hybrid product Ebetrexat® 10 mg tablets. MTX002 compared the proposed oral solution with Methotrexate "Lederle" 2.5 mg tablets, which belongs to the same global marketing authorisation as the originator injectable product (Methotrexat "Lederle" 25 mg/ml – Stechampulle).
Both studies met the bioequivalence criteria as all 90% geometric confidence intervals were within the predefined acceptance range of 80.00-125.00 %:

MTX001: *Summary of statistical analyses of plasma methotrexate primary pharmacokinetic parameters (n = 24)*

PK Parameter (unit)	LS Mean (Geometric Mean)		Mean Ratio (%) (Test/Ref.)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Ebetrexat® (Reference product)	Methotrexate (Test product)			
C_{max} (ng/mL)	250.757	257.158	102.55	95.46; 110.17	14.53
$AUC_{(0-t)}$ (h*ng/mL)	891.716	866.728	97.2	89.68; 105.35	16.35

MTX002: *Summary of statistical analyses of plasma methotrexate primary pharmacokinetic parameters (n = 24)*

PK Parameter (unit)	LS Mean (Geometric Mean)		Mean Ratio (%) (Test/Ref.)	90% Confidence Interval of Ratio	Intra-individual CV (%)
	Methotrexate oral solution (Test product)	Methotrexate "Lederle" tablet (Ref. product)			
C_{max} (ng/mL)	89.679	86.469	103.71	98.97; 108.68	9.5
$AUC_{(0-t)}$ (h*ng/mL)	250.349	253.248	98.86	93.96; 104.00	10.3

In each study, both Test and Reference formulations were well tolerated. No major side effects and no important differences in safety profiles were observed between the treatments.
As Bioequivalence was demonstrated between the proposed new formulation – Jylamvo – and the two marketed products for oral administration, the absence of new data on methotrexate ADME in the target population and its potential for drug-drug interactions is acceptable.

Methotrexate is an established drug which has been used in humans for over 50 years in the European Union (EU). It is currently authorised for long-term use in children and adults by oral and parenteral routes of administration. In the clinical overview of methotrexate and the oral solution, reference has been made to relevant published scientific literature (pharmacological monographs and peer-reviewed journals) to provide a critical assessment of the pharmacologic, pharmacokinetic, and clinical documentation on the active ingredient.

During the procedure the applicant was requested to reword the indication with regard to the malignant conditions ("Malignant tumours and haemoblastosis as part of a polychemotherapy regimen insofar as oral treatment is indicated") in order to adapt them to oncology indications only where oral methotrexate regimens are currently established. In view of the updated dosing guidelines released by the European Society of Medical Oncology considering parenteral methotrexate therapy only without mentioning an oral route for a number of cancers (gestational trophoblastic disease, breast cancer, follicular lymphoma, Hodgkin's lymphoma, mantle cell lymphoma, multiple myeloma, myelodisplastic syndromes, osteosarcoma and head and neck cancer [http://www.esmo.org/Guidelines]) and considering that the proposed parenteral doses are usually much higher than those proposed for oral administration, the applicant proposed to delete all oncological indications,

with the exception of ALL for which a suitable oral dose has been established for methotrexate. This was accepted by the CHMP and adequate dosing recommendations were included into the SmPC.

Taking into account that Methotrexate should be used with caution in patients with impaired renal function because of the unpredictable pharmacokinetics with a risk for fatal pancytopenia, the applicant updated the SmPC with dose adjustment tables to be applied to patients with renal impairment with rheumatic diseases and ALL.

In the proposed SmPC food intake recommendation was different depending on dose with a fasting recommendation at doses >15 mg and intake independently of food at doses <15 mg. Although the presence of a food effect was not assessed by the Applicant with the proposed methotrexate oral solution, significant food effect is not expected with a solution formulation, since there is no drug release from the formulation as methotrexate is completely dissolved at the time of administration. As these dosing recommendations could not be supported for the oral solution, the applicant deleted these recommendations from section 4.2 of the SmPC with which the CHMP agreed.

