LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metopen
(methotrexate disodium)

SE/H/301/02-11/DC

This module reflects the scientific discussion for the approval of Metopen. The procedure was finalised at 2013-07-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

medac GmbH has applied for a marketing authorisation for Metopen, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection, prefilled pen. The active substance methotrexate disodium is the same as in Metoject, solution for injection, prefilled syringe, 10 mg/ml (SE/H/301/01), marketed by medac GmbH since 2002. This PAR only concerns Metopen, no PAR has been prepared for the previous approved product Metoject, solution for injection, prefilled syringe, 10 mg/ml (SE/H/301/01).
For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Metopen is presented in the form of a solution for injection in prefilled pens containing methotrexate disodium in the concentration of 50 mg/ml. Each pen contains a total dose of 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg or 30 mg. The excipients are sodium chloride, sodium hydroxide and water for injections.

II.2 Drug Substance

The drug substance is methotrexate disodium. This substance is formed *in situ* during drug product manufacture (starting with methotrexate Ph. Eur.)

Methotrexate is included in Ph. Eur and the drug substance complies with the monograph in Ph. Eur. Certificate of suitability, CEP, has been issued for Methotrexate.

Methotrexate is a yellow or orange, crystalline, hygroscopic powder which is practically insoluble in water, in ethanol (96 per cent) and in methylene chloride. The structure of methotrexate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on e.g. polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Metopen prefilled pen is formulated using excipients described in the current Ph Eur. For all raw materials used in the product compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) has been demonstrated.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC when stored below 25°C outer carton in order to protect from light.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The Applicant has in support of this application submitted two local tolerance studies. Since the pharmacodynamics, pharmacokinetics and toxicology of methotrexate are well known local tolerance will be the main aspect in safety assessment.

III.2 Toxicology

One of the two local tolerance studies in rabbit was conducted according to GLP principles. The studies were performed in 2005 and 2006.

Report No. 20070/06 Local tolerance test of methotrexate 50 mg/ml in rabbits after a single intravenous, intramuscular, intraarterial, paravenous and subcutaneous administration
In total six male Himalayan rabbits were injected with a single dose of 50 mg/ml, 0.5 ml/animal, using intravenous, intramuscular, intraarterial, paravenous and subcutaneous administration. The control was 0.9% physiological saline, injected in the same animals under same circumstances on the adjacent side. Forty-eight, 96 hours and 14 days after administration, 2 animals, respectively, were sacrificed and the injection sites were examined macro-and microscopically. Macroscopically and microscopically no test item related changes were noted. No signs of systemic toxicity were seen.

Report No. 19015/05 Local tolerance test, single subcutaneous administration of two methotrexate formulations in rabbit
This study was not GLP compliant. In total 2 Himalayan rabbits, one male and one female, were subcutaneously administered 1.0 or 2.0 ml of 10 mg/ml or 50 mg/ml methotrexate solution, as a single dose. The control was 0.9% physiological saline, injected in the same animals under same circumstances. Local reactions were monitored macroscopically 2, 24, 48 and 96 hours after administration (after 96 hours both animals were sacrified). Macroscopically and microscopically no test item related changes were noted. No signs of systemic toxicity were seen.

III.3 Ecotoxicity/environmental risk assessment

No ERA was provided by the Applicant. Since the higher concentration (50 mg/ml) and the new injection device (pre-filled pen) do not involve the administration of a higher dose (but smaller injection volume), Metoject is not considered to increase the risk to the environment beyond or above that which may be caused by other methotrexate-containing products.

III.4 Discussion on the non-clinical aspects

Two single administration local tolerance studies in rabbit were submitted. One was GLP compliant and covered intravenous, intramuscular, intraarterial, paravenous and subcutaneous administration. No test item related local toxicity or signs of systemic toxicity were seen. The excipients of the methotrexate solution tested in the local tolerance studies were not stated in the study reports. However, since Metoject only contain sodium chloride, sodium hydroxide for pH adjustment and water in addition to methotrexate, the local tolerance of Metoject is regarded adequately tested.
No ERA was provided by the Applicant. However, Metoject is not considered to increase the risk to the environment beyond or above that which may be caused by other methotrexate-containing product products, since the higher concentration (50 mg/ml) and the new injection device (pre-filled pen) do not involve the administration of a higher dose (but smaller injection volume).

