LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Metotab
(methotrexate disodium)

SE/H/2110/01-03/MR

This module reflects the scientific discussion for the approval of Metotab. The procedure was finalised on 2021-09-28. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Metotab, 7,5 mg, 2,5 mg, 10 mg, Tablet.

The active substance is methotrexate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Metotab, 2,5 mg, 7,5 mg, 10 mg, Tablet is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Medac Gesellschaft für klinische Spezialpräparate mbH, applies for a marketing authorisation in AT through this mutual recognition procedure with Sweden acting as reference member state (RMS). The product was first approved through a National Procedure.

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 (MTX) are well known.
The non-clinical overview addresses the subcutaneous and the oral route of administration by summarizing the pharmacodynamic, pharmacokinetic and toxicological properties of MTX based on literature review and by study results from a GLP-compliant local tolerance study conducted by the

applicant. In the local tolerance study, no macroscopic and microscopic changes, systemic signs of toxicity or body weight changes related to treatment occurred in rabbits injected with a single dose of 50 mg/ml MTX solution by different parenteral (intravenous, intraarterial, intramuscular, paravenous and subcutaneous) routes and is considered to be of no concern. As methotrexate is a widely used and a well-known active substance no further studies are required. The overview based on literature review and local tolerance data is thus appropriate.

Environmental Risk Assessment (ERA)
The applicant has performed an environmental risk assessment according to the Guideline on the Environmental Risk Assessment of Medicinal Products of Human Use (EMEA/CHMP/SWP/4447/00 Rev.1). The $\log_{Kow}$ and $PEC_{surfacewater}$ values was below the action limits and in line with the guideline no further assessment is necessary.

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

IV. CLINICAL ASPECTS

Pharmacokinetics
Absorption
MTX bioavailability is good (80-100%) at low doses used for RA and psoriasis. When administered orally, maximum serum concentrations of MTX are achieved after 1-2 hours. Absorption is capacity-limited and decreases with increasing oral doses. There is major inter-and intra-individual variation, particularly with repeated dosing.

Distribution
Approximately 50 % of MTX is reversibly bound to serum protein. After entering the cell, MTX undergoes a variable degree of polyglutamation. MTX polyglutamates are not able to cross cell membranes unless they are hydrolysed to monoglutamate, thus MTX accumulates within cells in the form of polyglutamates. High MTX concentrations are achieved especially in the kidneys, gall bladder, spleen, liver, skin and bowel. Small or insignificant amounts cross the blood-brain barrier and enter cerebrospinal fluid following oral administration.

Biotransformation
Intrahepatically, MTX may be partly metabolised to 7-OH-MTX (main metabolite) and 2,4-diamino-N10-methylpteroic acid (a pharmacologically inactive metabolite). MTX is converted to 4-amino-deoxy-N10-methylpteroic acid by intestinal bacteria. The metabolite usually accounts for less than 5% of the administered dose, and is rarely detectable in human plasma and urine

Elimination
The elimination half-life for MTX following IV and oral administration was reported in most studies to be about 5-8 hours. However, in these studies the measurements were performed only up to 24 hours after administration. When measured over a 72-hour period, a half-life of 15-21 h was found after oral administration of 15 mg MTX. Patients with any third-space fluids (e.g. pleural effusion, ascites) may accumulate MTX, which then slowly distributes from this compartment back to the plasma. The half-life can be prolonged to 4 times the normal length in patients with a third distribution space.

MTX is mainly excreted by the kidney as intact drug. The drug is filtered by the glomeruli, and then undergoes both secretion and reabsorption process within the tubule. Approximately 10 % of MTX and 1-5 % of 7-OH-MTX are eliminated via the biliary tract. There is significant enterohepatic circulation.

Special populations

Elimination half-life was significantly increased and total clearance was significantly reduced with the degree of renal impairment. MTX should be administered with caution to patients with impaired renal function. Dose adjustments are proposed in the SmPcC:

The impact of hepatic insufficiency on the pharmacokinetics of MTX is not known. Nevertheless, MTX should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5 mg/dL (85.5 μmol/L), MTX is contraindicated.

Dose reduction should be considered in elderly patients due to the decrease in hepatic and renal function and folate levels with advancing age.

Interactions
The applicant has described the interaction potential of MTX adequately and provided relevant references in support. Several of the described interactions are mainly of interest for high dose MTX therapy used for treatment of cancer. Pharmacokinetic interactions are mainly due to effects on MTX renal clearance. The SmPC reflects the interaction potential of MTX appropriately.

