LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Methotrexate Sandoz
methotrexate

SE/H/2074/01-10/DC

2020-0345, 2020-0346, 2020-0347, 2020-0348, 2020-0349, 2020-0350, 2020-0351, 2020-0352, 2020-0353, 2020-0354

This module reflects the scientific discussion for the approval of Methotrexate Sandoz. The procedure was finalised on 2021-03-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Methotrexate Sandoz 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25mg, 27.5 mg and 30 mg, solution for injection in pre-filled injector, is submitted according to Article 10(3) of Directive 2001/83/EC. The applicant, Sandoz A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Germany as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Metoject, 10 mg/ml, Solution for injection in pre-filled syringe, authorised in Sweden since 2002, with medac Gesellschaft für klinische Spezialpräparate mbH as marketing authorisation holder.

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/EC 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

III.1 Discussion on the 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

No studies have been conducted.

Compared to the reference product Metoject 10 mg/ml solution for injection, Methotrexate Sandoz has a different pharmaceutical form ("pre-filled injector") and strength (50 mg/ml). The product development was done against 50 mg/ml strength of innovator drug product in pre-filled syringe which is similar in term of qualitative and quantitative composition.
Methotrexate Sandoz 50 mg/ml solution for injection in pre-filled injector (7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5 and 30 mg) contains the same active substance in the same concentration as Metoject 50 mg/ml pre-filled syringe (7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25 mg). Both Methotrexate Sandoz and Metoject are aqueous solutions containing sodium chloride and sodium hydroxide as excipients. Thus, the absence of bioequivalence studies is acceptable.

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 Plan

The MAH has submitted a risk management plan, 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 Methotrexate Sandoz.

Safety specification

Important identified risks	Opportunistic infections (e.g. *Pneumocystis jirovecii pneumonia*)
	Lymphomas
	Hematological toxicities
	Nervous system disorders (Leukoencephalopathy, impaired vision)
	Pulmonary toxicity
	Gastrointestinal hemorrhage
	Hepatotoxicity
	Renal toxicity
	Teratogenicity (Abortion and congenital disorders)
	Effects on fertility
	Medication errors due to inadvertent daily instead of once weekly dosing
Important potential risks	None
Missing information	Use in children less than 3 years of age

Pharmacovigilance Plan

10.1.1 Routine pharmacovigilance activities beyond Adverse Drug Reactions (ADRs) reporting and signal detection.

Specific adverse reaction follow-up questionnaires: Specific adverse event follow-up questionnaire will be used to collect further data to help further characterize the important risk of Medication errors. The follow-up questionnaire has been appended in Annex 4 of the RMP.

Risk minimisation measures

Summary of pharmacovigilance activities and risk minimization activities by safety concerns:

Safety concern	Risk minimization measures	Pharmacovigilance activities
Opportunistic infections (e.g. Pneumocystis jirovecii pneumonia)	**Routine risk communication:** SmPC sections 4.3, 4.4 and 4.8 PL section 2 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Lymphomas	**Routine risk communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Hematological toxicities	**Routine risk communication:** SmPC sections 4.3, 4.4, 4.5 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Nervous system disorders (Leukoencephalopathy, impaired vision)	**Routine risk communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Pulmonary toxicity	**Routine risk communication:** SmPC sections 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: None	**Additional pharmacovigilance activities:** None
Gastrointestinal hemorrhage	**Routine risk communication:** SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Hepatotoxicity	**Routine risk communication:** SmPC sections 4.3, 4.4, 4.5 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Renal toxicity	**Routine risk communication:** SmPC sections 4.2, 4.3, 4.4 and 4.8 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Teratogenicity (Abortion and congenital disorders)	**Routine risk communication:** SmPC sections 4.3, 4.4 and 4.6 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Effects on fertility	**Routine risk communication:** SmPC sections 4.4 and 4.6 PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Medication errors due to inadvertent daily instead of once weekly dosing	**Routine risk communication:** SmPC section 4.2, 4.4, and 4.9 PL sections 2 and section 3 Legal status: Prescription only Package: For tablet formulations of methotrexate containing products for oral use, bottles or tubes used as immediate packaging to be replaced by blisters. **Additional risk minimization measures:** DHPC Education materials for oral formulations only: • HCP guide • Patient card	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire: "Medication errors related to overdose" **Additional pharmacovigilance activities:** None
Use in children less than 3 years of age	**Routine risk communication:** SmPC sections 4.2 and 4.4 PL section 2 Legal status: Prescription only **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Summary of the RMP

The MAH has satisfactorily responded to the questions raised. **Issue is resolved**

The submitted Risk Management Plan, version 5.1signed 8 May 2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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:
Content: Injexate, SE/H/1431/001.
Layout: in house style tested in DE/H/717+719/01/MR (clozapine), DK/H/1430+1431+1432/01-02/DC (quetiapine)and DE/H/3330+3331/01-04/DC (ziprasidone).
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This is a hybrid application. The reference product is Metoject, 10 mg/ml, solution for injection in pre-filled syringe authorised in Sweden since 2002, with medac Gesellschaft für klinische Spezialpräparate mbH as marketing authorisation holder.

Methotrexate is a widely used, well-known active substance, and no further studies are required for an abridged application provided bioequivalence has been satisfactorily addressed. However, a bioequivalence study is not necessary in this case.

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

The benefit/risk ratio is considered positive and Methotrexate Sandoz 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25mg, 27.5 mg and 30 mg, solution for injection in pre-filled injector is recommended for approval.

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

<u>All methotrexate-containing products</u> Each MAH should implement the agreed targeted follow-up questionnaires for all medication errors resulting in overdose.	From the date of notification of the Commission Decision
<u>Methotrexate-containing products for oral use with at least one indication requiring once weekly dosing</u> Each MAH should operate a risk management system to be described in a risk management plan (RMP) which shall be submitted to the relevant Competent Authorities. The RMP should reflect the following additional risk minimisation measures to address the important identified risk of medication errors resulting in overdose: - educational material(s) for healthcare professionals developed in accordance with the key elements agreed; - the agreed patient card. For tablet formulations, the following measure should also be implemented: MAHs should replace any bottle or tube used as immediate packaging by blisters.	Within 3 months after Commission decision Within 4 years after Commission decision

VII. APPROVAL

The decentralised procedure for Methotrexate Sandoz 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25mg, 27.5 mg and 30 mg, solution for injection in pre-filled injector was positively finalised on 2021-03-18.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	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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