2.4.6. Conclusions on clinical aspects

Methotrexate is an established medicinal product which has been used in humans for over 50 years in the European Union (EU). It is currently authorised for long-term use in children and adults by oral and parenteral routes of administration. As demonstration of bioequivalence was not feasible against the reference product due to differences in formulation, two bioequivalence studies were provided. Bioequivalence to Methotrexate “Lederle” 2.5 mg tablets provided the bridge to the clinical data and product information of the originator including the rheumatologically indications.

Additionally and in support of the indication ALL, the applicant demonstrated bioequivalence to Ebetrexat® 10 mg tablets, an oral formulation of methotrexate which is authorised in oncological indications. The claimed oncological indication ALL for Jylamvo was further supported by dosing guidelines released by the European Society of Medical Oncology which define a suitable oral dose for methotrexate in the treatment of ALL.
As dosing guidelines released by the European Society of Medical Oncology only consider oral methotrexate therapy for ALL, and no further justification could be provided to maintain the broader oncological indication of malignant tumours and haemoblastosis as licenced for Ebetrexat® 10 mg tablets, the company agreed to limit the oncology indications to ALL, for which a suitable oral dose has been established for methotrexate.

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:

The PRAC considered that the risk management plan version 4.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

Safety concerns

Summary of safety concerns	
Important identified risks	Increased risk of neoplasia Haematological toxicity Hepatotoxicity Pulmonary toxicity Renal toxicity Medication error; overdose from inadvertent daily instead of weekly dosing in e.g. non-malignant indications
Important potential risks	Bone growth defects in the paediatric population Medication error due to the proposed dosage form (medication errors due to incorrect use of the oral dosing syringe and confusion between mg and ml) Progressive Multifocal Leukoencephalopathy
Missing information	Use in children younger than 3 years

Pharmacovigilance plan

There are no planned activities.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps) HLT: not applicable Increased risk of neoplasia (identified)	Adequately addressed in the proposed text in SmPC: Warning in section 4.4 Listed in section 4.8 Other routine risk minimisation measures - pack size and design - the legal (prescription) - status of the product use restricted to physicians with experience of the various properties of the medicinal product and its mode of action.	None proposed
SOC: Blood and lymphatic system disorders; LLT: Haematological toxicity (identified)	Adequately addressed in the proposed text in SmPC: Discussed in section 4.3 Warning in section 4.4 Discussed in section 4.5 Listed in section 4.8 Other routine risk minimisation measures - pack size and design - the legal (prescription) status of the product - use restricted to physicians with experience of the various properties of the medicinal product and its mode of action.	None proposed
SOC: Hepatobiliary disorders; LLT: Hepatotoxicity (identified)	Adequately addressed in the proposed text in SmPC: Discussed in section 4.2 Discussed in section 4.3 Warning in section 4.4 Discussed in section 4.5 Listed in section 4.8 Other routine risk minimisation measures - pack size and design - the legal (prescription) status of the product - use restricted to physicians with experience of the various properties of the medicinal product and its mode of action.	None proposed
SOC: Respiratory, thoracic and mediastinal disorders; HLT: Respiratory tract disorders NEC (identified)	Adequately addressed in the proposed text in SmPC Warning in section 4.4 Listed in section 4.8 Other routine risk minimisation measures	None proposed