Pharmacokinetic conclusion
The Applicant has provided an up to date clinical overview covering 324 references up to year 2020 with a focus on the low-dose MTX therapy for which the proposed product is intended. As this is a WEU-application a bridge to the literature supporting efficacy and safety is of importance. The Applicant has submitted two BE-studies which, in conjunction with a scientific discussion regarding the results, is considered an acceptable bridge to the literature. The basic ADME of MTX is adequately described and sufficiently supported by original references. The pharmacokinetic information is appropriately reflected in the SmPC. From a pharmacokinetic perspective the Application is recommended for approval.

Pharmacodynamics

Mechanism of action

MTX primarily acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA synthesis. The mechanism of action of MTX in autoimmune diseases such as RA is not yet fully elucidated although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effects. It is possible that several mechanisms are responsible for its overall effect.

Pharmacodynamic interactions with other medicinal products

The current approved SmPC section 4.5 includes the important pharmacodynamic interactions with other medicinal products (hepatotoxic medicinal products, haematotoxic medicinal products, medicinal products with adverse effects on the bone marrow, medicinal products which cause folate deficiency and other antirheumatic medicinal products).

Relationship between plasma concentration and effect

Cellular retention is a major determinant of MTX pharmacodynamic activity. The AUC of MTX has in certain studies been correlated to some measures of efficacy in RA and psoriasis. A clear dose-concentration-effect-relationship has not been shown and the predictive value of the administered dose for efficacy is poor.

Clinical efficacy and Clinical safety

Metotab 2.5 mg/7.5 mg/10 mg tablets are marketed in Germany since 1992, in Sweden since 2007 and in Poland since 2013. Metotab was nationally approved in Sweden (2007) in the treatment of RA and Psoriasis following a line extension to a bibliographic application, Metoject 10 mg/ml solution for injection. Renewal of the MA in Sweden for the Metotab 2.5 mg/7.5 mg/10 mg tablets was approved in 2012.

This application is a planned Mutual Recognition Procedure (MRP) for the Applicant's already nationally registered medicinal product "Metotab tablets".

The clinical overview for Metotab (dated 30 Sept 2020) submitted by the Applicant includes new literature references for the clinical efficacy and clinical safety, as compared with the previous clinical overview submitted for the Metotab dossier update in the treatment of RA and Psoriasis (type II group of variations (5.4.3-2019-38909)). These new literature references provided additional results supportive for the clinical efficacy; and no new significant safety information was identified from the added references suggesting an update of the SmPC for Metotab.

Thus the clinical efficacy and clinical safety evaluation/conclusion of the final assessment report for Metotab (dated 2019-11-20), based on assessment of the previous clinical overview submitted for the Metotab dossier update in the type II group of variations (5.4.3-2019-38909), remains unchanged.

Adult RA

Low-dose MTX (alone or in combination with other agents) has become well-established standard of care in the treatment of adult RA. Included among the 324 references in the list of references in the Clinical Overview are a number of clinical studies, with focus on reviews and meta-analysis as well as treatment guidelines, that appears to provide appropriate support the efficacy of low-dose MTX for this indication. According to the EULAR updated recommendations, therapy with DMARDs should be started as soon as the diagnosis of RA is made. As first strategy, the Task Force recommends oral or SC MTX (rapid escalation to 20-25 mg/week) plus short-term glucocorticoid, aiming at > 50% improvement within 3 and target attainment within 6 months.
As stated in the Overview, MTX is administered once weekly in rheumatic disease. The patient is to be explicitly informed about the unusual fact of administration once weekly. The prescriber should specify the day of intake on the prescription. This information is clearly provided in the SmPC.
In adult patients with RA, the recommended starting dose is 7.5 mg MTX once weekly, administered orally. Depending on the individual activity of the disease and patient tolerance, the initial dose may be increased in increments of 2.5 mg up to 25 mg once weekly. Response to treatment can be expected after approximately 4-8 weeks. This strategy was worked out mainly empirically, since there are few controlled studies available on the relationship between dose and onset of action or the intensity of the effect.

Adult psoriasis

MTX, is the cornerstone of systemic treatment of psoriasis. In the Clinical Overview the applicant refers to publications to support its use and the approved posology.
As in RA, MTX is administered once weekly with a starting dose of 7.5 mg/week to be increased gradually until the optimum response has been achieved, in general not exceeding 25 mg MTX/week. The MTX starting dose in RCTs varied from 5 to 25 mg/week, most commonly being either 7.5 mg or 15 mg; guidelines vary from 5 to 15 mg/week. A maximum dose of 25 mg/week MTX is suggested because the effect of a dose increase to 30 mg remains unclear.

