

Public Assessment Report

Scientific discussion

Metoject

(methotrexate disodium)

SE/H/643/01/DC

This module reflects the scientific discussion for the approval of Metoject. The procedure was finalised at 2 October 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Medac GmbH has applied for a marketing authorisation for Metoject, solution for injection, prefilled syringe, 50 mg/mL. The active substance methotrexate disodium is the same as in Metoject, solution for injection, prefilled syringe, 10 mg/mL, marketed by Medac GmbH since 2000. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Metoject is presented in the form of a solution for injection in prefilled syringes containing 54.8 mg/ml of methotrexate disodium which corresponds to 50 mg/ml of methotrexate. The excipients are sodium chloride, sodium hydroxide and water.

II.2 Drug Substance

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

An Active Substance Master File has been provided describing the manufacture of Methotrexate disodium. It is manufactured using Methotrexate as starting material. Methotrexate is included in Ph. Eur and the drug substance complies with the monograph in Ph. Eur. A certificate of suitability, CEP, has been issued for Methotrexate.

II.3 Medicinal Product

The aim of the pharmaceutical development was to administer the active ingredient methotrexate disodium in a high concentrated solution, which covers usually given doses up to 25 mg.

The development of the product has been described, the choice of excipients is justified and their functions explained.

The formulation contains the active ingredient methotrexate disodium in a simple aqueous solution and sodium chloride to enable isotonicity. The active principle can be obtained in two different ways:

- A) by dissolving the drug substance methotrexate in aqueous sodium hydroxide solution in order to generate the soluble methotrexate disodium salt
- B) by application of methotrexate disodium as starting material

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 20 batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. A bracketing design has been used. 18 months stability data have been provided and a shelf-life of 18 months with the storage instruction store below 25°C is judged acceptable.

III. NON-CLINICAL ASPECTS

The applicant submitted two local tolerance studies in support of this application. Since the pharmacodynamics, pharmacokinetics and toxicology of methotrexate are well-known, local tolerance was the main aspect in safety assessment.

III.1 Toxicology

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.

III.2 Ecotoxicity/environmental risk assessment

No ERA was initially provided by the applicant. The assessor agreed that Metoject was not considered to increase the risk to the environment beyond or above that which may be caused by other methotrexate-containing products, since the higher concentration (50 mg/ml) did not involve the administration of a higher dose (but smaller injection volume). However, an ERA was subsequently submitted, and it was judged acceptable.

III.3 Discussion on the non-clinical aspects

There were no objections to approval of Metoject from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application is mainly based on bibliographic documentation and did not contain any new efficacy studies. One report describing a clinical study performed by the applicant; a pharmacokinetic study on the relative bioavailability of Metoject 50 mg/mL (test product) as compared with Metoject 10 mg/mL (reference product), conducted in accordance with GCP guidelines. As part of the written response to the clinical comments, the applicant submitted a retrospective evaluative report of methotrexate in patients with juvenile idiopathic arthritis.

IV.2 Pharmacokinetics

When given in low doses, the bioavailability of MTX is high (80-100%), but decreases at doses above 30 mg/m². Peak serum concentrations are achieved within 1 to 2 hours after an oral dose. MTX is rapidly and completely absorbed following intramuscular (i.m.) administration with peak concentrations occurring within 30 to 60 minutes after an i.m. dose. MTX is distributed to tissues and extracellular fluid with a steady-state volume of distribution of 0.4 to 0.8 L/kg body weight. The plasma protein binding is about 50%. The main elimination pathway for MTX is renal excretion through glomerular filtration and active tubular secretion. Other less important elimination pathways are hepatic metabolism, forming the 7-hydroxy metabolite (7-OH-MTX), and biliary excretion. The plasma versus time profile follows a tri-phasic pattern with a terminal elimination half-life between 3 and 10 hours after low oral doses or 8 to 15 hours after high dose treatment. In the case of renal insufficiency, elimination is delayed significantly. Impaired elimination with regard to hepatic insufficiency is not known.

The administration of the higher strength (50 mg/mL) of MTX resulted in similar total exposure in terms of AUC, but somewhat higher C_{\max} (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 the 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.

The 7-hydroxy metabolite is a 10-fold less potent inhibitor of dihydrofolate reductase than methotrexate.

