Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for: Methotrexate

Proprietary Product Name: TREXJECT & TREXJECT IN

Sponsor: Link Medical Products Pty Ltd T/A Link Pharmaceuticals

June 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee for Prescription Medicines
ACR	American College of Rheumatology
AE	Adverse Event
AIHW	Australian Institute of Health and Welfare
API	active pharmaceutical ingredient
ARTG	Australian Register of Therapeutic Goods
AUC	Area Under the Curve
AUC_{0-t}	area under the plasma concentration-time curve calculated by linear trapezoidal rule from time zero to the end of the dosing interval at steady state
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time of administration to infinity
BMI	Body Mass Index
BP	British Pharmacopeia
BSA	Body Surface Area
CI	Confidence interval
C_{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CrCL	Creatinine Clearance
CRP	C-Reactive Protein
CS	Corticosteroids
CsA	Cyclosporine A
CV	Coefficient of Variation
DAS28	Disease Activity Score – 28 joint count
DMARD	Disease Modifying Anti-Rheumatic Drug
EDQM	European Directorate for the Quality of Medicines

Abbreviation	Meaning
EP	European Pharmacopeia
ESR	Erythrocyte Sedimentation Ratio
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
gMean	geometric mean
HAQ-DI	Health Assessment Questionnaire – Disability Index
ICH	International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IM	Intramuscular
ISR	Injection Site Reaction
IV	Intravenous
JIA	Juvenile Idiopathic Arthritis
LBS	Literature Based Submission
MTX	Methotrexate
NAPSI	Nail Psoriasis Severity Index
NSAID	Non-Steroidal Anti-Inflammatory Drug
PASI	Psoriasis Area Severity Index
PD	Pharmacodynamic
PhGA	Physician Global Assessment
PK	Pharmacokinetic
PO	Per oral
PSOR	Psoriasis
PsA	Psoriatic Arthritis
PtGA	Patient Global Assessment
SAE	Serious adverse event
RA	Rheumatoid arthritis

Abbreviation	Meaning
SC	Subcutaneous
T_{max}	Time to maximum plasma concentration
TNF	Tumour Necrosis Factor
TRAE	treatment related adverse event
TRSAE	treatment related serious adverse event
ULN	Upper Limit of Normal
UVA	ultraviolet A
UVB	Ultraviolet B
WCC	White cell count

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new presentation, new route of administration)
Decision:	Approved
Date of decision:	18 August 2015
Date of entry onto ARTG	25 August 2015
Active ingredient:	Methotrexate (as sodium)
Product names:	TREXJECT, TREXJECT IN
Sponsor's name and address:	Link Medical Products Pty Ltd T/A Link Pharmaceuticals
Dose form:	Solution for injection
Strengths:	7.5 mg/0.15 mL, 10 mg/0.20 mL, 12.5mg/0.25 mL, 15 mg/0.30 mL, 17.5 mg/0.35 mL, 20 mg/0.40 mL, 22.5 mg/0.45 mL, 25 mg/0.50 mL, 27.5 mg/0.55 mL, 30 mg/0.60 mL
Container:	Prefilled syringe
Pack sizes:	1,4, 6, 12 and 24 syringes
Approved therapeutic use:	*Psoriasis therapy (see WARNING box)* *TREXJECT IN/ TREXJECT may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.* *Rheumatoid arthritis therapy (see WARNING box)* *Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of on adequate trial of NSAIDs and one or more disease modifying drugs.* *Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.* *Steroids may be reduced gradually in patients who respond to methotrexate.* *Combined use of methotrexate with gold or penicillamine, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy OS indicated should be continued.*
Routes of administration:	Subcutaneous, intramuscular
Dosage:	For Rheumatoid Arthritis and Psoriasis A weekly dose of 7.5 to

	25 mg is recommended, depending on response and tolerability. For full information on dosage please see the Product Information.
ARTG numbers:	224969, 224970, 224974, 224975, 224976, 224977, 224978, 224979, 233714, 233715, 233716, 233717, 233718, 233719, 233720, 233721

Product background

This AusPAR describes the application by Link Medical Products Pty Ltd T/A Link Pharmaceuticals (the sponsor) to register Trexject and Trexject IN methotrexate (as sodium) solution for injection in prefilled syringe for the following indication:

> *Psoriasis therapy (see WARNING box)*
>
> *TREXJECT IN/ TREXJECT may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.*
>
> *Rheumatoid arthritis therapy (see WARNING box)*
>
> *Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.*
>
> *Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.*
>
> *Steroids may be reduced gradually in patients who respond to methotrexate.*
>
> *Combined use of methotrexate with gold or penicillamine, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.*

Methotrexate (MTX) is a folic acid antagonist that acts primarily by competitively inhibiting the enzyme dihydrofolate reductase. As a result, DNA synthesis and cell replication are inhibited. MTX has anti-proliferative, immunosuppressive and anti-inflammatory effects. Oral formulations of MTX are classified as an immunosuppressant drug. Systemic formulations of MTX are classified as anti-neoplastic agents.

Currently, methotrexate is approved in Australia for oral and parenteral (intravenous (IV) and intramuscular (IM)) administration in psoriasis patients. Only the oral presentation is currently approved for the rheumatoid arthritis indication. This submission is for a new route of administration (subcutaneous (SC)), and indication for rheumatoid arthritis via the parenteral route. The currently registered parenteral strengths of methotrexate solution are 5 mg/2mL, 20 mg/2mL, 50 mg/2 mL, 500 mg/5 mL, 500 mg/20mL, 1000mg/10 mL, and 5000 mg/50mL.

Rheumatoid arthritis (RA) affects an estimated 2% of the Australian population (2011-2012 estimate reported by Australian Institute of Health and Welfare (AIHW) 2014). Psoriasis (PSOR) is a T-cell mediated chronic inflammatory and hyper-proliferative skin disease characterised by erythematous plaques or patches of red skin covered with white scales. It affects approximately 1.8% of the Australian population (AIHW 2004 analysis of 2001 National Health Survey). Of those an estimated 10 to 30% has a severe form of the disease.

The sponsor initially proposed a single trade name Metoject for this product. It was identified that the sponsor intended to market a prefilled syringe with an embedded needle for subcutaneous injection only and a prefilled syringe without an embedded needle but a needle included in the pack to be used intravenously, intramuscularly or subcutaneously. The sponsor later advised that the latter presentation is designed to be used by health professionals only, and that the presentation with the embedded needle could be used by health professionals or patients. In subsequent correspondence the sponsor advised that the pre-filled syringe without the embedded needle would not have a needle supplied with the pack. Each syringe pack will have an alcohol swab to clean the skin (noting that there will be no antiseptic claims made for the alcohol swab). The sponsor has proposed Trexject IN for its pre-filled syringe without embedded needle and Trexject for its presentation with embedded needle.

Regulatory status

The products received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 25 August 2015.

Methotrexate is approved for intravenous, subcutaneous and intramuscular use in the UK and 27 European countries and several Central and South American Countries. The UK product, Metoject 50mg/mL, administered subcutaneously (SC), intramuscularly (IM) or intravenously (IV) is approved for the treatment of:

> *Active rheumatoid arthritis in adult patients*
>
> *Polyarthritic forms of severe, active juvenile idiopathic arthritis, when response to nonsteroidal anti-inflammatory drugs (NSAIDS) has been inadequate,*
>
> *- 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*
>
> *- mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.*

Methotrexate 50 mg/ml solution for injection, pre-filled syringe was first authorised in the United Kingdom on 21 November 2008. Further registrations were received by Decentralised procedure through 2011. Currently, methotrexate 50 mg/ml solution for injection, pre-filled syringe is registered in 27 countries. The trade name is Metoject 50 mg/ml in Austria, Belgium, Bulgaria, Chile, Columbia, Croatia, Czech Republic, El Salvador, Finalnad, France, Great Britain, Greece, Guatemala, Honduras, Hungary, Iceland, Ireland, Israel, Kazachstan, The Netherlands, Romania, Russia, Slovak Republic, Slovenia, Spain, South Korea, Switzerland, and Ukraine. In Sweden, the product is also available under the name Metotrexat medac 50 mg/ml. In Italy, the product is marketed under the name Reumaflex 50 mg/ml; while in Denmark, Estonia, Germany, Latvia, Lithuania, Norway, Poland, and Portugal it is marketed under the name Metex 50 mg/ml. The sponsor has not applied for registration in the USA and Canada.

The drug product, methotrexate 50 mg/ml prefilled pen (for subcutaneous administration). At the time the TGA considered this application, a similar application had been approved in USA (as Rasuvo)(10 July 2014); Germany (as metex PEN) (4 May 2012); Austria (November 2013); Belgium (November 2013); Bulgaria (October 2013); Czech Republic (January 2014); Denmark (September 2013); Estonia (September 2013), Finland (July 2014); Germany (September 2013); Greece (March 2015); Hungary (April 2014); Israel (August 2013); Latvia (November 2013); Lithuania (September 2013); Norway (September 2013); The Netherlands (April 2014); Poland (October 2013); Portugal (August 2014); Romania (October 2013); Slovakia (February 2014); Switzerland (March

2014); Spain (April 2014); Serbia (August 2013) United Kingdom (August 2013) and was under consideration in France.

Product information

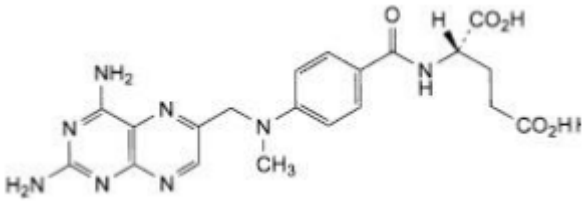
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

The drug substance, methotrexate (as sodium), has the structure shown in Figure 1.

Figure 1: Structure of methotrexate



In the products methotrexate is present as sodium salt. Methotrexate includes a chiral centre (S conformation).

Methotrexate is an antineoplastic that acts as an antimetabolite of folic acid. It also has immunosuppressant properties. Within the cell, folic acid is reduced to dihydrofolic and then tetrahydrofolic acid. Methotrexate competitively inhibits the enzyme dihydrofolate reductase and prevents the formation of tetrahydrofolate which is necessary for purine and pyrimidine synthesis and consequently the formation of DNA and RNA. Tissues with high rates of cellular proliferation, for example bone marrow, foetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are generally more sensitive to this effect of methotrexate.

Methotrexate is manufactured by chemical synthesis. It is practically insoluble in water, but dissolves in dilute solutions of alkali hydroxides. The conformation of the starting material is preserved in the synthesis of the drug substance.

The active pharmaceutical ingredient (API) is sourced from two manufacturing sites [information redacted]. European Directorate for the Quality of Medicines (EDQM) Certificates of suitability (CEPs) apply to API manufactured at these sites.

The drug substance specification meets the European Pharmacopeia (EP)/British Pharmacopeia (BP) requirements and includes tests and limits for specific optical rotation, enantiomeric purity, and also includes additional residual solvents limits as applied by the API manufacturers and that in line with the International Conference on the Harmonisation (ICH) guideline requirements.

Drug product

The proposed products are solutions for injection (each 1 mL contains 50 mg of methotrexate (as sodium) presented in pre-filled syringes containing 7.5 mg/0.15 mL; 10 mg/0.20 mL; 12.5mg/0.25 mL; 15 mg/0.30 mL; 17.5 mg/0.35 mL; 20 mg/0.40 mL; 22.5

mg/0.45 mL; 25 mg/0.50 mL; 27.5 mg/0.55 mL; 30 mg/0.60 mL methotrexate (as sodium).

The proposed products are sterile isotonic, clear, yellow-brown solutions for injection (pH 7.5 to 9.0) practically free from visible particles and contain no anti-microbial preservatives and are pre-filled syringes.

The following trade names are proposed:

- Trexject is proposed for presentations supplied as a procedure pack with an embedded needle and alcohol swabs. These presentations are for subcutaneous use only.
- Trexject IN is proposed for presentations supplied without a needle or swab. These presentations are for subcutaneous (SC), intravenous (IV) or intramuscular (IM) use.

Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens. Weekly dosage prescriptions should specify a particular day of the week.

- For rheumatoid arthritis, a weekly dose of 7.5 to 25 mg is recommended, depending on response and tolerability. Response to treatment can be expected after approximately 4 to 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.
- For psoriasis vulgaris, a weekly dose of 7.5 to 30 mg is recommended, depending on response and tolerability. Response to treatment can be expected after approximately 2 to 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

The manufacturing process for the solutions for injection in pre-filled syringes involves conventional compounding with water for injections sodium chloride, and pH adjustment sodium hydroxide and volume adjustment with water for injections, bulk solution filtration and syringe filling in a Grade A environment before aseptic sealing with rubber stoppers, labelling, imprinting with batch and expiry and packaging. Compounding and filling is under an inert atmosphere (nitrogen).

The filters and equipment used in manufacture are steam sterilised. The sterilisation of the components of the syringe barrel and plunger stopper is achieved by ethylene oxide and ionising radiation respectively.

Excipients are conventional. The products are direct scales.

The products are presented in a 1 mL type I glass pre-filled syringe sealed with a type I chlorobutyl rubber plunger stopper and HDPE, polystyrene or polypropylene plunger rod.

- 'Trexject' products in 1 mL graduated at 0.05 mL increments type I clear, colourless glass syringes (inside of glass barrel is siliconised) with an embedded integrated 27 G ½" stainless steel needle (type 304) protected by an elastomeric rubber needle shield, and rigid PP needle shield and siliconised EP type I rubber stopper (West PH701-50) with a HDPE, polystyrene or polypropylene plunger rod. The strengths/fill volumes use the following colour coded plastic backstops: 7.5 mg/0.15 mL red, 10 mg/0.20 mL green, 12.5 mg/0.25 mL light blue, 15 mg/0.30 mL purple, 17.5 mg/0.35 mL pink, 20 mg/0.4 mL dark red, 22.5 mg/0.45 mL dark green, 25 mg/0.50 mL blue, 27.5 mg/0.55 mL yellow and 30 mg/0.60 mL orange. These syringes with embedded needles are to be supplied as part of a procedure pack with alcohol swabs in cartons containing 1, 4, 6, 12 and 24 syringes. These syringes are for SC use only.
- 'Trexject IN' products in 1 mL graduated type I clear, colourless glass syringes (inside of glass barrel is siliconised) with luer tip and tip cap or luer lock polycarbonate adapter and siliconised EP type I rubber stopper (West PH701-50) with a HDPE,

polystyrene or polypropylene plunger rod. The strengths/fill volumes use the following colour coded plastic backstops: 7.5 mg/0.15 mL red, 10 mg/0.20 mL green, 12.5 mg/0.25 mL light blue, 15 mg/0.30 mL purple, 17.5 mg/0.35 mL pink, 20 mg/0.4 mL dark red, 22.5 mg/0.45 mL dark green, 25 mg/0.50 mL blue, 27.5 mg/0.55 mL yellow and 30 mg/0.60 mL orange. These syringes are to be supplied in cartons containing 1, 4, 6, 12 and 24 syringes without any needle or swabs. These syringes are for SC, IV and IM use.

The finished product specifications suitably control: Description; pH.; Assay; The R-enantiomer and related substances in line with the BP/EP finished product monograph; Fill volume that requires an injection volume of NLT label claim; uniformity of dosage units by mass variation; osmolarity; visible and sub-visible particles; sterility; and bacterial endotoxins.