Clinical safety

Because of extensive use (exposure) of MTX in the two approved indications, the safety profile of oral MTX in the approved once a week-posology is well-known and it is generally considered acceptable. The major risks include suppression of the haematopoietic system, gastrointestinal disturbances, pulmonary toxicity, hepatotoxicity and renal toxicity. The incidence and severity of undesirable effects depends on the dosage level and the frequency of administration. It is essential that patients are appropriately monitored.

In the Clinical Overview, the applicant refers to a meta-analysis that summarizes the safety of MTX in psoriasis and other chronic inflammatory conditions including RA. The Clinical Overview also includes an analysis and summary with reference to publications, of some selected adverse events including their frequency: infections, neoplasms (lymphoma), clinical consequences of bone marrow depression, immune system disorders (allergic reactions), metabolism and nutrition disorders (indications of precipitation of diabetes mellitus in a study), psychiatric disorders (depression, confusion, mood alterations), nervous system disorders (headache and tiredness common), visual

disturbances, cardiac disorders (pericarditis, pericardial effusion, pericardial tamponade), vascular disorders, respiratory disorders (lung toxicity; MTX-pneumonitis), GI toxicity (nausea, abdominal pain common), hepatobiliary disorders (abnormal liver function tests frequently observed but was often a transient problem), skin disorders, musculoskeletal and connective tissue disorders, renal and urinary disorders (inflammation and ulceration of the urinary bladder or vagina, renal impairment, and disturbed micturition reported occasionally with weekly low-dose MTX), reproductive disorders (inflammation and ulceration of the vagina) and wound-healing impairment.

The SmPC includes recommendations with regards to treatment follow-ups and safety measures. MTX causes embryotoxicity, abortion and foetal defects in humans and is contraindicated in pregnancy, as well as during breast feeding. Section 4.8 of the SmPC largely covers the AEs included in the meta-analysis refered by the applicant and includes infections, nausea/vomiting, mouth ulcer, abnormal liver function, abdominal pain, headache, alopecia, diarrhoea, cough, fatigue, different skin manifestations, dizziness, leukopenia, pruritus and malignancy (lymphoma).

Moreover, the current SmPC includes updates according to the outcome of the methotrexate Article-31 referral as well as the recommendations from the most recently completed PSUSA (EMEA/H/C/PSUSA/00002014/201910).

In summary, regarding the clinical aspects, there are no remaining issues to address within this procedure and the application for Metotab tablets (2.5, 7.5 and 10 mg) can thus be recommended for approval from a clinical point of view.

Risk Management Plan

The current Risk Management Plan (RMP) for Metotab (Methotrexate) is the version 0.3 dated 06 January 2020 (DLP 31 October 2019).

The RMP version 0.3 for Metotab (Methotrexate) is approved in April 2020 and updated according to the outcome of the methotrexate Article-31 referral.

The RMP is considered acceptable.

V. USER CONSULTATION

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 within the national variation Dnr 5.4.3-2019-38909. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Over the last three decades, low-dose methotrexate has been intensively investigated in patients with various autoimmune diseases, especially in patients with rheumatoid arthritis (RA). Methotrexate alone or in combination with other agents has become the standard of care in the treatment of RA. Methotrexate has been used in the treatment of psoriasis since the 1960s and has been proven to be particularly useful in patients that need prolonged therapy. Metotab was nationally approved in Sweden (2007) in the treatment of RA and Psoriasis; and renewal of the MA in Sweden for the Metotab 2.5 mg/7.5 mg/10 mg tablets was approved in 2012.

Low-dose po methotrexate is since long the anchor drug in RA treatment and is also the cornerstone of systemic treatment of psoriasis. Efficacy of methotrexate is established in these authorised indications

and safety profile of methotrexate is known. Over the years, the benefits and risks of this treatment have been thoroughly documented in numerous publications; the outcome of which is summarized in the Clinical Overview submitted by the Applicant which adequately reviews and presents the relevant and common knowledge on clinical aspects of the use of po methotrexate in the approved low-dose once-a-week posology for the treatment of RA and psoriasis.

The current SmPC for Metotab (attached) is considered acceptable. The RMP version 0.3 for Metotab approved in April 2020 is considered acceptable.

Overall, the submitted documentation supports the existing view that the Benefit-Risk of methotrexate in the approved posology continues to be positive for the approved indications.

In conclusion, there are no remaining issues to address within this procedure. The application for Metotab tablets (2.5, 7.5 and 10 mg) is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Metotab, 7,5 mg, 2,5 mg, 10 mg, Tablet was positively finalised on 2021-09-28.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se