IV.4 Clinical efficacy

Rheumatoid arthritis

The applicant proposed the following indication for Metoject 50 mg/mL: *treatment of active rheumatoid arthritis in adult patients*, which is not in complete accordance with Metoject 10 mg/mL (treatment of severe, active rheumatoid arthritis in adult patients).

The applicant provided an overview of the efficacy of methotrexate in rheumatoid arthritis based on a review of studies published in the literature. These included (older) placebo-controlled studies, comparative studies of oral versus parenteral methotrexate, comparisons with other DMARDs, combination regimens, and longer-term use.

Juvenile arthritis

The applicant proposed the following indication for Metoject 50 mg/mL: treatment of polyarthritic forms of severe, active juvenile idiopathic arthritis, which is not in complete accordance with Metoject 10 mg/mL (Polyarthritic forms of severe, active juvenile idiopathic arthritis when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate).

In support of this indication, the applicant submitted a clinical overview and a clinical summary with bibliographic data. The majority of the submitted studies were uncontrolled trials. Data from well-controlled clinical studies are sparse. In the opinion of the RMS and CMS, the applicant did not submit documentation that would justify to omit the restriction “when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate” of the currently approved indication for Metoject 10 mg/mL.

However, some CMS considered that the evidence of efficacy and safety for the juvenile indication was insufficient irrespective of the wording of this indication and the applicant chose to withdraw this indication.

Psoriasis vulgaris/psoriatic arthritis

The applicant proposed the following indication for Metoject 50 mg/mL (same as for Metoject 10 mg/mL): treatment of severe and generalized psoriasis vulgaris, especially plaque-type, and psoriatic arthritis in adult patients who are unresponsive to conventional therapy.

The applicant submitted a clinical overview and a clinical summary with bibliographic data. Per request of the CMS, this indication was reworded as follows: *Severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis in adult patients.* A requirement to establish diagnosis by biopsy/or after dermatological consultation has been included in the SPC section 4.4 Special warnings and precautions for use.

IV.5 Clinical safety

Methotrexate has long been used clinically in the treatment of rheumatoid arthritis, juvenile arthritis, and psoriasis and has a well-known side effect profile. Dosing recommendations for Metoject 50 mg/mL are unchanged from those currently approved for Metoject 10 mg/mL with a maximum recommended dose of 25 mg/week (or 20 mg/m² in children).

Most common adverse events include gastrointestinal symptoms (such as nausea) and a rise in liver enzymes. Development of liver cirrhosis is uncommon. Suppression of the hematopoietic system can also occur, as well as pulmonary effects, such as pneumonitis or a pulmonary fibrosis.

Prior to starting or reinstating methotrexate therapy, patients should be examined, with special focus on liver, renal, and pulmonary function. A complete blood count with differential and platelets should be obtained, as well as liver and renal function tests. A chest X-ray should be obtained. Patients should also be monitored regularly during therapy (see also Section 4.4 of the SPC).

IV.6 Discussion on the clinical aspects

The changes, compared with those approved for Metoject 10 mg/mL, in the indications treatment of active rheumatoid arthritis, psoriasis vulgaris and psoriatic arthritis in adult patients are acceptable.

Regarding the treatment of juvenile idiopathic arthritis, the applicant did not submit documentation that would justify an expansion of the currently approved indication for Metoject 10 mg/mL. However, some CMS considered that the benefit-risk for juvenile idiopathic arthritis, in general, was not positive and the applicant has withdrawn this indication. The RMS would have preferred to keep this indication as there is a need to provide a smaller injection volume in paediatric patients. However, the RMS recommends the applicant to further document this indication.

A risk management plan was requested and developed by the applicant. It was concluded that there is no important identified or potential risk for Methotrexate 50 mg/ml solution for injection for which additional risk minimisation measures are necessary, given that the revised SPC and PL address several safety concerns.

As this product contains methotrexate at a higher concentration than previously a Potential serious risk to public health concerning local tolerance was raised. The applicant provided acceptable documentation (results from preclinical tolerance studies and clinical experience) supporting adequate local tolerance.

Given that the maximum recommended dose of methotrexate is 25 mg/week, the proposed pre-filled syringe containing 30 mg of methotrexate could not be justified and may lead to dosing error. The applicant removed the 30 mg dose, thereby resolving the issue.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and is acceptable.

The risk/benefit ratio is considered positive and Metoject, 50 mg/mL, solution for injection, prefilled syringe is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Metoject, 50 mg/mL, solution for injection, prefilled syringe was successfully finalised on 20081002.

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)