The container safety was considered to be acceptable.

The microbiological aspects of the product were considered to be acceptable.

The endotoxin safety aspects of the product were considered to be acceptable.

The presentation strengths are distinguished by the labelling.

The stability data provided supports a shelf life of 2 years when stored below 25°C with the conditions 'Protect from light'.

Biopharmaceutics

The products are simple solutions for injection.

Advisory committee considerations

The application was not considered by the Pharmaceutical Subcommittee of the Advisory Committee for Prescription Medicines (ACPM).

Quality summary and conclusions

A number of issues were raised following the initial evaluation of this application. The sponsor has provided satisfactory responses to the issues raised by the quality evaluator, except for the following:

- The acceptability of the trade name 'Trexject IN' was referred to the Delegate. The Delegate advised that the suffix 'IN' may be confused with 'IM' and is not acceptable. It would be more appropriate to have the pre-filled syringe with the embedded needle named 'Trexject SC' and have the pre-filled syringe without the needle named 'Trexject'. This would differentiate the pre-filled syringe with the embedded needle (which is for subcutaneous use only) with the suffix 'SC' and 'Trexject' for IM, SC or IV use.
- Revised labels should be provided for all proposed products for review [details redacted]
- The Delegate has advised:

  To prevent confusion in dispensing and administration, the sponsor should use a different colour scheme for the two products to differentiate between the two products. In addition, the shades for 7.5 mg (light red) label and 20 mg (dark red) label; for 10 mg (green) label and 22.5 mg (dark green) label are very similar and may lead to confusion. The 12.5 mg label has an aqua shade with white writing which is

also quite hard to read. The 17.5 mg label has a pink shade with white writing which is also quite hard to read. The clinical perspective is that the aqua and pink label with black writing will be easier to read. Ideally, if the lower strengths have the lighter shades with black writing (pink, aqua, yellow, green, red), and the higher strengths have the darker shades with white writing (dark red, purple, dark green, blue, orange), it would be a pattern and be easier to pharmacist / dispensary technician / nurse to recognise which colour is which strength, provided the shades of green and reds are distinctive.

The PIs will require amendment, to reflect the above including revised trade names.

Provided that the above issues are addressed, there are no objections to registration with respect to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Link Medical Products Pty Ltd has applied for a major variation to register Trexject (methotrexate as sodium). Trexject comes as syringes pre-filled with 0.15 to 0.6 mL of 50 mg/mL methotrexate for parenteral administration. The proposed indications are the treatment of severe, recalcitrant psoriasis and rheumatoid arthritis. For psoriasis, this is an extension of administration route, from oral and intravenous and intramuscular injection, to include subcutaneous injection. For rheumatoid arthritis, the administration route is being expanded from oral to include intravenous, intramuscular and subcutaneous injection. In addition, minor amendments to dosing regimens are proposed.

In support of the proposed changes, the sponsor submitted two local tolerance studies. One GLP study reported no treatment related local tolerance effects of parenteral (intravenous, intramuscular, subcutaneous, intra-arterial and paravenous) administration of 50 mg/mL methotrexate solutions. A smaller, non-GLP study also found no local tolerance effects following subcutaneous administration of 50 mg/mL methotrexate. It should be noted that the provided studies did not administer methotrexate as sodium using the pre-filled glass syringes for which registration is being sought.

Nonclinical summary and conclusions

Methotrexate solutions (25 mg/mL and 100 mg/mL) are already registered on the ARTG for intravenous, intra-arterial, intrathecal and intramuscular injection. Pre-filled glass syringes of 50 mg/mL methotrexate are currently registered in 27 countries under the names Metoject, Metotrexat medac, Reumaflex and Metex. Based on the history of safe use and the provided studies, there are no nonclinical objections to the registration of Trexject.

The nonclinical evaluator assessed the PI but this is beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

This is a hybrid submission containing a mixture of sponsor initiated studies and published literature to register a new dose form (that is parenteral injection) of

methotrexate (MTX) for the treatment indications of rheumatoid arthritis (RA) and psoriasis (PSOR).

Methotrexate is currently registered as an oral preparation for RA and PSOR, and as an injectable product for PSOR and several malignancy indications such as breast and bladder cancer, squamous cell carcinoma of the head and neck, gestational trophoblastic disease, acute leukaemia, Non-Hodgkin's lymphoma, mycosis fungoides and osteosarcoma. MTX (by oral or parenteral administration) is also recommended in treatment guidelines for chronically active or frequently relapsing inflammatory bowel disease, but this patient group is not a registered treatment indication in Australia.

Clinical rationale

Rheumatoid arthritis (RA) is a chronic autoimmune disorder, which affects approximately 1% of the Australian population. The burden of the disease is significant. After 5 years, one-half of patients with RA have developed important changes in health status. Low dose MTX is recommended as the first-line, disease modifying treatment for patients with RA according to international guidelines.[1] MTX has been shown to be efficacious, with an acceptable toxicity profile, and is cost effective.[2]

Psoriasis is a common, inflammatory and proliferative skin disease with a genetic determinant. Although PSOR may occur at any age, 2 age peaks of onset are identified: second decade of life (early onset) and fifth decade (late onset). Chronic stable plaque PSOR (PSOR vulgaris) is the most common form of the disease, accounting for 85 to 90% of all cases. While the majority of patients have mild PSOR, studies have found that 25% of patients reported their disease as moderate, and 10% as severe. Psoriasis can be disabling, affecting the physical, social and psychological wellbeing of patients. Plaque PSOR manifests as thickened, well demarcated, erythematous patches of skin covered with silvery scales. The lesions often arise in predisposed areas such as the extensor aspects of the knees and elbows, but can be generalised. Other sites affected by PSOR include the nails, scalp, palms, soles and intertriginous areas. The skin lesions frequently cause symptoms of pruritus and discomfort. Topical agents such as salicylic acid, corticosteroids (CS) and vitamin D analogues are often used as a first line therapy, particularly if the PSOR is localised. Phototherapy with ultraviolet B (UVB) or psoralen + ultraviolet A (UVA) is often used as a first line treatment for widespread PSOR or as a second line treatment if topical therapy is insufficient. Systemic treatment with oral retinoids, MTX and cyclosporine (CsA) are indicated in severe forms of PSOR. All of the systemic treatments have demonstrated efficacy but their long-term use is limited by potential risks and toxicities. Biologic therapies such as anti-tumour necrosis factor (anti-TNF) drugs and ustekinumab have been demonstrated to be highly effective in the treatment of moderate to severe PSOR but their use is limited by the risk of significant Adverse Events (AEs) such as serious infection and malignancy potential. Despite the variety of treatment options available in PSOR, patients are often dissatisfied (> 70% prevalence) with current therapy options due to lack of sustained efficacy, adverse events and/or treatment inconvenience. Hence, there is an unmet need for additional therapies for patients with moderate to severe PSOR, which is refractory to topical treatment.

A folate analogue, MTX's mode of action in treating autoimmune disease is not entirely clear, although increasing adenosine levels and reducing pro-inflammatory cytokines seem to play an important role. The recommended dose of MTX for RA and PSOR can range from 7.5 to 25 to 30 mg/week, depending on guidelines. The sponsor has proposed an initial MTX dose of 7.5 mg once weekly, but a systematic literature review of MTX

[1] Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509
[2] Swierkot J and Szechinski J. Methotrexate in rheumatoid arthritis. *Pharmacol Rep* 2006; 58: 473-492

monotherapy in RA has recommended initial treatment with 10 to 15 mg orally, as well as dose increases to 20 to 30 mg/week if needed and tolerated.[3] Parenteral administration of MTX has been suggested to be more effective with fewer gastrointestinal adverse effects in patients with suboptimal response or intolerance to oral MTX.[4]

Guidance

CPMP/EWP/556/95 Rev 1. Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis.

CHMP/EWP/2454/02 Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis.

CHMP/EWP/QWP/1401/98 Rev.1/Corr Guideline on the investigation of bioequivalence.

Literature Based Submission (LBS) guideline: (http://www.tga.gov.au/pdf/pm-literature-based-submissions.pdf).

Contents of the clinical dossier

The submission contained the following clinical information:

- 2 in house comparative bioavailability studies (MC-MTX.7/PH and MC-MTX.9/PH) as well as 36 clinical pharmacology studies in the literature providing pharmacokinetic data.
- No population pharmacokinetic analyses.
- 1 pivotal efficacy/safety studies (MC-MTX.6/RH) in adult patients with RA supported by published cohort of RA subjects (Rau et al, 1991 onwards). [5, 6]
- No dose-finding studies.
- 2 additional in house efficacy/safety studies (MC-MTX.10/RH and MC-MTX.5/RH) in adult subjects with RA.
- Literature based submission containing 36 articles for the RA indication and 13 publications for the PSOR indication.
- No pooled analyses, meta-analyses or Integrated Summaries of Efficacy or Safety.
- methodology of the literature based submission including details and output of the database search.
- Clinical Overview and Clinical Summary for both of the proposed treatment indications (RA and PSOR; presented separately).

[3] Visser K, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. *Ann Rheum Dis* 2009; 68: 1086-1093
[4] Mouterde G, et al. Optimizing methotrexate therapy in rheumatoid arthritis: a systematic literature review. *Joint Bone Spine* 2011; 78: 587-592
[5] Rau R-2 et al. A double-blind comparison of parenteral methotrexate and parenteral gold in the treatment of early erosive rheumatoid arthritis. an interim report on 102 patients after 12 months. *Seminars in arthritis and rheumatism* 1991; 21(2 Suppl1): 13-20
[6] Rau R et al. Comparison of intramuscular methotrexate and gold sodium thiomalate in the treatment of early erosive rheumatoid arthritis. 12 month data of a double-blind parallel study of 174 patients. *British journal of rheumatology*. 1997; 36: 345-352

Paediatric data

The submission did include paediatric data in juvenile idiopathic arthritis (JIA) supporting the requested treatment indication of RA, but the sponsor is not proposing registration in any paediatric treatment indication in Australia.

Good clinical practice

All of the studies conducted by the sponsor in the Trexject clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

The literature based submission contained a total of 36 pharmacology studies (18 relating to bioavailability and 18 pharmacokinetic (PK) studies). All but 1 of the PK studies in the target populations were conducted in either adult subjects with RA or children/adolescents with JIA. The sponsor has also submitted 2 in-house comparative bioequivalence studies (MC-MTX.7/PH and MC-MTX.9/PH). None of the PK studies had significant methodological deficiencies that excluded their results from consideration, but many of the published trials had very small subject numbers to make clinically meaningful interpretation of their results.

Evaluator's conclusions on pharmacokinetics

In this submission, the PK properties of low dose parenteral MTX when used in patients with RA and PSOR was assessed from data published in the literature, which included 18 PK studies in total (17 in RA or JIA patients, and 1 small pilot Study in subjects with PSOR). The submission also contained 18 bioequivalence studies and 2 sponsor initiated trials evaluating comparative bioavailability. Many of the PK characteristics of low dose MTX are already known in both healthy volunteer subjects, as well as patients with RA, and to a lesser extent, PSOR.

The sponsor has presented data showing that the 10 mg/mL injection when given SC is bioequivalent to the IM injection in terms of the amount of drug distributed from the injection site (as measured by area under the curve (AUC)) in healthy volunteers receiving MTX 15 mg. They sponsor has also demonstrated that the 50 mg/mL injection is bioequivalent to the 10 mg/mL injection formulation for the amount of drug distributed from the injection site, when both products were given by the same route of injection. Cross study comparison of the 50 mg/mL product when given SC versus IM found a similar AUC but a slightly lower maximum plasma concentration (C_{max}) from the SC dose. The published supporting studies also report these observations. This PK result is unlikely to be of clinical relevance given the proposed maximum dose of 25 mg/week for the 50 mg/mL product is being requested. Analyses comparing parenteral dosing with oral administration over a dose range 7.5 to 40 mg/week showed that the AUC with oral dosing is on average lower than that with IM dosing.

The PK of low dose, orally administered MTX is known to be highly variable, particularly when the weekly dose is ≥ 15 mg. The presence of moderate to severe renal impairment significantly reduces the clearance of MTX, which is an observation regardless of the route of drug administration. Age does not appear to have significant effect on the PK of low dose MTX. Low dose MTX demonstrates significant inter-individual variability, the majority of which cannot be readily explained.

Pharmacodynamics

Studies providing pharmacodynamic data

This submission did not contain any new pharmacodynamic (PD) data.

Evaluator's conclusions on pharmacodynamics

The PD properties of MTX when used in adult patients with active RA and PSOR have been previously described in the literature. No new PD data was presented in this submission and the sponsor is not proposing any changes to the PD section of the PI that are different from alternative formulations of low dose MTX approved in Australia.

Dosage selection for the pivotal studies

The dose and administration frequency of MTX used in the pivotal Study MC-MTX.6/RH (15 to 20 mg/ week) is consistent with RA treatment guidelines. However, the commercially proposed 50 mg/mL formulation of Trexject has only been studied in Studies MC-MTX.9/PH (bioequivalence trial) and MC-MTX.10/RH (patient satisfaction study). The pivotal study in this submission (Study MC-MTX.6/RH) investigated the 10 mg/mL formulation of MTX. The literature based submission in both RA and PSOR have presented trials that have utilised the same doses and regimens of MTX that are generally in current clinical practice, but no specific dose finding studies have been performed in either treatment indication. The doses of previous and concurrent treatments (for example non-steroidal anti-inflammatory drug (NSAID) and corticosteroids [oral or topical]) used in the reported studies are also appropriate and consistent with contemporary clinical practice.

Efficacy indication 1

Indication 1: Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAID and one or more disease modifying drugs.

Studies providing efficacy data

- Study MC-MTX.6/RH
- Study by Rau et al [5, 6]

Other efficacy studies

- Study MC-MTX.10/RH
- Study MC-MTX.5/RH

Literature Based Studies in RA

- Efficacy in SC MTX Studies
- Efficacy in IM MTX Studies
- Efficacy in IV MTX Studies

For full details of these studies please see Attachment 2.

Evaluator's conclusions on efficacy – Indication 1

In support of the treatment indication of active RA in adult patients, the sponsor has provided data from one sponsor conducted, pivotal Phase IV trial (Study MC-MTX.6/RH) as well as one literature published cohort (Rau et al, 1991 onwards) as the core evidence of efficacy for the claimed indication. Supportive evidence of efficacy in RA is provided by 2 additional in house studies (MC-MTX.5/RH and MC-MTX.10/RH) and a TGA approved literature search strategy which identified 36 studies involving a total of > 1,000 patients administered parenteral MTX (IM, SC or IV injections) for the treatment of either RA or JIA. The submission meets the requirements of the EMA guideline of relevance, adopted by the TGA. [7]

In the pivotal Study MC-MTX.6/RH, a total of 384 subjects were randomised to receive MTX 15 mg/week by either SC injection (n = 194) or as oral therapy (n = 190) for up to 24 weeks. The study also had an early escape provision at 16 weeks if patients failed to demonstrate an American College of Rheumatology (ACR) ACR20[8] response, whereby patients receiving SC MTX could have their weekly dose of MTX increased from 15 mg to 20 mg, and those in the oral treatment group were switched to SC MTX 15 mg/week. The choice of comparator treatment in this study is appropriate and consistent with the current standard of care for patients with active RA. The trial design of the pivotal Study MC-MTX.6/RH is appropriate for the claimed treatment indication and the duration of follow-up is sufficient to adequately determine response in RA. The randomisation procedures, strategies to maintain blinding and statistical analysis were appropriately performed. The trial was performed according to GCP requirements, and the 2 minor protocol amendments did not have a significant impact upon the results.