	- pack size and design - the legal (prescription) status of the product - use restricted to physicians with experience of the various properties of the medicinal product and its mode of action.	
SOC: Renal and urinary disorders; HLT: Renal failure and impairment (identified)	Adequately addressed in the proposed text in SmPC: Discussed in section 4.2 Discussed in section 4.3 Warning in section 4.4 Discussed in section 4.5 Listed in section 4.8 Other routine risk minimisation measures - pack size and design - the legal (prescription) status of the product - use restricted to physicians with experience of the various properties of the medicinal product and its mode of action.	None proposed
SOC: Injury, poisoning and procedural complications LLT: Circumstance or information capable of leading to medication error (identified)	Adequately addressed in the proposed text in SmPC and PIL: SmPC: Discussed in section 4.2 Warning in section 4.4 Discussed in section 4.9 PIL: Warning in section 2 Discussed in section 3 Discussed in Annex Other routine risk minimisation measures - pack size and design - the legal (prescription) status of the product - use restricted to physicians with experience of the various properties of the medicinal product and its mode of action.	- Educational material for HCPs - Questionnaire to further collect information on medication errors
SOC: Musculoskeletal and connective tissue disorders; LLT: Bone development disorder (in the paediatric population) (potential)	Routine pharmacovigilance monitoring and signal detection. Other routine risk minimisation measures - pack size and design - the legal (prescription) status of the product - use restricted to physicians with experience of the various properties of the medicinal product and its mode of action.	None proposed
SOC: General disorders and administration site conditions; LLT: Medication error (due to the proposed dosage form) (potential)	Adequately addressed in the proposed text in PIL and SmPC: PIL: Information in section 3 Information in section 6	- Educational material for HCPs - Questionnaire to further collect information on medication errors

	Information in Annex SmPC: Information in section 1 Information in section 2 Information in section 4.2 Information in section 6.5 Other routine risk minimisation measures - pack size and design - the legal (prescription) status of the product - use restricted to physicians with experience of the various properties of the medicinal product and its mode of action..	
SOC: Nervous system disorders: LLT: Progressive Multifocal Leukoencephalopathy (potential)	Adequately addressed in the proposed text in SmPC: Discussed in section 4.2 Listed in section 4.8	None proposed
Use in children younger than 3 years (missing information)	Adequately addressed in the proposed text in SmPC: Discussed in section 4.1 Discussed in section 4.2	None proposed

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

To support this application, two bioequivalence studies were conducted. One of the studies, Study MTX002, compared the proposed oral solution with Methotrexate “Lederle” 2.5 mg tablets, which belongs to the same global marketing authorisation as the originator injectable product (Methotrexat “Lederle" 25 mg/ml – Stechampulle), in order to allow the bridging to the clinical data and Product Information of the originator. The other study, Study MTX001, compared the oral bioavailability of the 2 mg/mL oral solution with the hybrid product Ebetrexat® 10 mg tablets providing additional supportive data.

The test formulation of Jylamvo met the protocol-defined criteria for bioequivalence when compared with both products. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%].

Bioequivalence of the two formulations was demonstrated.

The proposed indications for Jylamvo were identical to those of the reference product Methotrexat “Lederle” 2.5mg tablets for all rheumatologically and dermatological disorders. The claimed oncological indications were in line with Ebetrexat® 10 mg tablets:

Jylamvo is for use in adults, adolescents and children aged 3 years and over.

In rheumatological and dermatological diseases

- Active rheumatoid arthritis in adult patients.
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- Severe, treatment-refractory, disabling psoriasis, which does not respond sufficiently to other forms of treatment such as phototherapy, PUVA therapy and retinoids, and severe psoriatic arthritis in adult patients.

In malignant tumours and haemoblastosis

Malignant tumours and haemoblastosis as part of a polychemotherapy regimen insofar as oral treatment is indicated.

Methotrexate is an established drug which has been used in humans for over 50 years in the EU. It is currently authorised for long-term use in children and adults by oral and parenteral routes of administration. The pharmacology, toxicity, kinetics and clinical adverse effects of methotrexate following oral and systemic administration are well known.

The reference product Methotrexat “Lederle" 25 mg/ml - Stechampulle is authorised for indications in oncology, which is not the case for Methotrexate “Lederle” 2.5 mg tablets to which bioequivalence was demonstrated to provide the scientific bridge to the clinical data and product information. Additional data to support the indications in oncology was provided by the results of the bioequivalence study to Ebetrexat® 10 mg tablets. Furthermore several protocol treatments for cancers use methotrexate as a well-established drug, and in ALL methotrexate oral treatment has a well-established role in maintenance.