IV. CLINICAL ASPECTS

IV.1 Introduction

The active ingredient methotrexate was initially synthesised in 1948. Methotrexate is a folic acid antagonist originally developed as an anti-neoplastic drug for the treatment of leukemias and solid malignancies. In addition methotrexate shows clinical activity in patients with rheumatoid arthritis (RA), psoriasis arthropathy, autoimmune diseases and other proliferative disorders.

IV.2 Pharmacokinetics

The pharmacokinetics of methotrexate is well known and summarized adequately by the applicant in the clinical overview. This application concerns a new strength of a methotrexate solution (50 mg/ml instead of the approved 10 mg/ml) and a new injection device (pre-filled pen instead of pre-filled syringe).

The Applicant has submitted one pharmacokinetic study (study no MC-MTX.9/PH) assessing the bioavailability of Metoject 50 mg/mL (test product) compared with Metoject 10 mg/mL (reference product). The administration of the higher strength (50 mg/mL) of MTX results in similar total exposure in terms of AUC, but somewhat higher maximum concentrations (15-20% higher), compared with the marketed lower strength (10 mg/mL) following both i.m. and s.c. administration. The relevance of these higher concentrations is considered to be clinically insignificant in perspective of the individual dose titration.

IV.3 Pharmacodynamics

Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as anti-metabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriasis arthritis, and chronic polyarthritis is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

IV.4 Clinical efficacy

Metoject solution for injection, pre-filled pen, contains a prefilled syringe with 50 mg/mL methotrexate.
This application concerns the marketing of this prefilled pen of several doses for the treatment of RA, polyarticular JIA, Psoriasis and Psoriatic arthritis. The application is submitted as an application according to Art. 10a of Directive 2001/83/EC – so called "well established use". The company has provided an extensive reference list regarding efficacy and safety. MTX has been marketed and used to treat rheumatology diseases for decades. Despite the development of several new biological agents it remains the standard backbone of treatment of patients with RA. Its efficacy for other indications such as psoriasis and psoriasis arthritis is also well established. Therefore there are no objections from a clinical point of view to approval of the current application on "well established use" basis.

IV.5 Clinical safety

For the treatment of rheumatoid arthritis, psoriasis arthritis and severe psoriasis methotrexate has been used for almost fifty years. Comparable medicinal products are on the market in Germany (e. g. Metex® Injektionslösung 7,5 mg/ml and tablets, Lantarel®, Metex 50 mg/ml solution for injection) and the European Union. Methotrexate solution for injection for treatment of rheumatological diseases in concentrations up to 50 mg/ml is marketed by medac for about 10 years. The 3-year PSUR submitted in 2011 shows that "the benefit-risk profile of methotrexate containing medac products has shown to be in accordance with previous experience".

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This application concerns the marketing of a prefilled pen containing a prefilled syringe with 50 mg/mL methotrexate. 10 different volumes are provided, dose 7.5 mg-30.0 mg in steps of 2.5mg. MTX has been widely used for rheumatologic and dermatological conditions for decades, both orally and administered subcutaneously, and "well established use" is considered to be fulfilled for the subcutaneous administration of the compound. The current strength applied for, 50 mg/ml is currently registered in a prefilled syringe in several European countries. Therefore, this strength has been assessed in an earlier approval process and found to have a positive benefit risk balance.

Further to the amendment of the PU the benefit risk of this product can be considered to be positive.

User consultation
PL information; sections 1, 2, 4, 5 and 6: 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 Metoject 50 mg/ml solution for injection, pre-filled pen. The bridging report submitted by the applicant has been found acceptable.

PL information; section 3 and Instructions for use; PL lay-out: The package leaflet has been evaluated via user consultation studies in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results 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.

The risk/benefit ratio is considered positive and Metopen, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection, prefilled pen is recommended for approval.

VI. APPROVAL

The decentralised procedure for Metopen, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg and 30 mg, solution for injection, prefilled pen was successfully finalised on 2013-07-09.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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