The population examined in Study MC-MTX.6/RH and the supporting studies are similar in demographics to the subjects that would be treated with RA in Australian clinical practice. The vast majority of subjects were middle-aged, Caucasian, and with a female gender predominance. The generalisability of the trial results is satisfactory with some noteworthy caveats. In general, the studies only enrolled patients with moderately to severely active disease, with normal renal and hepatic function, and a relatively low risk of significant infection.

The choice of efficacy endpoints in the pivotal and supporting studies is acceptable, but not ideal. For the pivotal Study MC-MTX.6/RH, the primary efficacy outcome was the percentage of patients in each treatment group who obtained an ACR20 response at 24 weeks. All of the supporting studies used various efficacy endpoints that were relevant at the time of publication such as changes in DAS28[9] score, remission or response rates,

[7] CPMP/EWP/556/95 Rev 1 "Points to consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis"

[8] The ACR response (ACR) criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with RA. A patient with an ACR 20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen (maximum of 66) and tender (maximum of 68) joint counts, as well as a 20% improvement in any 3 of the 5 core-set measures which include Patient's Global Assessment (PtGA), Physician's Global Assessment (PhGA) of disease activity, Patient's Assessment of Pain score (on 10 cm VAS), Disability (Index of the HAQ), and acute phase reactants (ESR or CRP). The analyses of ACR50 and ACR70 included the same criteria as ACR20, but with the use of a higher percentage improvement (50% or 70%) instead of 20%.

[9] The 28 joint Disease Activity Score (DAS28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), CRP, and the patient's assessment of general health using a 10 cm visual analogue scale. The final score is derived by a complex mathematical calculation of the individual elements. The DAS28 score is a continuous scale ranging from 0 to 9.4, and most scores range from 2 to 7. According to EULAR guidelines, DAS28 > 5.1 indicates high disease activity, < 3.2 indicates low disease activity, and clinical remission is indicated by a DAS28 score of < 2.6. A change of 1.2 (that is, 2 times the measurement error) of the DAS28 score in an individual patient is considered a significant change. The EULAR response criteria classify patients as good, moderate or non-

and changes in CS dose requirements. The primary efficacy endpoint in the pivotal MC-MTX.6/RH trial was achieved. At 24 weeks, 78.2% (147 out of 188) of patients in the SC MTX group achieved ACR20 response compared to 70.1% (131 out of 187) of patients in the oral treatment arm, which met the protocol specified, statistical margin of treatment difference (p = 0.0412 by Cochran-Mantel-Haenszel (CMH) test). Therefore, SC MTX demonstrated superiority to oral MTX in the treatment of active RA in adult patients who were naïve to MTX. Various secondary efficacy endpoints in Study MC-MTX.6/RH supported the primary efficacy outcome, such a higher rate of ACR70 response, median DAS28 score change over time and the proportion of patients meeting EULAR[10] response criteria.

The study reported by Rau et al [5, 6] was the other trial nominated by the sponsor as being pivotal in this application. The trial was a randomised, double blind, parallel group study of 174 adult patients with early active erosive RA comparing IM MTX 15 mg/week with IM gold sodium thiomalate 50 mg/week (87 subjects in each treatment arm). The key efficacy findings were:

- 40 to 50% reduction in the mean number of tender and swollen joints over 6 to 12 months of treatment (statistically similar in both treatment groups)
- approximately 50% reduction in the duration of morning stiffness and serum inflammatory markers after 6 months of therapy (statistically similar in both treatment groups) and
- X-ray data showing a slowing of radiographic progression (similar to that observed with IM gold therapy) over 12 months.

The literature search identified a total of 36 published studies (some controlled, many uncontrolled, and some abstracts and case reports) in which patients with RA or JIA received low dose parenteral MTX therapy in a regimen similar to that being requested by the sponsor. The data shows that injectable MTX therapy results in clinically important improvements in RA and JIA disease activity (for example ACR 20 or Pedi 30[11] responses). This data provides further support for the claimed indication. The sponsor has also submitted 2 additional in house studies (MC-MTX.10/RH and MC-MTX.5/RH) which support the utility and tolerability of injectable MTX in adult patients with RA.

Overall, the data in this submission supports the efficacy of SC MTX in the treatment of adult patients with active RA, but there is no evidence that it is superior to the currently available conventional disease modifying anti-rheumatic drugs (DMARDs). Parenteral MTX offers another treatment strategy in area of medicine with an unmet therapeutic need.

Efficacy indication 2

Indication 2: Symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment.

The clinical efficacy of low dose weekly MTX given by any administration route (orally, SC, IM or IV injection) as a treatment for PSOR is well established, with several oral and

responders. To be classified as a good EULAR responder a patient must reach low disease activity (DAS28 score of < 3.2). Moderate EULAR response is the attainment of a DAS28 score between 3.2 and 5.1.

[10] The EULAR (European League against Rheumatism) response criteria are based on the assessment of disease activity using the Disease Activity Score (DAS), a statistically-derived index consisting of number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.

[11] The American College of Rheumatology (ACR) Pediatric 30 criteria are a set of criteria that are used as a primary outcome measure for trials of biologic therapies and for second line therapies. It has been prospectively validated

injectable products currently listed on the ARTG. Existing products for this indication prescribe starting doses as low as 10 mg/week, which can subsequently be titrated up to a maximum weekly dose of 50 mg. The proposed dosing recommendations in this application differ from MTX therapies currently approved in Australia by the addition of the SC administration route, reducing the starting dose to 7.5 mg/week and reducing the maximum weekly dose to 25 mg.

In this submission, the clinical efficacy of low dose MTX (7.5 to 30 mg/week) when given by SC injection in adult patients with PSOR is supported by 1 randomised controlled trial (Gumusel et al, 2011)[12] and 2 case series (Zackheim et al, 1992[13] and Arthur et al, 2001[14]). The application also contains another 9 randomised controlled studies, which provide supporting data for the use of low dose MTX (oral administration; 5 to 30 mg/week) in patients with PSOR. All of the additional supporting studies used a MTX dosing regimen, which incorporates at least some of the key components of the regimen proposed in this submission. In 4 of the 9 studies, a dosing schedule very similar to that proposed in this submission was used, including a low initiation dose (7.5 mg) followed by a gradual escalation in dose, according to response, up to a maximum of 25 mg/week. Two of those 4 studies included a placebo control arm.

Studies providing efficacy data

- Study reported by Gumusel et al (2011)[12]
- Case Series using MTX by SC Injection
  - Zackheim et al (1992)[13]
  - Arthur et al (2001)[14]

Other efficacy studies (Low dose oral MTX in PSOR Patients)

- Study reported by Saurat et al (2008)[15]
- Study reported by Reich et al (2011)[16]
- Study reported by Ho et al (2010)[17]
- Study reported by Akhyani et al (2010)[18]
- Study by Flystrom et al (2008)[19]
- Study by Heydendael et al (2003)[20]

[12] Gumusel M, et al. Evaluation of the efficacy of methotrexate and cyclosporine therapies on psoriatic nails: a one- blind, randomised study. *Journal of the European Academy of Dermatology and Venereology* 2011; 25: 1080-1084.
[13] Zackheim HS. Subcutaneous administration of methotrexate. *Journal of the American Academy of Dermatology*. 1992; 26: 1008.
[14] Arthur V, et al. Self-injection of gold and methotrexate. Journal of Rheumatology. 2001; 28: 1.
[15] Saurat J-H, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis. (CHAMPION). *British Journal of Dermatology* 2008; 158: 558-566.
[16] Reich K et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. *New England Journal of Medicine*. 2011; 365: 1586-1596.
[17] Ho SGY, et al. Methotrexate versus traditional Chinese medicine in psoriasis a randomised, placebo-controlled trial to determine efficacy, safety and quality of life. *Clinical and Experimental Dermatology* 2009; 35:717-722.
[18] Akhyani M, et al. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology*. 2010; 24: 1447-1451.
[19] Flystrom I, et al. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *British Journal of Dermatology*. 2008; 158: 116-121.
[20] Heydendael VMR, et al. Methotrexate versus cyclosporine in moderate-to- severe chronic plaque psoriasis. *New England Journal of Medicine.* 2003; 349: 658-665.

- Study by Fallah Arani et al (2011)[21]
- Study by Barker et al (2011)[22]
- Study by Dogra et al (2012)[23]
- Analyses performed across trials (pooled analyses and meta-analyses) a systematic review published by Montaudie (2011)[24]

For the full description and details of the evaluation of these reports please see Attachment 2.

Evaluator's conclusions on efficacy – Indication 2

In support of the proposed indication of symptomatic control of severe PSOR, which is not adequately responding to other forms of treatment (particularly, after topical treatment has failed), the sponsor has provided data from 10 randomised controlled trials, 2 small case series and 1 systematic review. Only 1 of the submitted trials (Gumusel 2011)[12] used a SC dosing regimen of low dose MTX, but many of the other included studies had elements consistent with the proposed Trexject posology, such as the initiation of low dose MTX 5 to 7.5 mg/week with an up titration of dose to 25 mg/week. Although the studies reported different efficacy outcomes, the majority reported psoriasis area severity index (PASI) 75[25] response as an outcome. For patients with moderate to severe PSOR, PASI 75 response is considered to be clinically relevant. According to the TGA adopted guideline of relevance,[26] PASI 75 response in the target population is appropriate to define efficacy. The current submission for Trexject meets the requirement of demonstrating sufficient efficacy for low dose MTX therapy compared to placebo in treating the symptomatic manifestations of moderate to severe PSOR, in individuals who have failed to respond to other therapies (mainly, prior topical treatment and varying rates of systemic and/or phototherapy).

The included studies have administered MTX for periods ranging from 12 to 52 weeks, which is a sufficient duration of treatment follow-up to ascertain the effectiveness of MTX in PSOR. Some of the studies reported maintenance of treatment effect after the cessation of therapy, which is an element recommended in the EU guideline. The studies also show that MTX is frequently inferior to biological therapies (for example infliximab) but there is a place for MTX (oral and injectable) as a treatment option for adult patients with moderate to severe PSOR.

[21] Fallah Arani SF, et al. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled trial. *British Journal of Dermatology* 2011; 164: 855-861.
[22] Barker J, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). British Journal of Dermatology. 2011; 165: 1109-1117.
[23] Dogra S, et al. Efficacy and safety of systemic methotrexate in two fixed doses of 10mg and 25mg orally once weekly in adult patients with severe plaque-type psoriasis: a prospective, randomized, double-blind, dose-ranging study. *Clinical and Experimental Dermatology.* 2012; 37: 729-734.
24 Montaudie H, et al. Methotrexate in psoriasis: a systemic review of the treatment modalities, incidence, risk factors and monitoring of liver toxicity. *Journal of the European Academy of Dermatology and Venereology.* 2011; 25(Suppl. 2): 12-18.
[25] PASI 75 A 75% reduction in the Psoriasis Area and Severity Index (PASI) score (PASI 75) is the current benchmark of primary endpoints for most clinical trials of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).
[26] CHMP/EWP/2454/02 corr. Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis.

Safety

Studies providing safety data

There were no studies in this submission that assessed safety as the primary outcome.

The sponsor has provided a single pivotal efficacy study (MC-MTX.6/RH) in adult patients with RA, which collected the following safety data:

- General AEs were assessed by adverse event reporting and physical examinations, both of which occurred weekly for the first 4 weeks, every 2 weeks between Weeks 6 and 12 and thereafter every 4 weeks until Week 24.
- Injection site reactions (ISR) were an AE of particular interest, assessed at each scheduled visit.
- Laboratory tests, including haematology and biochemistry, as well as urinalysis testing were performed at baseline, weekly for the first 4 weeks, every 2 weeks between Weeks 6 and 12 and thereafter every 4 weeks until Week 24.

The non-pivotal efficacy studies providing safety data are as follows:

- Study MC-MTX.10/RH provided data on 131 adult patients with RA treated with SC MTX 20 mg/week for up to 6 weeks (up to 4 of the 6 injections were self-administered by the patient).
- Study MC-MTX.5/RH provided data on 87 adult patients with RA treated with SC MTX 15 to 25 mg/week for up to 6 weeks (the first 2 weekly injections were done by the investigator and the last 4 injections were done by the patient under supervision).
- Population cohort published in various journals (mainly Rau et al, 1997)[6] provided data over 12 months of follow-up in 184 subjects (87 subjects in each treatment group) with RA treated with either IM MTX or IM gold.
- Both the RA and PSOR literature based submissions provided safety data as well on general AEs, serious AEs and laboratory abnormalities.

For the full details of the clinical evaluation of the safety aspects please see Attachment 2.

Safety issues with the potential for major regulatory impact

Liver toxicity

Increased serum transaminases are a relatively laboratory abnormality associated with low dose MTX therapy in adult patients with RA or PSOR. The liver function test abnormalities are usually transient and asymptomatic. Chronic hepatotoxicity (including fatty change, periportal fibrosis and cirrhosis) has been associated with chronic cumulative use of low dose MTX in the requested treatment indications in this submission. Parenteral MTX does not appear to have an increased risk of hepatotoxicity compared with chronic low dose oral MTX therapy. The proposed PI for Trexject contains information on the risk of liver toxicity associated with MTX and the risk factors for its development. This report contains details of the incidence and pattern of abnormal liver function tests observed with low dose parenteral MTX in adult patients with RA and PSOR.

Haematological toxicity

Myelosuppression including neutropenia, thrombocytopenia and anaemia are an uncommon but significant toxicity associated with low dose MTX therapy (given by any route of administration). This is reflected in the current submission and the parenteral administration of MTX does not appear to change the risk of significant haematological toxicity compared to administration of same dose MTX therapy by oral ingestion. The risks

of low dose MTX with respect to myelosuppression are contained in the proposed Trexject PI.

Risk of infection

Low dose MTX treatment is associated with an increased risk of severe or serious infection, including opportunistic infection, and the current submission for parenteral MTX is consistent with expectations (incidence and pattern of serious infection) for low dose weekly therapy in the target treatment populations. More details about infection related SAEs is provided in this report.

Injection site reactions

The submission contained data showing a similar incidence of injection site reactions (ISRs) (6.5 to 7.1% of subjects) in the 2 treatment groups (SC MTX versus oral MTX with placebo injections) in the pivotal RA Study MC-MTX.6/RH. The supporting literature and trials in both RA and PSOR patients report a low incidence of ISRs, typically rated as mild in severity, and rarely resulting in a patient having to cease MTX.

Safety in special populations

Low dose MTX therapy (by any route of administration) should be avoided in any pregnant or lactating women. Older patients (> 65 years of age) do not appear to be at an increased risk of toxicity from low dose weekly therapy if their renal and hepatic function is normal, and their body folate stores are replete. The Trexject PI contains the same information as other MTX approved medicines on this issue.

Safety related to drug-drug interactions and other interactions

Low dose MTX treatment has been associated with many potential drug-drug interactions including those with probenecid, various antimicrobial drugs (such as ciprofloxacin, doxycycline and trimethoprim with sulfamethoxazole), folinic acid and proton pump inhibitors. Although not specifically examined for in the Trexject clinical development program, the reported incidence of drug-drug interactions was low and would not be expected to occur at a higher incidence if patients receive parenteral versus oral low dose weekly MTX for RA or PSOR.