However, in view of the updated dosing guidelines released by the European Society of Medical Oncology in which only for ALL a suitable oral dose has been established for methotrexate, the oncological indication initially claimed was adapted to “*Maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over*.”

In general, the incidence and severity of acute side effects of methotrexate are related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate to the target organs The most common dose-related toxic effects of methotrexate are on the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leucopenia, thrombocytopenia, and anaemia may all occur.

Methotrexate is associated with liver damage, both acute (notably after high doses) and, more seriously, chronic (generally after long-term use). Hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity, and have led to eventual death. Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions (sometimes severe), alopecia, and ocular irritation. Neurotoxicity may be seen: leukoencephalopathy, paresis, demyelination are associated particularly with intrathecal use and are more likely when cranial irradiation is also given. Intrathecal use may also produce arachnoiditis, an acute syndrome of headache, nuchal rigidity, back

pain, and fever. Other rarer reactions may include megaloblastic anaemia, osteoporosis, precipitation of diabetes, arthralgias, necrosis of soft tissue and bone, and anaphylaxis. Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired (this may be reversible). Like other folate inhibitors it is teratogenic, and it has been associated with foetal deaths. Lymphomas (generally reversible on withdrawal of treatment) have occasionally been reported with methotrexate therapy, although the association has been questioned [Martindale, 2014]. The respective side effect profile is adequately described in the SmPC in accordance with the reference product and appropriately managed by the adopted RMP.

As Jylamvo, in contrast to the reference product, combines oncological and rheumatological indications in an oral formulation the wording in section 4.4 of the SmPC was strengthened and a box warning was included to warn health care professionals about the risks associated to prescribing or dispensing the correct dose of the product according to the corresponding indication and to advise them that Patients with rheumatological or dermatological diseases must be informed unequivocally that treatment is to be taken just once a week and not daily.

Further risk minimization measures such as separating the oncological and rheumatologically indications were not considered necessary at this time. Together with the adopted educational material to be put in place the risk is considered sufficiently managed.

A positive benefit/risk ratio 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 additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Jylamvo is not similar to Atriance, Xaluprine, Blincyto and Iclusig within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

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

<u>In rheumatological and dermatological diseases</u>

- Active rheumatoid arthritis in adult patients.
- Polyarthritic forms of active, severe juvenile idiopathic arthritis (JIA) in adolescents and children aged 3 years and over when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- Severe, treatment-refractory, disabling psoriasis which does not respond sufficiently to other forms of treatment such as phototherapy, psoralen and ultraviolet A radiation (PUVA) therapy and retinoids, and severe psoriatic arthritis in adult patients.

<u>In oncology</u>

- Maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Jylamvo in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that, in each Member State where Jylamvo is marketed, all healthcare professionals who are expected to prescribe or dispense Jylamvo have access to the following educational package:

- The Summary of Product Characteristics
- The patient leaflet
- Guide for healthcare professionals

The **Guide for healthcare professionals** shall contain the following key elements:

- Remarks on the importance of reporting ADRs

- A statement about the responsibility of the prescribing physician to determine which patients may be suitable for home or self-administration of Jylamvo. With every prescription, healthcare professionals should advise the patient and/or caregiver on how to measure the prescribed dose.
- Detailed description regarding strength of the solution and the dose volumes to help clarify the appropriate dose of the oral solution.
- Information on treatment with Jylamvo, administration and posology. Doctors should always prescribe the dose in mg with ml equivalence based on the correct age of the patient.
- Potential fatal overdose due to medication errors (ME)
- Causes of ME, severity and outcomes.
- Reminder to counsel the patients about inadvertent daily instead of weekly dosing in e.g. non-malignant indications
- Recommendation to monitor patients for signs and symptoms of overdose (these predominantly affect the haematopoietic and gastrointestinal systems)
- Management of overdose (including the use of calcium folinate and dose interruption).