

Public Assessment Report

Scientific discussion

Metoject

Metojectpen

(methotrexate disodium)

SE/H/643/01/DC
SE/H/643/02-11/DC

This module reflects the scientific discussion for the approval of Metoject and Metojectpen. The procedure for Metoject (SE/H/643/01/DC) was finalised at 2 October 2008. For information on changes after this date please refer to the module 'Update'. The procedure for Metojectpen (SE/H/643/02-11/DC) was finalised on 9 July 2013.

I. INTRODUCTION

medac GmbH have applied for marketing authorisations for Metoject, solution for injection, prefilled syringe, 50 mg/ml and Metojectpen, solution for injection, prefilled pen, 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. 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. 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. Metojectpen 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.

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. 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 (Metoject only)

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on a

satisfactory number of batches. The batch analysis results show that the finished products meet the specifications proposed.

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 Discussion on the non-clinical aspects

The application is based on bibliographic documentation and did not contain any new studies. As methotrexate is a widely used, well-known active substance, no further studies are required. There were no objections to approval of Metoject/Metojectpen 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 reinstituting 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 consultation

SE/H/643/01/DC: The package leaflet has been evaluated via a user consultation study 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.

SE/H/643/02-11/DC: 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 Metoject, 50 mg/mL, solution for injection, prefilled syringe and Metojectpen, 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 are recommended for approval.

VI. APPROVAL

The decentralised procedure for Metoject, 50 mg/mL, solution for injection, prefilled syringe was successfully finalised on 2008-10-02.

The decentralised procedure for Metojectpen, 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.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/643/01/II/02	Following a Type II variation, a new indication was approved for Metoject: - polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate	Yes	2010-03-24	Approval	N/A
SE/H/643/01/II/03	Following a Type II variation, an additional pack size (30 mg) was approved for Metoject.	Yes	2010-03-24	Approval	N/A
SE/H/643/01/II/08	Following a Type II variation, a new indication was approved for Metoject:, mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.	Yes	2013-06-05	Approval	N/A
SE/H/643/02-11/DC	Extension application to add a new pharmaceutical form: "solution for injection, prefilled pen".	Yes	2013-07-09	Approval	N/A
SE/H/643/02-11/II/28	Following a Type II variation, a modification of an indication was approved for Metojectpen: moderate to severe psoriasis in adult patients who are candidates for systemic therapy, and severe psoriatic arthritis in adults.	Yes	2018-03-28	Approval	In the variation, the indication regarding psoriasis were broadened to include moderate psoriasis based on a literature review provided by the applicant. In addition, the text was modified to harmonize with CHMP approved systemic products for psoriasis. No changes were made regarding the psoriasis arthritis indication, since no justification were provided. An update in 4.4 was also made to reflect the new wording of the psoriasis indication.

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