Post-marketing data

The most recent PSUR (covering data collected between 2008 and 2012) identifies a total of 185 case reports of AEs with parenteral MTX therapy in treating patients with RA, polyarthritic forms of JIA or PSOR. The estimated exposure to Trexject 50 mg/ml from sales data has been calculated as 329,879 patient years of treatment (assumes average weekly MTX dose of 17.5 mg). A total of 60 AE reports have also been received for off label treatment indications including inflammatory bowel disease, SLE, dermatomyositis, Wegener's granulomatosis, pemphigoid, ankylosing spondylitis and temporal arteritis. The post-marketing experience with Trexject did not identify any new safety concerns with low dose MTX use, or an increased frequency of known side effects with parenteral therapy. In particular, the expected incidence of malignancies (solid cancers and lymphoproliferative disorders) appears to be within expectations for the target treatment populations. Injection site reactions from either SC or IM injection of MTX appears to be an uncommon AE affecting < 1% of subjects and rarely resulting in treatment discontinuation. However, lipoatrophy at the injection site does appear to be more common in women and when injections are given in a thigh location.

Evaluator's conclusions on safety

The sponsor did not include an integrated analysis of safety data in this submission, which is appropriate because of the heterogeneity of the studied populations and different

methods of data collection. The total clinical safety dataset for the RA consists of a patient exposure of 1,147 patients who have IM MTX 7.5 to 30 mg/week, 850 subjects who have received SC MTX 5 to 45 mg/week and 80 patients who have received IV MTX 7.5 to 500 mg/week. The RA control data also includes 750 patients who have taken low dose, weekly, oral MTX. The PSOR safety dataset comprises 343 patient years of information published in the literature.

The current safety dataset provides sufficient information about the short and medium term risks (up to 2 years) associated with parenteral MTX in the 2 target populations such as liver and haematological toxicity, infections, injection site reactions, and discontinuations due to adverse events. However, the extent of long term follow-up (several years) is relatively small and may not be adequate to assess for some potential AEs of concern that may have a long latency between drug exposure and AE occurrence, particularly malignancy, some opportunistic infections and cardiovascular safety. The study populations had baseline characteristics, disease activity and concomitant medications indicative of the intended target populations for the claimed indications.

Key safety conclusions identified in the pivotal RA Study MC-MTX.6/RH safety dataset are as follows:

- At 24 weeks, the overall incidence of AEs, drug related AEs, SAEs and serious infections were similar in the oral and SC MTX treatment groups.
- Most common individual types of AEs (occurring in > 5% of patients in either treatment group) were nausea, abdominal pain, abnormal investigation results, anorexia, diarrhoea and non-serious infection, all of which occurred at a similar incidence in both MTX groups apart from a higher incidence of gastrointestinal AEs with SC versus oral MTX (45.6% versus 38.3%).
- Permanent discontinuations from MTX due to AEs were more frequent in the SC MTX group (9.3% at 6 months) than the oral MTX arm (4.3% at 6 months), mainly due to a higher incidence of gastrointestinal AEs.
- At 6 months of follow-up, the overall incidence of SAEs was similar in the 2 treatment groups (4.3 to 5.7%) with the most frequent type of SAE being major cardiovascular events (coronary ischemia and stroke).
- The most frequent type of investigation abnormality in both treatment groups involved elevated serum transaminases, which occurred at a similar frequency in both arms (21.3 to 22.5%). Most of these abnormalities were asymptomatic and transient, and infrequently prompted permanent discontinuation from MTX.

In the supportive RA studies (including the published cohort by Rau et al[5, 6]), more than 2,000 subjects in total have received parenteral treatment with MTX (with doses ranging from 5 to 45 mg/week), and treatment follow-up was typically limited to 6 to 12 months. The overall incidence and pattern of AEs in these studies is similar to that observed in the pivotal sponsor initiated trial MC-MTX.6/RH. In particular, a higher frequency of gastrointestinal AEs is associated with the SC administration of MTX in patients with RA (versus IM and oral therapy) and treatment discontinuations occur at a frequency of 5 to 10% over 6 to 12 months. The published data does not identify any new potential safety concerns with MTX. In the PSOR studies, a similar pattern and incidence of AEs was generally observed with low dose MTX. Gastrointestinal AEs, non-serious infections and headache are the most common AEs, as well as low incidence of pruritus and non-specific musculoskeletal pain (which is different to the RA experience). The consistent, key safety finding from all of these supportive studies is that major cardiovascular events and occasional serious infections are the most common type of SAE.

Death has been reported in at least 38 subjects with RA and in 1 patient with PSOR exposed to parenteral MTX (35 in the RA LBS, 3 in the publication by Rau et al and 1 PSOR

patient in the published literature). Fifteen of the deaths (all in RA subjects) have resulted from major cardiovascular events (myocardial ischemia or stroke). However, the mortality rates and types of deaths observed in the RA and PSOR studies is probably consistent with those expected in the target populations. A total of 6 malignancies in RA treated patients have also been identified, which is also within expectations. No specific type of malignancy was observed at a heightened frequency.

MTX is associated with an increased risk of opportunistic infection, including pneumocystis pneumonia (although no confirmed cases have been reported in patients in this submission dataset), but major infections (including 1 reported fatality) have been recorded in this population.

All of the studies (in both RA and PSOR) have demonstrated a relatively high frequency of abnormal liver function tests with low dose MTX (by any route of administration) which is a known AE of such therapy. The incidence of abnormal liver function tests does not appear to be affected by the route of administration of low dose MTX. There are also sporadic reports of thrombocytopenia, leukopenia and anaemia in this submission affecting both patients with RA and PSOR. This is known uncommon AE of MTX therapy.

Injection site reactions occurred in 6.5 to 7.1% of subjects in the pivotal RA Study MC-MTX.6/RH, with a similar proportion of reported AEs in each of the treatment groups (SC MTX versus oral MTX with placebo injections). The supporting literature and trials in both RA and PSOR patients report a low incidence of ISRs with patient rarely having to cease treatment due to an ISR.

In summary, the safety data indicates that parenteral MTX has an overall comparable safety profile to the current standard of care (oral MTX or other active comparator therapies) in patients with moderately to severely active RA or PSOR. There are some significant safety concerns including the risk of serious infection, abnormalities of liver function, malignancy potential and cytopenias (leukopenia and thrombocytopenia). Significant pharmacovigilance would be recommended if approval were granted for Trexject. This would include vigilance for opportunistic infections, malignancy, all cause death, and significantly abnormal laboratory results.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Trexject in the proposed usage are:

- Slightly higher rate of ACR20 response [8](which is the minimal clinically detectable improvement) in MTX naïve RA patients with early disease when given low dose weekly MTX (15 to 20 mg/week) by SC injection versus oral therapy (as observed in Study MC-MTX.6/RH).
- Injectable MTX achieves a clinical response (improvement) in adult patients with RA that is superior to placebo therapy, but similar in magnitude to other conventional DMARD treatment, such as IM gold.
- For the proposed indication of moderate to severe PSOR, low dose MTX by SC injection was only examined in 1 study[12] and was found to be equivalent to oral Cyclosporine A (CsA). The majority of supporting efficacy data in PSOR compared low dose oral MTX to a variety of active treatments and showed a clinical effect better than placebo but inferior to biological treatment.
- Patients with RA report high levels of satisfaction and local tolerance with self-administered Trexject injections.

- The availability of colour coded, prefilled syringes in multiple doses and specific to patients with RA and PSOR has the potential to reduce the risk of medication administration errors.
- Potential for improved response to low dose MTX therapy in RA and PSOR patients who have failed to adequately respond to oral therapy; and therefore subsequent treatment with biologic agents may be avoided or delayed.

First round assessment of risks

The risks of Trexject in the proposed usage are:

- Higher incidence of gastrointestinal AEs and discontinuations from therapy with SC versus orally administrated low dose weekly MTX in adult patients with active RA and PSOR.
- Low risk of serious infections and injection site reactions with parenteral low dose MTX.
- High incidence of abnormal liver function tests with regular low dose MTX in both RA and PSOR patients, which is not affected by the route of administration.
- Potential for off-label use in adult patients with other autoimmune conditions such as inflammatory bowel disease, psoriatic arthritis and systemic lupus erythematosus.
- Potential for off-label use in paediatric patients with JIA. MTX is frequently used in JIA and Trexject is approved in several countries (including the EU) for use in polyarthritis subtypes of JIA.
- Potential for overdose with serious clinical consequences if Trexject is given at an inappropriate dose schedule such as daily for several days versus the recommended once weekly regimen.
- Currently available parenteral preparations of MTX in Australia include 2.5 mg/mL, 25 mg/mL and 100 mg/mL. The availability of Trexject will add another MTX presentation (50 mg/mL), which has the potential to increase the risk of medication error (dispensing and administration).
- Potential for cytotoxic exposure to healthcare workers and consumers (including pregnant women) if handling and drug disposal recommendations are not correctly adhered.

First round assessment of benefit-risk balance

Overall, the benefit-risk balance of Trexject, given the proposed usage (low dose weekly therapy given by SC or IM administration) in the target populations of adults with moderately to severely active RA or PSOR, is favourable.

First round recommendation regarding authorisation

Overarching issues

The evaluator recommends acceptance of the sponsor's proposed indications for Trexject subject to satisfactory response to the questions raised, and regular periodic safety update reports (PSURs). The sponsor is applying for registration for 3 routes of parenteral administration (SC, IM and IV injection). There is a sufficient volume of data with Trexject to recommend registration of the SC and IM routes of administration (in both treatment indications) but only a small volume of data from other injectable formulations of MTX to

support the IV route of administration. The evaluator did not recommend registration of the IV route of administration for Trexject. In addition, the submission does not provide sufficient clarity about the appropriate clinical setting for the IV administration of Trexject to occur, nor whether the presentation device is suitable for IV administration.

The sponsor proposed commercial formulation (50 mg/mL) of Trexject has only been studied in Studies MC-MTX.9/PH (bioequivalence trial) and MC-MTX.10/RH (patient satisfaction study). The pivotal study in this submission (Study MC-MTX.6/RH) investigated the 10 mg/mL formulation of MTX. Nonetheless, there is sufficient volume of supporting data to suggest that the 50 mg/mL formulation is acceptable for registration.

The submission contains a sufficient volume of data to support the sponsor proposal for self-administration of Trexject by SC or IM administration. The supporting evidence for such practice is provided by data in Studies MC-MTX.10/RH (patient satisfaction trial) and MC-MTX.5/RH (local tolerability trial). In both of these in house studies, MTX was self-administered by SC injection for up to 6 weeks in adult patients with RA at a dose of 15 to 25 mg/week. The results show that self-injection of MTX did not result in a higher incidence of AEs (specifically, local injection reactions) compared with administration by a healthcare professional, and was acceptable by patients. In both studies, the self-administration of MTX did not identify any new or more frequent safety concerns with low dose MTX use in adult patients with RA. The LBS also contained 3 small studies in paediatric patients with rheumatic disease whereby trained parent or carer SC administration of weekly low dose MTX was acceptable to patients and parents.

Specific treatment indications

Rheumatoid arthritis

Although the proposed indication wording in RA is consistent with other injectable formulations of MTX registered in Australia, the indication wording could be amended (shortened) to be consistent with contemporary literature and worldwide best clinical practice. The treatment indication should simply state:

"Treatment of moderately to severely active rheumatoid arthritis in adults".

Low dose weekly MTX (oral or parenteral) should be considered first line therapy in adult patients with RA of moderate to severe activity, and not only be considered after a trial of NSAID and/or other conventional DMARDs. The use of concurrent NSAID and/or low dose CS is acceptable (and supported by the current submission as well as literature) but the evaluator would viewed this additional information as being of limited value in the treatment indication wording.

The sponsor proposes the following dosage regimen for Trexject in RA: "*The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should not be exceeded. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4 to 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose*." The posology wording is highly similar to that for low dose oral MTX in Australia, as well as the overseas registration wording of injectable MTX. However, the dosing regimen wording could be simplified to be consistent with contemporary literature and worldwide best clinical practice. The dosage regimen should simply state "*that a weekly dose of 7.5 to 25 mg is recommended, depending on response and tolerability*". The evaluator also agreed with keeping the last proposed sentence relating to the back-titration of MTX to the lowest effective maintenance dose once disease remission is achieved. Published evidence does not support the slow upward titration of MTX from

7.5 mg/week in RA patients with severely active disease, and starting doses as high as 15 mg/week have been investigated.

Psoriasis

The evaluator concurred with the sponsor proposed treatment indication wording for PSOR.

The sponsor proposes the following dosage regimen for Trexject in PSOR: "*The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. In a few exceptional cases a higher dose might be clinically justified, but should not exceed a maximum weekly dose of 30 mg of methotrexate. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression. Response to treatment can generally be expected after approximately 2 to 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose*." Like RA, the posology wording could also be amended (shortened). The dosage regimen should state "*that a weekly dose of 7.5 to 30 mg is recommended, depending on response and tolerability*". The evaluator would also agree with keeping the last proposed sentence relating to the back-titration of MTX to the lowest effective maintenance dose once clinical remission is achieved.

Clinical questions

1. The current application is proposing the administration of Trexject by the subcutaneous (SC), intramuscular (IM) and intravenous (IV) routes of administration in adult patients with RA and psoriasis. Can the sponsor clarify if it wishes to seek registration for administration by the IV route, and if so comment on the suitability and safety of self-administration of Trexject (pre-filled syringes; possibly presented in a pen device) by the IV route. If the IV route administration is being requested, can the sponsor outline the clinical setting for safe and appropriate administration of Trexject, and how this may differ from the proposed SC and IM administration setting?
2. Can the sponsor also clarify the suitability of the presentation device and safety of self-administration of Trexject (pre-filled syringes) by the IM route as the data included in this submission (Studies MC-MTX.10/RH and MC-MTX.6/RH; as well as the supporting literature based trials) about self-administration relates principally to SC administration of low dose MTX?

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2, (extract from the clinical evaluation report).

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical efficacy information was requested or submitted in the sponsor's response. Accordingly, the benefits of Trexject are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

In response to questions, the sponsor has provided clarification regarding the clinical setting for self-administration (SC route only) and the presentation packaging of Trexject for use by various routes of administration. Despite these clarifications, the risks of Trexject are unchanged from those identified in first round assessment of risks.

Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, there is no change to the opinion expressed the first round assessment of benefit-risk balance. The benefit-risk balance of Trexject in the proposed treatment indications of adult patients with RA and PSOR is favourable when the drug is given by the SC or IM route of administration. In addition, there is sufficient data to support the proposal for self-administration by the SC route of administration in selected patients using the embedded needle device. The evaluator would not recommend registration of Trexject by the IV route of administration. The current submission does not contain a sufficient volume of directly obtained clinical data to support the safe use of Trexject in this setting.

Second round recommendation regarding authorisation

The evaluator recommends acceptance of the sponsor's proposed treatment indications for Trexject that is, adult patients with RA or psoriasis. The sponsor is applying for registration by 3 routes of parenteral administration (SC, IM and IV injection). There is a sufficient volume of data with Trexject to recommend registration of the SC and IM routes of administration. In addition, there is a sufficient volume of data to support the registration of self-administration by the SC route. However, there is only a small volume of data from other injectable formulations of MTX to support the IV route of administration. The evaluator did not recommend registration of the IV route of administration for Trexject. In addition, the evaluator would recommend the dosage regimen for Trexject use in RA and PSOR be amended as per the recommendations outlined in the first round recommendation regarding authorisation.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan Metoject EU-RMP version 2 dated 1 February 2013 (data lock point 1 February 2013), Australian Specific Annex dated June 2014 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 1.

