LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Methotrexate Afortas
(methotrexate)

SE/H/2473/01/DC

This module reflects the scientific discussion for the approval of Methotrexate Afortas. The procedure was finalised on 2024-11-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Methotrexate Afortas, 2,5 mg, Tablet.

The active substance is methotrexate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Methotrexate Afortas, 2,5 mg, tablet is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ledertrexato, 2,5 mg tablet authorised in Portugal since 1984, with Laboratórios Pfizer, Lda. as marketing authorisation holder.

The reference product used in the bioequivalence study is Ledertrexato, 2,5 mg tablet from Portugal with Laboratórios Pfizer, Lda. as marketing authorisation holder.

Potential similarity with orphan medicinal products
The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal products under market exclusivity.

Conclusion
Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Methotrexate Afortas is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Besponsa. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Besponsa in the treatment of B-cell acute lymphoblastic leukaemia, does not prevent the granting of the marketing authorisation of Methotrexate Afortas. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Methotrexate Afortas is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Blincyto. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Blincyto in the treatment of acute lymphoblastic leukaemia, does not prevent the granting of the marketing authorisation of Methotrexate Afortas. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Methotrexate Afortas is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Kymriah. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Kymriah in the treatment of B-lymphoblastic leukaemia/lymphoma, does not prevent the granting of the marketing authorisation of Methotrexate Afortas. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Methotrexate Afortas is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Tecartus. Therefore, with reference to Article 8 of

Regulation (EC) No. 141/2000, the existence of any market exclusivity for Tecartus in the treatment of acute lymphoblastic leukaemia, does not prevent the granting of the marketing authorisation of Methotrexate Afortas. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of methotrexate are well known. As methotrexate is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Impurities
Shelf-life limits above the qualification threshold (0.2%) have been proposed for Impurity B (NMT 0.5%) and Impurity C (NMT 1.0%) and Impurity I (NMT 0.3%). A toxicological justification has been provided as summarized below.
Methotrexate-related impurity B is 99% similar to the parent methotrexate and Impurity C is 95% similar to methotrexate (as determined by using QSAR Toolbox 4.4.1 – a software that ranks the similarity of chemicals based on physicochemical and other data). Impurity B or aminopterin, like methotrexate, is a known antifolate compound. The mutagenicity of the methotrexate-related impurities B and C along with the parent API methotrexate, were investigated in a validated QSAR software program (Leadscope), that includes both expert rule- and statistical-based models, see below.

Model	Methotrexate	Impurity B	Impurity C
Genetox Expert Rule: Bacterial Mutation	Positive	Indeterminate	Negative
Genetox Statistical Rule: Bacterial Mutation	Positive	Negative	Negative

Methotrexate and Impurity B share the same alerting structure, identified as the aryl amine. Methotrexate has mixed results in the Ames assay (Benedict 1977; IARC 1987) but is positive in mammalian mutagenicity assays (IARC 1987) and is not classified as a human or mammalian carcinogen based on *in vivo* animal studies. Given that all three are likely antifolate compounds it is also likely that they share with methotrexate the ability to cause mutagenicity in some mammalian bioassays but are not carcinogenic. Impurity C lacks the phenyl amine alerting structure (where there is a carbonyl instead) and is therefore predicted negative for genotoxicity.

Impurity B (aminopterin) is an antifolate with clinical applications (Cole 2008). It has the same mechanism of action as methotrexate but is more bioavailable and has a longer systemic half-life, in part explaining its increased toxicity (Siritnak 1975; Cole 2008). It is about 18 to 20- fold more toxic than methotrexate. The maximum tolerated clinical dose (MTD) of aminopterin is an oral 2 mg/m^2 in two doses 12 hours apart which is equivalent to 108 µg/kg/day or 5,400 µg/day fora 50 kg adult (Nair 2016; Ratliff 1998). Dividing this aminopterin clinical dose of 5,400 µg/day by the current MDI of 228 µg/day is 4.2%, and therefore at the proposed specification limit in methotrexate aminopterin is over 20-fold below the clinical MTD. Since the aminopterin impurity could contribute significantly to the overall toxicological profile of the drug product the specification limit for aminopterin should be kept low based on the clinical data and the potency of this antifolate compound. A NMT 0.5% equates to an MDI of 380 µg/day and be 14-fold below the clinical MTD for aminopterin.

Impurity C (methopterin), a known impurity of methotrexate, does not share the same mutagenic alerting structure with methotrexate as do impurity B. Of the impurities, "C" is the most similar to folic acid (Cabrerizo 2005), sharing the carbonyl group and lacking one of the amine groups on the pteridine ring. In studies impurity C was found to be less potent than methotrexate as an inhibitor of dihydrofolate reductase isolated from L1210 mouse leukemia cells (Valerino 1972), which is consistent with its structure being more similar to folie acid (Cabrerizo 2005) and less like the other methotrexate analogues which have an intact pteridine ring with a primary amine (Palmer 1988; Rosowsky 1985; Montgomery 1979). Therefore, Impurity C is likely to be less toxic than either methotrexate or the analogue (i.e. Impurity B) and more like folic acid, an endogenous compound. A daily intake of 760 µg/day of Impurity C at the specification limit of 1.0% of the methotrexate MDD is within the range of values specified in ICH impurity guidance and within the range of TTCs identified in the literature for nongenotoxic compounds.

