LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Methotrexate Orion Pharma
(methotrexate)

SE/H/1442/01-02/DC
2015-0824, 2015-0825

This module reflects the scientific discussion for the approval of Methotrexate Orion Pharma. The procedure was finalised on 2016-07-06. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Methotrexate Orion Pharma, 2.5 mg is generic application made according to Article 10(1) of Directive 2001/83/EC. However, the application for Methotrexate Orion Pharma, 10 mg, tablets, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC.

The applicant, Orion Corporation applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CZ, DK, EE, FI, HU, IE, IS, LT, LV, NO, PL, SK, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is originator product Methotrexat "Lederle" 2.5 mg and 10 mg Tabletten authorised in Germany since 1985, with Pfizer Pharma GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Methotrexat "Lederle" 10 mg Tabletten from Germany with Pfizer Pharma GmbH as marketing authorisation holder. A Biowaiver for 2.5 mg tablets is applied for.

For approved indications, see the Summary of Product Characteristics.

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

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

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Methotrexate has an oral bioavailability of 80-100 % when low doses are administered. The absorption is saturated at higher doses (above 30 mg/m^2). Following an oral dose of methotrexate maximal plasma concentrations occur at approximately 1-2 hours. The pharmacokinetics of methotrexate is not significantly affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

The pharmacokinetics of methotrexate is non-linear with a less than proportional increase in AUC with increasing dose at higher doses (above 30 mg/m^2; corresponding to an absolute dose of 15-20 mg) due to saturation of active absorption. The pharmacokinetics may thus be considered linear in the dose interval relevant for biowaiver of strengths (2.5-10 mg).

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

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Methotrexate, 10 mg, tablets with Metotrexat Lederle, 10 mg, tablets, under fasting conditions. Blood samples were collected pre-dose and up to 16 hours post-dose. The study design is considered acceptable. Plasma concentrations of methotrexate were determined with an adequately validated LC/MS/MS method. 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%.

Based on the submitted bioequivalence study, Methotrexate, 10 mg, tablets are considered bioequivalent with Metotrexat Lederle, 10 mg, tablets. From a pharmacokinetic point of view, absence of studies with the additional strength 2.5 mg is acceptable, as the pharmacokinetics of methotrexate can be considered linear between 2.5 mg and 10 mg.

IV.2 Discussion on the Clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plans

A Risk Management Plan (RMP) for the Methotrexate 2.5 mg and 10 mg tablet (version 1), valid from 08-07-2015 with data lock point 08-05-2015, was submitted within this application.
The RMP was updated (Version 1.1); with date of final sign off on 16 May 2016.
The RMP was further updated (Version 1.2); with date of final sign off on 23 June 2016.

Safety specification

The following safety concerns have been proposed by the applicant.

Summary of safety concerns	
Important identified risks	• Medication error/dose related toxicity • Hepatotoxicity • Renal and urinary toxicity • Immunosuppression/Immunotoxicity • Gastrointestinal toxicity • Pulmonary toxicity • Haematotoxicity • Administration during pregnancy and lactation
Important potential risks	• Infertility • Use in elderly patients
Missing information	• Use in children under 3 years of age

Pharmacovigilance plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed, which is considered acceptable based on the well-known safety profile of methotrexate.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed, which is considered acceptable based on the well-known safety profile of methotrexate.

RMS recommendation
The RMP is approved.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the package leaflet for Methotrexate 2,5 mg, 10 mg tablets (UK/H/3956/01-02/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the hybrid product, Methotrexate Orion Pharma, is found adequate. There are no objections to approval of Methotrexate Orion Pharma, from a non-clinical and clinical point of view. The product information is acceptable.

The application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure was positively finalised on 2016-07-06.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se