Table 1: Ongoing safety concerns

Ongoing safety concerns	
Important identified risks	Dermatitis, erythematous rashes, pruritus, urticaria Photosensitivity, depigmentation/hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis

Ongoing safety concerns	
	Nail changes Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme Bone marrow suppression (leukocytopenia, neutropenia, thrombocytopenia, anaemia) Pancytopenia, aplastic anaemia, agranulocytosis Megaloblastic anaemia Pericarditis, pericardial effusion Vasculitis, hypotension, thromboembolic events Mucositis (gingivitis, pharyngitis, stomatitis, glossitis), anorexia, nausea, vomiting, diarrhoea, abdominal distress Gastrointestinal ulceration and bleeding, intestinal perforation, enteritis, haematemesis, melena Toxic megacolon, malabsorption Elevated transaminases Cirrhosis, periportal fibrosis, atrophy, necrosis and fatty metamorphosis of the liver, acute hepatitis, decrease in serum albumin Cystitis, dysuria, haematuria Severe nephropathy, renal failure, azotaemia Vaginitis, vaginal discharge, urogenital or menstrual dysfunction, loss of libido, impotence, defective oogenesis or spermatogenesis, transient oligospermia Abortion, foetal defects, foetal death Interstitial pneumonitis, interstitial fibrosis, reversible eosinophilic pulmonary infiltrates, respiratory fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, alveolitis Headache, drowsiness, dizziness Conjunctivitis, eye discomfort, blurred vision and serious visual changes of unknown aetiology including transient blindness Opportunistic infections with for example pneumocystis carinii, nocardiosis, histoplasmosis, cryptococcosis, Herpes zoster, H. simplex, cytomegalovirus Lymphoma Precipitation of diabetes mellitus Arthralgia, myalgia, osteoporosis Redness, swelling, itching, pain, haematoma at the injection site
Important potential risks	None
Important missing information	None

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the safety concerns. No additional pharmacovigilance is proposed.

Risk minimisation activities

The sponsor states: 'There is no important identified or potential risk for methotrexate 50 mg/mL solution for injection for which additional risk minimisation measures are necessary.

Reconciliation of issues outlined in the RMP report

Table 2 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 2: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
The sponsor should provide contact details, such as the office phone number, an email address, of the personnel responsible for the RMP in the ASA.	The details are included in the RMP ASA.	The sponsor's response is satisfactory.
The sponsor has identified a list of important drug interactions in the table 'summary of Safety Concern and Planned Pharmacovigilance Actions'. The listed drug interactions should also be included on the list of ongoing safety concerns.	A combined list of ongoing safety concerns and planned pharmacovigilance actions is included in the RMP ASA section 3.1 Risk Minimisation Activities Referenced in the EU-RMP. The revised (tracked) ASA is included.	The evaluator has noted the relevant changes in the updated ASA. The sponsor's response is satisfactory.
The sponsor recognises the potential for off-label use and paediatric off-label use in the EU-RMP. It is noted that many of the uses are approved for other methotrexate products in Australia. However, the sponsor should still provide its	The sponsor has modified the ASA to include additional risk minimisation procedures for the following potential risks: The potential for dosage and/or administration errors as a result of self-administration via subcutaneous injection The potential for off-label use. A physician and patient education booklet will be made available prior to product launch. The physician booklet will advise how to educate patients correctly with regard to the self-	The sponsor's response is satisfactory. The evaluator has noted the relevant changes in regard to the additional risk minimisation activities in the updated ASA. The sponsor should provide the

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
conclusion in regard to the need for risk minimisation activities for these issues.	administration of methotrexate via subcutaneous injection. In this booklet, emphasis will be placed on the dosage regimen, especially with regard to dose frequency. The physician booklet will also include a directive to enter dosing dates into the patient information booklet to ensure correct and regular dosing is maintained by the patient in the home setting. The patient information booklet will include detailed information with regard to the correct administration and dosing procedures as well as a calendar where the treating physician will nominate the required dosing dates. It is anticipated that the relevant treating physicians (currently treating RA and psoriasis patients) would be advised in writing of the availability of the abovementioned educational materials, to which the physician would respond requesting the required number of copies. In order to address the potential for off-label use, the relevant treating physicians identified above would also be advised/ reminded, in the same letter, of the approved indications for the product. The revised (tracked) ASA is included.	educational materials to the TGA for review before they are distributed.
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the PI be revised to include warnings for the use of methotrexate in patients with the following existing conditions: 'immunosuppression', 'lymphoproliferative disease within the last five years', and 'clinically important pneumonitis (due to RA) or interstitial lung disease'. Consideration should also be given to the fact that unlike most of the other approved methotrexate products, the proposed indications do not include neoplastic	An additional immunosuppression paragraph was added to the precautions section. A review of the ARTG indicates that the proposed PI wording in relation to other suggested warnings is consistent with other published methotrexate PI's. The proposed indications do not include neoplastic conditions because the MTX dose used to treat patients with neoplastic diseases is usually higher than that used in patients with autoimmune diseases. The largest presentation of the prefilled syringes contains only 30 mg MTX. Furthermore, in oncological indications MTX is usually dosed on mg/m^2 body surface area. Therefore, the prefilled syringes are not suited for use in neoplastic diseases and these indications were not included and discussed in the PI."	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
conditions with a much higher mortality.		
The product is expected to be used at home in community settings. The proposed indications would mean that some carers are expected to handle the product. It is important for the consumers to be reminded of the protective recommendations. Therefore, it is recommended to the Delegate that the 'Instructions for handling' in the proposed PI be also provided in the CMI.	The 'Instructions for handling' in the proposed PI are also included in the CMI. Please refer to the submitted dossier.	The evaluator has noted the changes in the draft CMI document as recommended, the sponsor's approach is satisfactory. However, It should be noted that advices such as 'all items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration' may not be clearly understood or practical in community settings. Therefore, it is recommended to the Delegate that advices that are practical to community settings 'regarding safe and appropriate disposal post-injection' being provided in the CMI.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

The RMP evaluator supports the recommendation made in the clinical evaluation report. It should be noted that advices such as 'all items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration' may not be easily understood or practical in community settings. Therefore, it is recommended to the Delegate that advices that are practical to community settings 'regarding safe and appropriate disposal post-injection' being provided in the CMI.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA request for information the sponsor provided an updated Australian Specific Annex dated January 2015. Key changes from the version evaluated at Round 1 are summarised below in Table 3.

Table 3: Key changes to the updated RMP

Key changes to the updated RMP	
Safety specification	The following important identified interactions have been added: Medicinal products with high plasma protein binding Oral antibiotics Hypo-lipidaemic compounds Products containing folic acid or folinic acid Non-steroidal anti-inflammatory agents Probenicid Proton-pump inhibitors Medicinal products which cause folate deficiency Amiodarone Retinoids Hepatotoxic medicinal products Theophylline Mercaptopurine PUVA therapy Vaccination
Pharmacovigilance activities	Routine pharmacovigilance has been added to monitor all of the added safety concerns.
Risk minimisation activities	A physician education booklet and a patient education booklet have been added to mitigate the following risks: The potential for dosage and/or administration errors as a result of self-administration via subcutaneous injection The potential for off-label use

Suggested wording for conditions of registration

RMP

Implement Metoject EU-RMP version 2 dated 1 February 2013 (data lock point 1 February 2013), with Australian Specific Annex dated January 2015, and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Methotrexate (MTX) is a folic acid antagonist that acts primarily by competitively inhibiting the enzyme dihydrofolate reductase. As a result, DNA synthesis and cell replication are inhibited by blocking the conversion of folic acid to folinic acid. MTX has anti-proliferative, immunosuppressive and anti-inflammatory effects. Oral formulations of MTX are classified as an immunosuppressant drug with the ATC code L04AX03. Systemic formulations of MTC are classified as anti-neoplastic agents with the ATC code L01BA01.

Methotrexate has a chiral centre (S conformation). It is almost insoluble in water but dissolves in dilute solutions of alkali hydroxides. The currently registered parenteral strengths of methotrexate solution are 5 mg/2mL, 20 mg/2mL, 50 mg/2 mL, 500 mg/5 mL, 500 mg/20mL, 1000mg/10 mL, and 5000 mg/50mL.

Methotrexate is approved for IV, SC and IM use in the UK and 27 European countries and several Central and South American Countries. The UK product, Metoject 50mg/mL, administered SC, IM or IV is approved for the treatment of:

> *Active rheumatoid arthritis in adult patients*
>
> *Polyarthritic forms of severe, active juvenile idiopathic arthritis, when response to nonsteroidal anti-inflammatory drugs (NSAIDS) has been inadequate,*
>
> *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*
>
> *Mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines.*

The sponsor has proposed Trexject IN for its pre-filled syringe without embedded needle and Trexject for its presentation with embedded needle.

Quality

The quality evaluator noted there were several issues unresolved regarding the trade names and labelling of the proposed methotrexate 50 mg/mL solution in a pre-filled syringe but had no objections to its registration provided these issues are resolved. The drug substance met the EP/BP requirements, including tests and limits for optic rotation, and enantiomeric purity. It includes acceptable additional residual solvents limits. The stability data supports a shelf life of 2 years when stored below 25°C with the conditions 'Protect from light'.

Nonclinical

The nonclinical evaluator had no objections to the registration of the proposed methotrexate pre-filled syringe. No local tolerance issues were noted in tolerance studies conducted in rabbits using parenteral administration of 50 mg/mL methotrexate solutions, including SC and paravenous administration however the evaluator noted that the studies did not administer methotrexate as sodium. The nonclinical sections of the

proposed PI were noted to be based on PI documents for other methotrexate products previously approved by the TGA and the EU Summary of Product Characteristics.

Clinical

The clinical dossier was a hybrid submission of clinical trials and published literature comprising:

- Two comparative bioavailability studies (MC-MTX.7/PH and MC-MTX.9/PH)
- 36 published clinical pharmacology studies
- 1 pivotal efficacy and safety study in adult patients with RA (MC-MTX.6/RH) supported by a published cohort of RA subjects
- 2 additional efficacy/safety studies in adult patients with RA (MC-MTX.10/RH and MC-MTX.5/RN)
- 36 publications supporting the RA indication
- 13 publications supporting the PSOR indication
- There were no population PK analyses.

Pharmacology

Oral MTX is absorbed from the proximal jejunum via active transport by the proton-coupled folate transporter, a system which is polymorphic and capacity limited. Low dose (< 25 mg/m^2) administration of oral MTX has an estimated bioavailability of 70 to 80%, but intra and inter-individual variability increases with increasing doses. The apparent volume of distribution is 0.87 to 1.43 L/kg and it is about 50% plasma protein bound. Uptake into cells is via active transport and there is intracellular conversion of MTX to active moieties. The 7-OH-MTX from hepatic metabolism has about 10% of the biological activity of MTX. About 80% of the absorbed drug is renally excreted through a combination of glomerular filtration and active tubular secretion. About 10 to 30% of MTX clearance is from biliary excretion, a small about is metabolised by intestinal bacteria and there is some enterohepatic circulation. Elimination occurs in a triphasic manner from plasma. The β phase half-life is between 6 to 15 hours and the median terminal half-life is 55 hours.

Study MC-MTX.7/PH compared the PK characteristics of MTX 15 mg of a 10 mg/mL solution given IM (reference) versus SC (test). The geometric mean (gMean) ratio of AUC_{0-t} SC/IM was 97.84% (90% confidence interval (CI): 91.07 to 105.11). The gMean C_{max} SC/IM was 58.16% (90% CI: 47.61 to 71.06). Similar results for AUC of the 7-OH active metabolite were reported and the gMean C_{max} SC/IM was about 85%. The SC time to maximum plasma concentration (T_{max}) was approximately 1 hour and IM T_{max} was approximately30 minutes.

Study MC-MTX.9/PH compared the relative bioavailability of MTX 15 mg given by IM and SC injection for 50 mg/mL and 10 mg/mL formulations. Half the subjects had SC dosing with the 50 mg/mL and 10 mg/mL formulations (cross-over by formulation not route of administration), the other half had IM dosing with the two formulations.

For SC dosing 50 mg/mL: 10 mg /mL

- AUC_{0-t} 97.56% (90% CI: 89.90 to 105.88%)
- C_{max} 114.93% (90%CI: 90.96 to 145.22%).

For IM dosing 50 mg/mL: 10 mg /mL

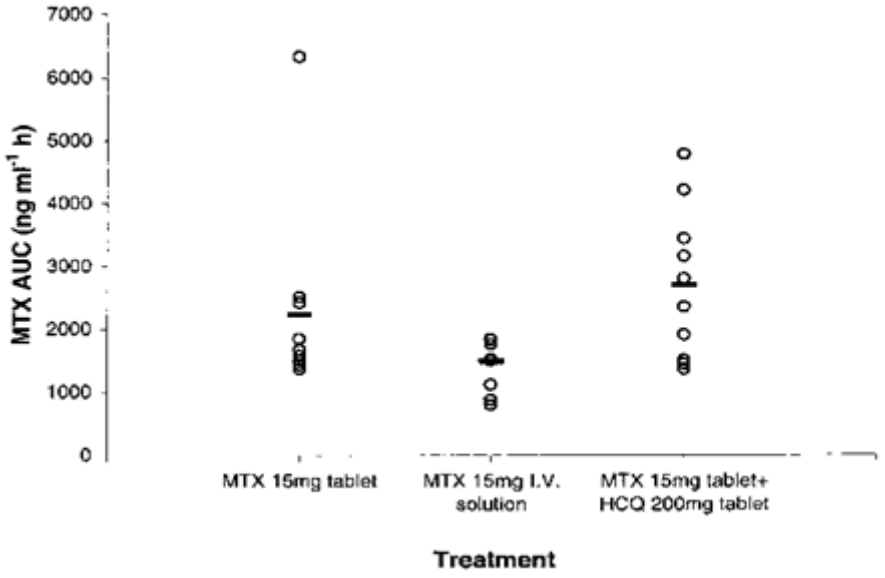
- AUC_{0-t} 91.85% (90% CI: 84.63 to 99.68%)
- C_{max} 120.67 (90% CI: 95.51 to 152.48%).

In a cross group comparison of the 50 mg/mL formulation SC/IM AUC_{0-t} was 123.9 (90% CI: 112 to 137%) and C_{max} SC/IM was 69.2% (90%CI: 53 to90).

The sponsor did not provide a bioequivalence study comparing the proposed formulation and any Australian registered oral MTX products. The sponsor compared the biopharmaceutical properties of MTX formulations currently available in Australia and its own product and concluded these were highly similar.