Environmental Risk Assessment (ERA)
As the procedure was initiated before 1 Sept 2024, the 2006 CHMP ERA guideline is applicable. A Phase I+ ERA waiver based on the total exposure/substitution principle has been provided and was found acceptable. Consumption data (kg/year) for the relevant countries (Denmark, Finland, Norway, and Sweden) was provided between 2018 and 2023, showing that there has been no increase in the total exposure.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Methotrexate Afortas (Methotrexate sodium) with the reference product Ledertrexato.

Pharmacokinetic properties of the active substance

Absorption: Methotrexate has an oral bioavailability of 80-100 % when low doses are administered. Following an oral dose of methotrexate maximal plasma concentrations occur at approximately 1-2 hours. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: The absorption is saturated at higher doses (above 30 mg/m^2).

Elimination: The terminal half-life is 3-10 hours for low-dose treatment and 8-15 hours for high-dose treatment.

Study METHO3821 (2.5 mg, fasting conditions)

Methods

This was a single-dose, two-way crossover study conducted in 28 healthy volunteers (20 completed), comparing Methotrexate sodium, 2.5 mg, tablet with Ledertrexato, 2.5 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of methotrexate were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2021-09-20 and 2021-10-01.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for methotrexate, n=20.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**195.453 ± 39.784**	**68.939 ± 18.749**	**0.75 (0.50-1.67)**
Reference	**191.010 ± 44.694**	**63.478 ± 15.100**	**0.75 (0.50-2.67)**
***Ratio (90% CI)**	**102.49 (96.65-108.69)**	**107.44 (99.03-116.56)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The bioanalytical method was adequately validated.

Based on the submitted bioequivalence study, Methotrexate Afortas, 2.5 mg, tablet is considered bioequivalent with Ledertrexato, 2.5 mg, tablet.

Pharmacodynamics

The Applicant presented in the Clinical Overview a summary of the pharmacodynamic properties of methotrexate. No new clinical data was presented.

Clinical efficacy

No new clinical studies were submitted. The efficacy of methotrexate in the relevant therapeutic

indications has been well documented in clinical studies and literature publications.

Clinical safety
No new clinical studies were submitted. The safety of methotrexate in the relevant therapeutic indications has been well documented in clinical studies and literature publications.

In 2019 (referral EMA/587673/2019), EMA recommended new measures to prevent serious and potentially fatal errors with the dosing of methotrexate for treating inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease. The recommendations resulted from a review of reports that patients are using methotrexate incorrectly despite previous measures to prevent errors. In response to the LoQ, the Applicant has implemented all these additional risk minimisation measures.

Risk Management Plan
The MAH has submitted an updated risk management plan version 0.2 in response to the questions previously raised, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Methotrexate Afortas.

Part II Safety specification

Summary of safety concerns	
Important identified risks	Medication errors due to inadvertent daily instead of once weekly dosing (potential for overdose)
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors due to inadvertent daily instead of once weekly dosing (potential for overdose) (Important Identified Risk)	Routine risk minimisation measures: *SmPC sections 4.2, 4.4 and 4.9* *PL section 2 and 3* Legal status: Prescription only Package: Blisters. Additional risk minimisation measures: Educational material (including a guide for health care professionals and a patient card).	Routine pharmacovigilance activities beyond adverse reactions and signal detection: Targeted follow-up questionnaires for all medication errors resulting in overdose. Additional pharmacovigilance activities: None.

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 0.2 signed 03-Jun-2024 is considered acceptable.

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Jylamvo EMEA/H/C/003756/0000.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Methotrexate Afortas, is found adequate. There are no objections to approval of Methotrexate Afortas, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**
  Prior to launch of the product 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 the product is marketed, all healthcare professionals who are expected to prescribe or dispense the product have access to the following educational package:

• The Summary of Product Characteristics
• The patient leaflet
• Guide for healthcare professionals
• Patient Card

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 the product. With every prescription, healthcare professionals should advise the patient and/or caregiver on how to measure the prescribed dose.
• Information on treatment with the product, administration and posology.
• Information on the importance to fill in prescriptions with clear instructions about once weekly dosing, defined day of intake, and to not use abbreviations;
• The need to inform patients and relatives/carers about the once weekly dosing;
• The pharmacist should counsel the patient about the inadvertent daily instead of once-weekly dosing. • The potential for fatal overdose due to medication errors (ME), including daily instead of once weekly use;
• Causes of ME, severity and outcomes.
• 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).

The patient card shall contain the following key elements:
• Reminder that patients who use methotrexate for an indication requiring a weekly dosing schedule to take the product only once weekly and to write the day of the week for intake on the card
• Inform on serious adverse effects that may be fatal and on the symptoms of overdose and steps to be taken should symptoms arise to enable the patient to seek medical help in time
• Recommendation to always show the card to and alert new HCPs about the once weekly dosing of the patient's methotrexate (e.g. on hospital admission, change of carer, etc.)

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The MAH should implement a targeted follow-up questionnaires for all medication errors resulting in overdose.	From the date of notification of the Commission Decision*

*Referral EMEA/H/A-31/1463

VII. APPROVAL

The decentralised procedure for Methotrexate Afortas, 2,5 mg, Tablet was positively finalised on 2024-11-27.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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