LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metoject
(methotrexate)

SE/H/939/002-06/DC

This module reflects the scientific discussion for the approval of Metoject. The procedure was finalised on 2017-12-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

medac Gesellschaft für klinische Spezialpräparate mbH has applied for a marketing authorisation for Metoject, 7,5 mg, 10mg, 15mg, 20mg, 25mg, Solution for injection in pre-filled pen. The active substance methotrexate is the same as in Metotrexat medac, 50 mg/ml, injektionsvätska, lösning, förfylld spruta, marketed by medac Gesellschaft für klinische Spezialpräparate mbH since 2012.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

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

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 and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Metoject is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV. CLINICAL ASPECTS

IV.1 Introduction

The application is based on literature review which covers literature publications up to year 2016.
The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Metex Injektionslosung 7.5mg/ml, Solution for infusion authorised in DE since 1992, with medac GmbH as marketing authorisation holder.

IV.2 Pharmacokinetics

No bioequivalence studies have been submitted in this application.
The applied product Metoject (7,5 mg, 10 mg, 15 mg, 20 mg, 25 mg, Solution for injection in pre-filled pen) is to be administered as a subcutaneous solution containing the same active substance and the same excipients in the same concentration as the previously authorised product Metotrexat medac, 50 mg/ml, solution for injection, prefilled syringe. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) and the absence of bioequivalence studies are considered acceptable.

IV.3 Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. The overview covers literature describing efficacy and safety aspects of methotrexate use in rheumatoid arthritis in adults and psoriasis. The clinical efficacy and safety profile of methotrexate when used in approved indications is well known. The clinical overview on efficacy and safety is adequate from a clinical point of view.

IV.4 Risk Management Plans

The MAH has submitted a risk management plan (RMP), 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 Metoject.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	Opportunistic infections (e.g. Pneumocystis jirovecii pneumonia)
	Lymphomas
	Haematological toxicities
	Nervous system disorders Leukoencephalopathy, impaired vision
	Pulmonary toxicity

	Gastrointestinal haemorrhage
	Hepatotoxicity
	Renal toxicity
	Teratogenicity (Abortion and congenital disorders)
	Effects on fertility
Important potential risks	Medication error
Missing information	Use in children less than 3 years of age

Pharmacovigilance Plan

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

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed in RMP

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Opportunistic infection (e.g. pneumocystis jirovecii pneumonia)	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC 4.8 Undesirable effects:* Pneumocystis **jirovecii** pneumonia (frequency: rare) is listed as an undesirable effect. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Lymphomas	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC Section '4.4 Special warnings':* "Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.' *SmPC Section '4.8 Undesirable effect':* Lymphoma is listed as a very rare undesirable effect. "There have been reports of individual cases of lymphoma which subsided in a number of cases once treatment with methotrexate had been discontinued. In a recent study, it could not be established that methotrexate therapy increases the incidence of	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	lymphomas." *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	
Haematological toxicities	Prescription only medicine The prescription of Metoject solution for injection in pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC Section '4.4 Special warnings':* "Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets." *SmPC Section '4.8 Undesirable effects':* Leukocytopenia (frequency: common), thrombopenia (frequency: common), anaemia (frequency: common), pancytopenia (frequency: uncommon) and agranulocytosis (frequency: very rare) are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Nervous system disorders (Leukoencephalopathy, impaired vision)	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC Section '4.4 Special warnings':* "Encephalopathy/leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications." *SmPC Section '4.8 Undesirable effects':* Leukoencephalopathy (frequency: unknown) and impaired vision (frequency: very rare) are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Pulmonary toxicity	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC Section '4.4 Special warnings':* "Assessment of respiratory system: Alertness for symptoms of lung function impairment and, if necessary lung function test." *SmPC Section '4.8 Undesirable effects':* Interstitial alveolitis / pneumonitis (frequency: common) and pulmonary fibrosis (frequency: rare) are listed as undesirable effects. *Patient Information Leaflet (PIL)*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	The PIL includes similar information as the SmPC in lay language.	
Gastrointestinal haemorrhage	Prescription only medicine The prescription of Metoject solution for injection in pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC Section '4.4 Special warnings':* Diarrhoea and ulcerative stomatitis can be toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur. *SmPC Section '4.8 Undesirable effects':* Gastrointestinal ulcer and bleeding (frequency: uncommon) are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Hepatotoxicity	Prescription only medicine The prescription of Metoject solution for injection in pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC section '4.2 Posology / Method of Administration':* In patients with hepatic impairment MTX should be administered with great caution. *SmPC section '4.4 Special warnings':* If clinically indicated, hepatitis should be excluded before beginning or reinstituting methotrexate therapy after a rest period. "Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate *unless clearly necessary* and the consumption of alcohol should be avoided or greatly reduced." "Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide)." *SmPC Section '4.8 Undesirable effects':* Elevated transaminases (frequency: very common), acute hepatitis (frequency: rare), cirrhosis (frequency: uncommon), fibrosis and fatty degradation of the liver (frequency: uncommon) are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Renal toxicity	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. Severe renal impairment is listed as a contraindication.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC section '4.2 Posology / Method of Administration': In patients with renal impairment MTX should be used with caution. *SmPC section '4.4 Special warnings':* Before beginning or reinstituting methotrexate therapy after a rest period a renal function test is recommended. "Renal function should be monitored by renal function tests and urinanalysis." "Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently." *SmPC Section '4.8 Undesirable effects':* Renal impairment (frequency: uncommon), renal failure (frequency: rare), oliguria (frequency: rare) and anuria (frequency: rare) are listed as undesirable effects. *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	
Teratogenicity (Abortion and congenital disorders)	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. Pregnancy and breast-feeding are listed as a contraindication. Teratogenicity in animal species described in section 5.3 of the SmPC. *SmPC section '4.6.Fertility, pregnancy and lactation':* "Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death and/or congenital abnormalities." *Patient Information Leaflet (PIL)* The PIL includes similar information as the SmPC in lay language.	None
Effects on fertility	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC section '4.4.Special warnings':* "Methotrexate affects spermatogenesis and oogenesis during the period of its administration which may result in decreased fertility." *SmPC section '4.6. Fertility, pregnancy and lactation':* "As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy."	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Potential Risks		
Medication error	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. To prevent overdosage section '4.2. Posology / Method of Administration' of the SmPC clearly states the weekly injection of MTX. Symptoms of overdose and recommended treatment measures are sufficiently described in detail in section 4.9 of the SmPC. SmPC section 6.6 describe the subcutaneous use of Metoject solution for injection pre-filled pen in detail.	None
Missing Information		
Use in children less than 3 years of age	Prescription only medicine The prescription of Metoject solution for injection pre-filled pen is only recommended to physicians that are familiar with the various characteristics of the medicinal product and its mode of action. *SmPC section 4.2. Posology / Method of Administration:* "Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population (see section 4.4)." *SmPC section 4.4. Special warnings and precautions for use:* "Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population (see section 4.2)."	None

Summary of the RMP

The RMP is approvable.

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 for content and layout making reference to Metoject 7.5 mg/10 mg/12.5 mg/15 mg/17.5 mg/20 mg/22.5 mg/25 mg/27.5 mg/30 mg solution for injection, pre-filled pen, SE/H/0643/002-011/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, Metoject, is found adequate. There are no objections to approval of Metoject, from a non-clinical and clinical point of view. The product information is acceptable.

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Metoject is approvable.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 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 Mutual recognition/Decentralised procedure for Metoject, 7,5 mg, 10mg, 15mg, 20mg, 25mg, Solution for injection in pre-filled pen was positively finalised on 2017-12-18.

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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)

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