The comparison of oral and parenteral preparations was presented as published papers. Hoekstra et al (2004)[27] demonstrated the mean bioavailability of 30 mg oral MTX compared to 30 mg SC was 64% (range 21 to 96%) in 15 adult patients with RA. This difference was seen in a second study using 10 mg doses. Compared with IM dosing the oral bioavailability of a 10 mg dose was 70%. One study (9 RA patients) compared oral, IV and IM for a 15 mg dosing but did not report the AUC for the IV dose. Four small studies (total number of patients 32) included patients with RA and demonstrated bioequivalence between the parenteral dose forms. A small study (Carmichael 2002)[28] compared the bioavailability 15 mg oral and 15 mg IV MTX in 10 healthy volunteers as part of a study to investigate the interaction between hydrochloroquine and MTX. The mean $AUC_{0-\infty}$ (SD) ng mL $^{-1}$h for oral MTX was 1775 (415) and for IV was 1489(415) (see Figure 2).

Figure 2: Distribution of AUC measurements for each MTX treatment in Carmichael et al (2002). The mean is represented by the horizontal line



The kinetics of 10 mg IM and IV MTX was compared in parallel group study of patients with either RA or psoriatic arthritis. Mean $AUC_{0-\infty}$ (SD) was 4.12 (0.59) µmol/h for the IV group and 4.26 (1.26) µmol/h for the IM group. C_{max} was not reported for both groups.

[27] Hoekstra M. et al. Bioavailability of Higher Dose Methotrexate Comparing Oral and Subcutaneous Administration in Patients with Rheumatoid Arthritis. *Journal of Rheumatology* 2004; 31: 645-648
[28] Carmichael SJ et al. Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *Journal of Rheumatology* 2002; 29: 2077-2083

There was a linear relationship between creatinine clearance and MTX clearance and half-life after IM MTX 7.5 to 15 mg /week in patients with RA (clearance 3.82 L/hr and t ½ 22.7 hours with creatinine clearance (CrCL) < 45 mL/min (n = 7); clearance 6.91 L/h and t ½ 10.8 hours with CrCL > 80 mL/min (n = 30). A slow decline in MTX clearance was demonstrated with age but age adjustment was not required based on age alone if renal function as preserved. Hepatic fibrosis in patients with PSOR did not impact PK compared with patients with PSOR and normal hepatic function.

In the clinical overview the sponsor has presented the argument that parenteral MTX has the advantage of bypassing variable oral absorption of MTX and that although it is likely that parenteral administration of the 50 mg/mL infection may result in higher plasma levels than achieved from the same oral dose or 25 mg/mL or 10 mg/mL products the peak plasma levels are within those reported from the general population over the proposed dose range. The sponsor has suggested that the risk for the individual could be addressed by a dose reduction from oral to parenteral administration to ameliorate the risk of increased exposure, but has not proposed a method by which the dose adjustment should be calculated.

No new pharmacodynamic information was provided in this submission.

Efficacy studies for rheumatoid arthritis

Study MC-MTX.6/RH

This was a Phase IV randomised, double blind, parallel group study to evaluate the efficacy and safety of SC MTX (single 15 mg injection of methotrexate 10 mg/mL) compared to oral MTX (two tablets of 7.5 mg strength) in 384 MTX naïve adults subjects with active RA (DAS28 ≥ 4). The study had an active treatment period of 24 weeks with a fixed weekly dose of 15 mg, but the study medication could be changed at week 16 in ACR20[8] non-responders. Patients could continue stable NSAID and low dose prednisolone (≤ 10 mg/day) if stable for 2 weeks prior to randomisation.

Exclusion criteria were extensive but included patients at increased risk of infection; with, or at increased risk of liver disease; patients with upper gastrointestinal ulceration; with impaired haematopoiesis; renal impairment; use of conventional DMARDs 2 weeks (4 weeks for leflunomide) prior to randomisation; prednisolone ≥ 10 mg daily; prior use of biological agents. Technical issues prevented the patient blinding of the subcutaneous injections in this study, although investigators were blinded to the treatment. Premature discontinuations occurred in 23 (12%) of the SC group and 30 (15%) of the oral group. The study population was mostly female (76.8%), with a median age of 59 years and a median body weight of 74 kg. The median duration of RA prior to study entry was 2.5 months in the SC group and 2.1 months in the oral group. Most (75%) of the patients had not received any previous DMARD therapy for RA. Most (70.7% in the SC group and 66.8% in the oral group) had received low dose steroid within 2 weeks of study commencement and 62.2% and 64.2% had received concomitant NSAIDs. Most (63%) were rheumatoid factor positive. The median DAS28 score was high in both groups (6.1 and 6.3). Median baseline C-reactive protein (CRP) was 8.6 m/g/L in the SC group and 11.6 mg/L in the oral group. Protocol deviations occurred due to a change in the dose of NSAID (11.2% and 11.8% in the SC and oral groups, respectively) or corticosteroids (8.6% in both groups). Approximately one third of patients in each group had an efficacy assessment outside the scheduled visit. The study had an 80% power to detect a 15% difference in the ACR20 response at 24 weeks (55% in the oral MTX treatment group versus 70% in the SC arm).

The primary efficacy endpoint was ACR20 response at 24 weeks and was observed in:

- 78.2% of the SC group (p = 0.0412 versus oral)
- 70.1% of the oral group.

Subgroup analyses of the primary endpoint for baseline prognostic factors revealed a differential treatment effect for patients diagnosed for 1 year or more prior to treatment in the SC group (46 out of 52; 88.5%) compared to the oral group (29 out of 46; 63%).

Secondary endpoints: The median time to initial ACR 20 response was 6 weeks in both groups. ACR 70 was achieved in 41% of the SC group compare to 33.2% of the oral groups ($p = 0.0343$) but there was no statistically significant difference for ACR50 (62.2% and 59.4% in the SC and oral groups, respectively). There was a greater reduction in the number of tender and swollen joints and the CRP in the SC group compared with the oral group. All other individual parameters were similar. The DAS28 median score was greater in the oral group compared with the SC group and weeks 16 (3.4 versus 3.8 for the SC and oral arms, respectively) and 24 (3.3 and 3.7 for the but there was not difference in the earlier evaluation time points of Weeks 4, 6, 8, 10 and 12). Similar results were seen for EULAR response criteria over time.

The 30 ACR20 non-responders in the oral group at 16 weeks switched to 15 mg SC MTX/week, and 30% achieved an ACR20 8 weeks later. The 22 ACR20 non-responders in the SC group increased the dose from 15mg to 20 mg SC MTX/week, 20 were evaluated and 5 (25%) responded 8 weeks later.

Published study by rau et al

Published study by Rau et al (various publications dating from 1991 to 2002)[5, 6,29,30,31,32,33,34]: This was a randomised, double blind, parallel group trial comparing IM MTX 15 mg/week (methotrexate concentration 25 mg/mL) to gold sodium thiomalate 50 mg/week in the treatment of 174 adult patients with early active RA over a 12 months period. Eligible patients had a diagnosis of RA for at least 4 months duration and active disease defined and 3 of the following 4 criteria (erythrocyte sedimentation ratio (ESR) > 20 mm/h in men or 30 mm/h in women; morning stiffness > 1 hour, ≥ 6 swollen joints and ≥ 9 tender joints), at least 1 erosion on plain X-ray of the hands and feed but were excluded if they had established deformities (subluxation or ulnar deviation) Other exclusion criteria were prior treatment with gold or MTX, other DMARD therapy < 3 months before study commencement, history of alcohol abuse, malignancy, active peptic ulcer disease or other serious so-morbidity, and laboratory abnormalities (serum creatinine < 115 µmol/L, serum transaminases or bilirubin > 2 x upper limit of normal (ULN), platelet count < 150 x 10^6/mL, white cell count (WCC) < 3500/mL). Patients could continue on prior NSAID or prednisolone < 10 mg/day but doses needed to be stable for the first 6 months and then could be reduce or ceased. Half doses of the randomised treatment were given for 2 weeks and full doses thereafter. No folate supplements were given. Mean age was 54.2 years in the MTX group and 56.8 in the gold group, most were female 60% and 72% for the MTX and gold groups, respectively. Median

[29] Herborn G, et al. Interim report on 102 patients after two years in a double blind comparison of intramuscular methotrexate and gold sodium thiomalate in early erosive rheumatoid arthritis. *Zeitschrift für Rheumatologie* 1992; 51: 163-171.
[30] Menninger H. et al. A 36 month comparative trial of methotrexate and gold sodium thiomalate in the treatment of early active and erosive rheumatoid arthritis. *British journal of rheumatology* 1998; 37: 1060-1068.
[31] Rau R et al. Radiographic outcome after three years of patients with early erosive rheumatoid arthritis treated with intramuscular methotrexate or parenteral gold. Extension of a one-year double-blind study in 174 patients. *Rheumatology* 2002; 41: 196-204.
[32] Rau R. et al. Progression in early erosive rheumatoid arthritis. 12 month results from a randomized controlled trial comparing methotrexate and gold sodium thiomalate. *British journal of rheumatology* 1998; 37: 1220-1226.
[33] Rau R-2.et al. Longterm combination therapy of refractory and destructive rheumatoid arthritis with methotrexate (MTX) and intramuscular gold or other disease modifying antirheumatic drugs compared to MTX monotherapy. *Journal of Rheumatology*, 1998; 25: 1485-1492.
[34] Sander O. et al. Prospective six year follow up of patients withdrawn from a randomised study comparing parenteral gold salt and methotrexate. *Annals of the Rheumatic Diseases* 1999; 58: 281-287.

disease duration was approximately 11 months for each group, 38% and 33% of the MTX and gold groups, respectively were taking prednisolone, 9% and 13% had previous DMARD treatment, and 68% and 54% were rheumatoid positive. There were similar elevations of ESR and CRP between the groups. The mean baseline modified Sharp Score[35] was 5.8 in the MTX group and 4.6 in the gold group. Approximately 39% of the gold group and 16% of the MTX group did not complete the study (32 out of 34 of the discontinuations from the gold group and 6 out of 14 of the discontinuations from the MTX group were due to adverse effects).

The clinical parameters were statistically significantly improved from baseline for both treatment groups. Marked clinical improvement from baseline (≥ 50%) occurred in 47% (34 out of 73) of the MTX and 65% (34 out of 53) of the gold patients, including 14% of the MTX group and 25% of the gold group in clinical remission, specifically:

- 40 to 50% reduction in the mean number of tender and swollen joints over 6 to 12 months of treatment (similar in both treatment groups)
- approximately50% reduction in the duration of morning stiffness and serum inflammatory markers after 6 months of therapy(similar in both treatment groups) and
- X-ray data showing a slowing of radiographic progression (similar to that observed with IM gold therapy) over 12 months.

There was no statistically significant difference in the mean Sharp score progression between the treatment groups at 6 and 12 months. Both reduced the progression rate in the second half of the year compared with the first.

Study MC-MTX.10/RH

Study MC-MTX.10/RH This Phase III open label, repeat dose within patient controlled trial conducted in adult patients with active RA had the primary aim of investigating patient's satisfaction with a weekly 20 mg SC MTX dose given either as 2 mL of 10 mg/mL solution from a pre-filled syringe without a fixed needle or 0.4 mL of a 50 mg/mL solution from a pre-filled syringe with a fixed needle by questionnaire. Most patients (99.1%) preferred the fixed needle with the 50 mg/mL syringe and 87.5% preferred the smaller volume. Similar results were reported by physicians and study nurses.

Study MC-MTX.5/RH

Study MC-MTX.5/RH This exploratory, Phase II, open label, single group trial conducted in 82 adult patients with RA had the primary aim of assessing the local tolerability of repeated SC injections of MTX 10 mg/mL solution (as pre-filled syringes) at stable doses of 15 to 25 mg/week over 6 weeks (either oral or parenteral). The first 2 injections were given by the investigator and the last 4 by patients under supervision of the investigator. Tolerability was the only outcome. Global tolerability was assessed as good or very good by 93.1% of the patients and moderate and by 1.4% each. Reactions were mostly dermal but of the 19 dermal reactions in 14 patients only 2 were classified readily visible, definite erythema, oedema or popular reactions (the rest were barely perceptible minimal erythema) 1 patient recorded severe redness and 1 each reported itch and local pain (both moderate severity events). The majority of patients (94.2% were satisfied or very satisfied) with the administration system and 87% stated they would like to continue treatment without weekly visits to the physician.

[35] Total Modified Sharp Score (TMSS) is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change.

Additional publications in support of parenteral methotrexate for RA

Additional literatures support for SC use was provided by 4 controlled studies (n = 215 patients) and 5 uncontrolled studies (n = 170 patients) with a 12 to 26 week follow-up including data from the German (paediatric) MTX registry for children with JIA. This showed no difference in achieving ACR Pedi 30 improvement between oral (111 out of 152, 73%) and SC MTX (186 out of 259; 72%) after 6 months of therapy. One study compared SC with oral MTX in adult patients with inadequate RA control on oral MTX 15 mg/week. Patients switched to SC MTX achieved ACR 20 (93% versus 80%) and ACR 50 response (89% versus 72%).

Two controlled and 5 uncontrolled studies provided support for the use of IM MTX in RA compared with placebo over 6 to 12 weeks (29 patients). Another 5 studies (311 patients) compared MI MTX with gold or other active therapies, and there were 2 open label studies in children (724 patients). Most studies used 10 to 15 mg /week and treated patients for 6 months. Overall IM MTX reproduced a greater response than placebo in clinical outcomes and was similar to gold or oral MTX or leflunomide.

Six studies (80 patients) included IV administration of MTX for RA for 4 to 12 weeks. Only one (15 patients) was randomised and blinded and comparator was prospidine IV (not registered in Australia).[36] A 30 mg/week MTX IV induction dose for 4 weeks was followed by oral maintenance of 7.5 to 15 mg/week MTX. After 4 weeks 85% of the prospidine treated subjects demonstrated clinical improvement that was sustained in 73% of patients at 6 months. In the MTX arm 40% had a significant reduction in disease activity which improved to 57% at 6 months. Improvement in ESR and CRP was also significant within 4 weeks of receiving IV MTX. Another study used a single IV induction dose of MTX 15 mg/week followed by MTX 7.5 mg/week either orally or IV for up to 26 weeks. The number of patients receiving IV therapy beyond the initial induction dose is unclear from the study. Two other studies were limited by the lack of clinical efficacy data or study size, and the last two used very high doses outside the proposed dosage regimen.

Efficacy studies for psoriasis

The PSOR component of this submission was literature based. The sponsor has provided one clinical trial, and a case series in support of subcutaneous administration of MTX in PSOR. The sponsor provided 9 additional studies using oral MTX, 4 of which used a similar dosage regimen to that proposed by the sponsor.

Gumusel et al[12]

This single centre, single blinded randomised controlled (PROBE) trial compared the efficacy and safety of SC MTX with oral cyclosporin in 37 patients with moderate to severe PSOR with nail involvement. MTX was administered as 15 mg SC weekly for the first 3 months of the study and 10 mg /week for the remaining 3 months. The oral cyclosporine was given as 5 mg/kg for 3 months reducing to 2.5 to 3.5 mg for the second 3 months period. Apart from mail involvement other eligibility criteria included > 10% body surface area (BSA) involvement with PSOR, baseline PASI[37] score ≥ 10 and nail psoriasis severity

[36] Benenson EV. Timina OB. Prospidine versus methotrexate pulse in highly active rheumatoid arthritis: a controlled 6-month clinical trial. *Clinical Rheumatology*, 1994; 13: 54-59.

[37] The Psoriasis Area and Severity Index (PASI) is an assessment of 4 anatomic sites (head, upper extremities, trunk, and lower extremities) for erythema, induration, and desquamation using a scale of zero (the best evaluation, no symptoms) to four (the worst evaluation, very marked). The extent of lesions in a given area is assigned a numerical value from one (< 10%) to six (90 to 100%). The PASI score is then calculated from a weighted average based on the % of body surface area (BSA) of the anatomic site (head, 10%; upper extremities, 20%; trunk, 30%; and lower extremities, 40%). The PASI score has a range from 0 (no disease) to 72 (maximal disease).

index (NAPSI)[38] score of ≥ 10 (patients with distressing or topical treatment resistant nail involvement were eligible if BSA involvement or PASI < 10 could also be included). All patients had received prior phototherapy, systemic or topical treatments. The mean age of the MTX group was 42.5 years, and 38.4 years for the cyclosporine group. More participants were male in the MTX (59% [10 out of 17]) than in the cyclosporine group (47% [8 out of 17]). The mean duration of disease was 12.6 years in the MTX group, and 13.6 years in the cyclosporine group. The mean baseline NAPSI and PASI for the MTX group were 39.1 and 10.7, respectively and for the cyclosporine group 42.1 and 12.9, respectively. Premature discontinuations were because of adverse events (1 in the MTX group from elevated transaminases and 2 in the cyclosporine group from increased serum creatinine and increased lipid profiles).

The primary efficacy endpoint was the mean reduction in NAPSI score from baseline to 24 weeks:

- MTX group: baseline 39.1 to 24 weeks 18.3 (43.3% reduction)
- Cyclosporine group: baseline 42.1 to 24 weeks 25.4 (37.2% reduction).

PASI was a key secondary endpoint:

- PASI reduction from baseline to 12 weeks (prior to the dose reduction) in MTX group was 6.7 (63%) and cyclosporine group was 9.1(71%).
- PASI reduction from baseline to 24 weeks in MTX group was 4.5 (42%) and cyclosporine group 7.9 (61%)

Approximately 59% of the MTX group showed mild clinical improvement and 41% showed moderate clinical improvement. Of the cyclosporine group 47% showed mild clinical improvement and 41% showed moderate clinical improvement, with 1 patient (5.8%) showing complete resolution of PSOR.

Case series

One case series reported favourable tolerability outcomes for SC compared to IM MTX in 7 adult patients with PSOR and 3 with cutaneous T-cell lymphoma treated with SC MTX. Nine of the ten patients received weekly MTX. In a second case series no patients had PSOR but two of the 8 cases had Psoriatic arthritis (PsA).

The second case series (letter to the editor) of 8 patients included 4 patients with rheumatoid arthritis and 2 with PsA but no patients with PSOR. All patients were receiving stable weekly IM MTX dose for their various conditions. Patients were switched to SC MTX administered initially by nursing staff for 3 doses, then by patients in the clinic for 3 doses and finally at home for 3 doses. Clinical outcomes were not described in detail but no differences between the groups were reported. The patients preferred SC administration because it reduced pain and allowed them to self-inject. A reply to the letter noted experience with more than 100 patients taking stable injectable doses of gold or MTX who had not had serious AEs in the preceding 6 months.

Other supportive studies

The remaining studies reported oral MTX use in psoriasis, within a similar dosage range to that proposed for SC administration. None of these studies compared oral and SC MTX.

Safety

Safety data were derived from the clinical studies provided by the sponsor and any safety information reported in the literature.

[38] The Nail Psoriasis Severity Index (NAPSI) is a validated way of determining severity of nail PSOR affecting the nail bed and nail matrix. It has range of 0 to 80 (each of the 10 nails are scored 0 to 8) with a higher score indicating more severe nail PSOR.

Rheumatoid arthritis

A total of 2,077 patients exposed to at least one dose of MTX parenterally (1,147 patients IM MTX 7.5 to 30 mg/week of whom 164 were children with JIA, 850 patients SC MTX 5 to 45 mg/week and 80 patients IV MTX 15 mg/m^2 /week to 500 mg/m^2 /fortnight). Another 750 patients received oral weekly MTX.

Study MC-MTX.6/RH (24 weeks) AEs were reported in 66.3% of the SC and 61.7% oral groups, respectively. In the Rau cohort study AEs occurred in 66.7% and 83.9% in the IM MTX and IM gold groups, respectively. In MC-MTX.10/RH AEs were reported in 19.1% (10.7% in the IM MTX 10 mg/mL group and 11.5% in the IM MTX 50 mg/mL group). Approximately 12% of patients in MC-MTX.5/RH reported AEs. Gastrointestinal adverse effects were common across all studies (45.6% SC versus 38.3% oral: 20.7% IM MTX versus 9.2% IM gold: 6%: 6% in studies MC-MTX.6/RH: Rau et al: MC-MTX.10/RH: MC-MTX.5/RH, respectively). In the RA literature gastrointestinal AEs were reported in 36%/11%/13% in SC/IM/oral MTX dosing. Headache and dizziness was also reported in the literature and in 2.1% of SC MTX and 4.3% of oral MTX patients in MC-MTX .6/RH. Alopecia and rash were reported in 20% of patients taking IV MTX.

Only the sponsor led studies reported treatment related adverse events (TRAEs) (ADRs). Most common were the gastrointestinal AEs mentioned above and abnormal laboratory findings.

No deaths were reported in any of the sponsor led studies. In the literature no deaths were reported for SC or IV MTX (trials of ≤ 6 months duration) but 35 deaths (12 were cardiac, 6 were vascular, 6 respiratory 2 from neoplasms and 1 from infection) were reported among patients taking IM MTX studies involving follow-up for up to 3 years. In total there were 6 cases of cancer reported in the submitted literature (2 cases each of acute leukaemia and colon cancer, and 1 case each of gastric and oropharyngeal malignancies but there was no apparent higher risk with parenteral MTX. Not all studies had control arms and comparative rates are difficult to determine.

SAEs were most frequently reported due to cardiac disease, and the need for surgical procedures. A treatment related serious adverse event (TRSAE) was reported in a patient with pneumonitis from the SC MTX arm of study MC-MTX.6/RH. SAEs of facial fracture and non-specific back pain in study MC-MTX.10/RH were thought unrelated but mastoiditis 28 days after the conclusion of the study was thought possibly related. Neoplasia was reported but infrequently.

Discontinuation due to adverse events in study MC-MTX.6/RH occurred in 9.3% of the SC group and 4.3% of the oral treatment group. Most were due to gastrointestinal events (4.7% SC MTX versus 1.6% oral MTX) and anorexia (2.1% versus 1.6%). Infection (1 case each of bronchitis, nasopharyngitis and gastrointestinal fungal infection) and psychiatric disorder (1 case each of anxiety, confusion and sleep disorder) made up the remainder of the SC MTX discontinuations. In study MC-MTX.10/RH 1 patients each withdrew because of cough, dizziness and nausea with dry mucosa and pain.

Psoriasis

The exposure in the PSOR literature comprises 343.3 patient years. Overall, the reporting of AEs was limited. When reported, AEs occurred in about 85% of MTX treated patients, which was similar to the active comparators in these studies. The most common types of AEs were gastrointestinal, non-serious infections (mostly nasopharyngitis and viral infections), nervous system related (headache) and musculoskeletal (non-specific arthralgia and myalgia). Pruritus was reported for 2% of the patients. Injection site reactions were reported in ≤ 1.5% of the PSOR population using parenteral MTX. There was one death from oesophageal rupture. An additional 17 non-fatal SAEs were noted: 7 infections, 2 diverticulitis and abnormal LFT and one each of intestinal polyp, sacroilitis,

erythrodermic PSOR, vertigo, angioedema, urthicaria, intermittent claudication, and hepatitis. Discontinuations occurred at a median rate of 5% in the first 6 months of therapy, mostly due to elevated serum transaminases or gastrointestinal events.

Haematological toxicity

One patient developed leukopenia and thrombocytopenia taking MTX in the sponsor-led studies. This resolved at study conclusion. Decrease WCC was reported in 2.3% of the Rau et al study. There was no thrombocytopenia. Overall in the RA literature the frequency of abnormal haematology was 0.8 to 3% for parenteral MTX and 0.7% for oral MTX

In the PSOR literature one case each of transient thrombocytopenia and anaemia were reported.

Hepatotoxicity

Increased ALT > 2 x ULN was noted in 1.6% of SC MTX and 4.3% of oral MTX groups in MC-MTX.6/RH. In Rau et al transaminases < 3 x ULN occurred in 34.5% with IM MTX. From the RA literature 8 to 14% of patients receiving parenteral MTX reported liver enzyme abnormalities and about 9% with oral MTX use.

Abnormal laboratory results were reported in 3.8% in study MC-MTX.10/RH.

In the PSOR literature there were 63 reports of elevated or abnormal LFT (mostly elevated serum transaminases), most were mild and asymptomatic, some were associated with known confounders, and < 10% resulted in permanent discontinuation of MTX.

Injection site reactions

In study MC-MTX.6/RH injection site reactions occurred in 6.5% and 7.1% of the SC MTX and placebo injection (oral MTX) groups. The types of reactions were similar, although redness and itching was slightly more common with MTX. All were mild or moderate and none resulted in withdrawal from the study.

Infection was reported infrequently for MTX in both the sponsor-led studies and the literature for MTX.

Post market experience

Post market experience with Trexject 50 mg/mL (329,879 patient years from 2008 to 2012) identified a total of 185 cases with AEs in patients with RA polyarticular JIA and Psoriasis but did not identify any new safety concerns. In particular there were no signals for increased risk of malignancy. Injection site reactions were uncommonly reported, although lipoatrophy appeared more common in women when injections are given in the thigh.

Clinical evaluator's recommendation

The clinical evaluator had no objection to the registration of the methotrexate 50 mg/mL solution in a pre-filled syringe for the proposed indications for the new presentation and had no objections to the approval of SC and IM administration, and for patient self-administration of subcutaneous injections for both proposed indications. The clinical evaluator recommended rejection of the IV administration in the treatment of RA because of insufficient evidence to support its use.

Risk management plan

The Post Market Surveillance Branch has accepted the EU Risk Management Plan for Metoject version 2 dated 1 February 2013 (data lock point 1 February 2014) with Australian Specific Annex dated January 2015. The sponsor has made an undertaking to

provide educational materials for physicians and patients to explain the subcutaneous use of MTX. MTX is a cytotoxic drug and the issue of disposal of used syringes as well as other materials used in the injection of MTX has been raised. The sponsor has proposed that SC MTX using the Trexject (with the embedded needle) could be self-administered by patients raising the concern about patients managing a cytotoxic product in a home setting. Protocols are in place in hospitals to manage cytotoxic waste disposal.

The RMP evaluator has identified multiple drug-drug interactions as sources of potential risk in the RMP.

The RMP evaluator advised that the sponsor should incorporate the changes to the trade names and details of the syringes and contents of the packages in their next update of the RMP.

Risk-benefit analysis

Delegate's considerations

Pharmacology

A number of concerns have arisen from the pharmacology data.

- The application is for a new concentration of methotrexate. The sponsor has not demonstrated bioequivalence with the formulations currently available in Australia for parenteral use in psoriasis. It has demonstrated that although there are similarities in AUC between the 50 mg/mL and 10 mg/mL formulations there was a higher C_{max} with the 50 mg/mL formulation. If C_{max} is concentration dependent this may have relevance for patients changing to this product from another parenteral methotrexate product for the treatment of psoriasis. The ACPM will be requested to provide comment on the clinical relevance of this observation.
- There were differences in bioavailability between the routes of administration. The cross group AUC of the SC group was 123.9% of the AUC of the IM group. In addition for SC dosing C_{max} was approximately 59 to 69% of the IM comparator in study MCMTX.7/RH in a crossover study using a 10 mg/mL formulation and in a cross-group comparison from study MC-MTX.9/RH.
- In published literature there were differences in bioavailability between oral and IM and oral and IV routes of administration. In small studies bioequivalence was demonstrated between different parenteral routes of administration.
- There were no direct comparisons between SC, IM and IV dosing with the proposed formulation but from the PK studies and such comparisons are relevant because there are no distinctions between the routes of administration proposed for the Dosage and Administration section of the PI for the requested RA and PSOR indications.

Efficacy

Rheumatoid arthritis

The sponsor provided a single sponsor-led study and literature reports in support of its proposed indications. The pivotal study used a 10 mg/mL concentration methotrexate product, not the product for which registration is sought. The efficacy of the 10 mg/mL formulation was characterised in this study, and its superiority over oral methotrexate (also an overseas product) was demonstrated. It is unknown if the 50 mg/mL solution would have resulted in similar effect and effect size (relative risk (RR) for difference in ACR20 1.12[95%CI 1.01 to 1.24]).

The study reported by Rau and others[5, 6, 29, 30, 31, 32, 33, 34] demonstrated that IM MTX had a similar efficacy to IM gold for a number of clinical endpoints and radiological progression. The comparative efficacy of IM and SC routes of administration was not demonstrated. Extrapolation of the PK data would be required but because of the differences noted above it is unknown whether these differences are of clinical relevance.

The efficacy for the use of IV MTX for the treatment of RA was limited, and only one study of 15 patients was randomised and blinded. The study comparator is not registered in Australia.[36] The initial IV dose exceeded the sponsor's maximum recommended dose and was followed by oral maintenance therapy. The other studies had deficiencies that limited their generalisability. No studies compared IV with other parenteral administration routes.

The sponsor also provided two tolerability studies that identified the preference of patients for higher concentration (and lower volume) dosing for SC use and use of an embedded needle compared to an attachable needle for the pre-filled syringe.

Psoriasis

The efficacy evidence in support of the use of the proposed formulation for psoriasis is literature based. The majority of studies used oral methotrexate or the route of administration was not clearly defined. Those using oral methotrexate mostly administered the weekly dose in three divided doses at 12 hour intervals in accordance with the Weinstein and Frost protocol. The evidence to support the SC use of MTX in general was provided by the study by Gumusel et al in 17 patients with moderate to severe PSOR with nail bed involvement.[12] The concentration of the 15 mg SC MTX dose was not mentioned in the publication. Efficacy for a further 7 adults were reported in an uncontrolled case series. Subcutaneous administration for methotrexate is not currently approved in Australia. It is not considered that these small numbers of patients is sufficient to support the registration of a new route of administration for the treatment of psoriasis. The ACPM will be asked to comment.

Self-administration of SC injection if the clinical situation permits

There is very limited evidence provided in the submission to support the home use of parenteral MTX. The sponsor is requested to further discuss this issue.

Safety and RMP

The sponsor has provided its own studies and literature that provide some information on the safety of 2,077 patients with RA and approximately 340 patient years for psoriasis. In the pivotal study gastrointestinal disorders were more common in the SC group than the oral group, suggesting a systemic rather than local cause. It is not known if this observation is related to a higher bioavailability for the SC dose compared with the oral dose. The ACPM will be asked for comment on the implications for clinical safety from the differences in PK between routes of administration. The completeness of AE reporting is difficult to ascertain from the literature, although a picture emerged of an increased risk of gastrointestinal events with the parenteral administration of MTX. Within the limitations of the safety data no new safety signals were detected. The sponsor has proposed to include the same boxed warning and precautions that are common to oral and other parenteral methotrexate products in Australia. The relatively small patient numbers in many of the studies and the relatively short duration of treatment, considering both RA and PSOR are chronic diseases, did not allow for the detection of rare adverse events and those related to prolonged exposure to be detected specifically related to long term parenteral use of this formulation. Because there were no long term comparisons of different parenteral routes of administration of methotrexate for either indication the comparative risks from local administration such as injection site reactions, pain, haematoma formation, lipoatrophy and local infection have not been well characterised. In

addition, the largest sponsor-led study of the longest duration did not use the 50 mg/mL concentration so it is difficult to determine the likelihood of local reactions with prolonged use. There was a difference in C_{max} and AUC between SC and IM administration of the proposed product. It is not known if these differences would be important for long term safety, particularly for events such as hepatic, renal and pulmonary adverse effects. Clinical trial data using the proposed formulation would have been more supportive of its safe use in patients.

Specific issues of concern

There is limited efficacy and safety data provided in support of intravenous use for the management of rheumatoid arthritis. The dosage regimen proposed for Trexject does not describe a dosage regimen consistent with those used in the clinical studies presented in support of its use. There is no information in this section to reflect the IV use in the studies for induction of control of RA. Only one study was identified where a comparison of IV and oral pharmacokinetics was clearly described. The clinical studies provided for the efficacy of IV MTX are of insufficient duration and with insufficient patient numbers to support use of MTX for this indication. Parenteral formulations of MTX are already registered for the indication of the treatment of recalcitrant psoriasis.

The proposed dosage range for psoriasis is inconsistent with the currently approved dosage regimen; specifically the maximum proposed dose of 30 mg is greater than the 25 mg upper limit of the usual dosage range described in the methotrexate PI for other parenteral methotrexate products. In addition the currently approved products allow for a dose of up to 50 mg in exceptional circumstances but multiple injections would be required. The sponsor will be requested to provide a justification for its dosage regimen in psoriasis.

Dose

The proposed Dosage and Administration instructions are the consistent with those approved for use in the United Kingdom for Metoject. The instructions are not consistent with the current Dosage and Administration instructions in Australia for parenteral methotrexate therapy for psoriasis. The PIs for Australian methotrexate solutions for injection also do not provide advice about the expected time for response. The most recent amendment to this section has insufficient detail to guide prescribers about the maximum usual dose. The maximum dose for PSOR exceeds the upper limit of the usual dosage range recommended for other Australian parenteral preparations of methotrexate for the PSOR indication and the presentations do not allow for the maximum recommended dose (although that is not considered a major deficiency as doses > 30 mg are likely to be associated with increased toxicity).

Conclusion

There are a number of concerns with the submission that have led to the conclusion that additional justification and analysis is required of the sponsor. These concerns are as follows:

- Significant toxicities with methotrexate have been reported with methotrexate in the proposed dosage range for the requested indications. Differences in the observed PK findings for the 50 mg /mL and 10 mg/mL formulations and for different routes of administration may be of importance for the efficacy and safety of SC administration for both proposed indications.
- No head to head study comparing IM and SC methotrexate administration in either RA or psoriasis indications has been provided to give assurance that any differences in PK parameters have no clinical consequence.

- IV therapy studies in RA were very limited in patient numbers and duration and were insufficient to support registration of this route of administration.
- The sponsor has proposed patient self-administration of the SC dose that could take place outside the hospital or clinical setting. Limited evidence for the use in this way has been provided but the sponsor has not addressed the practical issues of using cytotoxic solutions in the home environment.

The sponsor is requested to address these issues in the responses to the questions below.

Data deficiencies

Data deficiencies include a lack of head to head comparison of different routes of administration of methotrexate to support either indication. There is insufficient evidence to guide dose adjustment when transitioning to and from oral and parenteral routes of administration. There is no direct clinical trial efficacy and safety data to support the proposed formulation. Extrapolation is required from both published literature and sponsor-led studies. Very little data have been provided supporting SC administration of MTX in PSOR.

Conditions of registration

The following are proposed as conditions of registration:

Implementation of the Metoject EU-RMP version 2 dated 1 February 2013 (data lock point 1 February 2013), with Australian Specific Annex dated January 2015, and any future updates.

Summary of issues

- Whether the differences in C_{max} between the SC and IM administration in the PK studies is of relevance for efficacy, toxicity and interchangeability with other methotrexate products, given the upper bound of the 90% CI for C_{max} is outside the usual acceptable limits for bioavailability.
- Whether it is acceptable to extrapolate the findings of a study MC-MTX.6/RH to the proposed concentrations.
- Whether the evidence presented in the submission is sufficient to support the SC and IM routes of administration for MTX.
- Whether it is acceptable to extrapolate the PK data for SC and IM administration to IV use in RA.
- Whether the 30 mg maximum dose is an acceptable dosage maximum for the treatment of psoriasis given all other parenteral methotrexate products suggest a usual dosage range of 10 to 25 mg IM or IV per week.
- Whether it is acceptable for the sponsor to offer a different dosage regimen for this parenteral methotrexate for psoriasis compared with other parenteral methotrexate formulations for the same indication.
- Whether the sponsor has sufficiently addressed the safety of patient self-injection, including whether the handling and disposal information is sufficient to support the safe use of parenteral methotrexate in the home.

Questions for the sponsor

1. Please provide a brief summary of the basis upon which the sponsor has requested the following:
    a. Subcutaneous administration for RA
    b. Intramuscular administration for RA

c. Intravenous administration for RA

d. Subcutaneous administration for psoriasis

In the response please indicate where there is direct evidence for the 50 mg/mL presentation, where there is extrapolation from other evidence, and any assumptions the sponsor has made to sponsor's conclusions regarding the safety and efficacy of Trexject and Trexject IN.

2. Please discuss if there are differences in bioavailability in patients with body mass index (BMI) > 30.

3. Please provide a justification for the different maximum doses for the requested indications. Please provide an overview of the evidence for the use of doses of MTX > 25 mg weekly in either of the proposed indications.

4. Please indicate how the prescriber should dose-adjust when changing from oral to SC and between parenteral routes of administration for example IM to SC or IV to SC given the differences.

5. Please indicate the reason the PI does not contain a mention of the potential interaction with nitric oxide, and does not include the list of incompatibilities included in the PIs of other methotrexate products in Australia.

6. Please discuss the safety of self-administration of SC MTX outside the clinic setting and include the following:

   The sponsor has proposed instruction in the Dosage and Administration section that personnel handling methotrexate injection should wear disposable gloves and masks. Given this medication is a cytotoxic agent how does the sponsor propose patients dispose of used syringes and waste from any spills?

7. How does the sponsor ensure the complete dose is expelled from the syringe? Is there any information the patient/health professional should be aware of for example small air bubble or small residual volume in the syringe. How will this be conveyed to the clinician providing instruction to the patient?

Proposed action

The Delegate was not in a position to say, at this time, that the application for (the product) should be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The proposed methotrexate parenteral product has a concentration of 50 mg/mL. The PK studies have identified the following:

   - A difference in C_{max} between formulations with a MTX concentration of 50 mg/mL and 10 mg/mL,
   - A difference in AUC and C_{max} between SC and IM administration.

   Could the committee please comment on the potential clinical significance of these findings?

2. Does the committee consider that the PK differences between the 10 mg/mL solution and the 50 mg/mL solution allow the findings of study MC-MTX.6/RH to be extrapolated to the proposed methotrexate product?

3. Has the sponsor provided sufficient evidence to support (a) the intravenous and (b) the intramuscular routes of administration of methotrexate for the proposed RA indication?
4. Can the RA and PK study data for the 10 mg/mL formulation be extrapolated for the SC use in psoriasis patients?
5. Has the safety of patient self-injection been sufficiently addressed in the submission?
6. The sponsor has proposed advice on the monitoring of liver functions tests for the PI in the Precautions section under the heading 'Recommended examinations and safety measures before and during use' that differs from the PIs of other methotrexate products. Please comment on the appropriateness of the advice in the Australian clinical context.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Delegates questions for the sponsor

Delegate's question 1

1. *Please provide a brief summary of the basis upon which the sponsor has requested the following:*
    a. *Subcutaneous administration for RA*
    b. *Intramuscular administration for RA*
    c. *Intravenous administration for RA*
    d. *Subcutaneous administration for psoriasis*

    In the response please indicate where there is direct evidence for the 50 mg/mL presentation, where there is extrapolation from other evidence, and any assumptions the sponsor has made to sponsor's conclusions regarding the safety and efficacy of Trexject and Trexject IN.

Sponsor's response:

Response: a and b. Subcutaneous/Intramuscular administration for RA

Most rheumatologists prefer a parenteral route of administration, either IM or SC, especially during the initial treatment phase with low dose MTX. Apart from assured compliance and a reduction in gastrointestinal adverse effects, the main reasons are a more reliable absorption and improved bioavailability with an earlier onset of action.

The applicant has performed several clinical trials that evaluated the efficacy, safety, and pharmacokinetics of different routes of administration of MTX (SC; IM, oral (PO)) as well as different MTX concentrations (10 mg/mL, 50 mg/mL) in healthy subjects and patients with RA. Results of two pharmacokinetic trials (MC-MTX.7/PH and MC-MTX.9/PH) in healthy volunteers, one efficacy and safety study (MC-MTX.6/RH) in 384 RA patients, and two safety studies in RA patients (MC-MTX.5/PH and MC-MTX.10/PH) have been presented in this application.

One question raised by the clinical evaluator was the differences in C_{max} between the SC and IM administration and its relevance for efficacy, toxicity and interchangeability. It should be noted that both PK trials were not designed to demonstrate bioequivalence according to the rules of the applicable EU guidance.[39] The primary aim of the trials was to

[39] CPMP/EWP/QWP/1401/98 Rev. 1/Corr: Guideline on the investigation of bioequivalence

compare the pharmacokinetics of IM versus SC administration of the same MTX formulation (10 mg/mL) (MC-MTX.7/PH), and the pharmacokinetics of a low (10 mg/mL) versus a high concentration (50 mg/mL) of MTX using the same administration route (MC-MTX.9/PH). The expectation was that there might be differences in the rate of MTX absorption (C_{max}, T_{max}). Drug absorption is generally known to be slower after SC than IM injection, due to poorer vascularity. Furthermore, the rate of absorption of a drug is known to be proportional to the drug concentration gradient across the absorption barrier.

The other expectation was that this should not significantly impact the total exposure (extent of absorption) of the drug as measured by the AUC. The trials have shown that higher maximum serum concentrations of MTX are observed after IM administration and after use of the higher concentrated MTX formulation. However, these differences did not have an impact on the degree of absorption of MTX. Indeed, the 90% confidence intervals (CI) for all AUC ratios (SC versus IM (MC-MTX.7/PH); 10 mg/mL versus 50 mg/mL (MC-MTX.9/PH)) were completely within the equivalence limits of 80 to 125%.

Furthermore, trial MC-MTX.9/PH has even shown that the 90% CI of the ratios of AUC as well as C_{max} of the primary metabolite of MTX (7-OH-MTX) are completely within the equivalence limits of 80 to 125%. This result supports the conclusion that the higher MTX concentration did not impact the overall exposure to the drug. The clinical relevance of the difference in C_{max} must also be considered in regard to the mode of action of MTX. It slows the progress of the disease by inhibiting the proliferation of lymphocytes and other factors responsible for inflammation. Once administered, MTX is transported into the cell by folate receptors, with a portion of MTX metabolized to polyglumates (MTX-glu) in the same manner as naturally occurring folates. It is thought that the intracellular MTX-glu are the true anti-inflammatory agents. Consequently C_{max} is relatively less critical to efficacy of MTX compared to AUC.

The conclusion of these data is that both routes of administration and both formulations are interchangeable. This conclusion is also supported by literature data. [40],[41]. The question now is whether the slightly lower maximum serum concentration of MTX observed after SC injection compared to the IM route does have any impact on the safety and efficacy of MTX. Until today, no study has so far been performed that compared IM and SC route with respect to efficacy and safety. However, several publications focussing on the pharmacokinetics of methotrexate as well as on efficacy upon different administration pathways were identified that indicated that AUC, rather than C_{max} is the decisive parameter for the efficacy of methotrexate. If any effect of different C_{max} values was postulated, high values of C_{max} were rather regarded as associated with increased side effects, and thus poorer tolerability, than with enhanced efficacy. It thus does not appear that decreased C_{max}, along with similar systemic exposure (indicated by AUC) as observed for methotrexate administration via SC as opposed to IM route, may be associated with lower efficacy. In addition, several original studies and literature reviews describing the efficacy and tolerability of SC administered methotrexate were encountered. No direct comparison between the two parenteral administration routes was found. However, several authors explicitly described SC administration as efficacious and as the preferable of the three administration routes (oral, SC, IM). [42],[43],[44],[45],[46]

[40] Jundt J W et al. A comparison of low dose methotrexate bioavailability: Oral solution, oral tablet, subcutaneous and intramuscular dosing. *Journal of Rheumatology*. 1993; 20: 1845-1849.
[41] Brooks PJ. et al. Pharmacokinetics of methotrexate administered by intramuscular and subcutaneous injections in patients with rheumatoid arthritis. *Arthritis & Rheumatism* 1990; 33: 91-94
[42] Cipriani P et al, Methotrexate in Rheumatoid Arthritis: Optimizing Therapy among Different Formulations. Current and Emerging Paradigms *Clinical Therapeutics* 2014; 36: 427-436.
[43] Verstappen S, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer assisted management in early rheumatoid arthritis (CAMERA, and open-label strategy trial). *Ann Rheum Dis* 2007; 66, 1443-1449.

Finally the PSUR on methotrexate 50 mg/ml solution for injection, pre-filled syringe, which is already authorized in 27 countries, reports no lack of efficacy concerns and the safety reports indicate infrequent adverse events have similar profiles for oral and SC dosing. In summary, the difference in C_{max} between SC and IM has no clinical consequences and both forms of administration are expected to result in a similar profile in terms of efficacy and safety. Similarly, a study performed by the applicant (MC-MTX.6/RH) compared the efficacy of MTX after SC and oral administration at the same applied concentration (15 mg MTX per week) and found that efficacy was higher, both regarding primary and secondary endpoints, in the SC group. Scott et al. (2014)[47] also noted after review of the literature that SC administrated MTX is greater in efficacy than orally administered MTX due to its higher bioavailability, that is, AUC. As only AUC, but not C_{max} was found to differ between the SC and oral administration, it appears that AUC, rather than C_{max}, is a decisive parameter for methotrexate efficacy and that the greater systemic exposure (indicated by AUC) is responsible for the enhanced efficacy of SC as opposed to orally administered methotrexate in RA patients. This view was also expressed in the publications quoted above. C_{max} on the other hand was the parameter suspected to be relevant in terms of side effects rather than efficacy by most authors. In summary, it thus does not appear that decreased C_{max}, along with similar systemic exposure (indicated by AUC) as observed for methotrexate administration via SC as opposed to IM route, may be associated with lower efficacy. The difference in C_{max} between SC and IM has no clinical consequences and both forms of administration are expected to result in a similar profile in terms of efficacy and safety.

Response c. intravenous route of administration for RA

The sponsor did not conduct any studies with the intravenous route of administration of MTX in RA or psoriasis patients; the data presented were based on studies published in the literature. While the applicant asserts that the literature data are supportive of the IV route of administration, the IV route is today no longer used by rheumatologists as oral as well as IM or SC route is the preferred administration route. It is on this basis, and as a result of extensive internal discussion that the applicant has made a decision to withdraw the request for approval for the IV route of administration for Trexject IN. Instead the applicant wishes to pursue only the IM and SC routes of administration, in accordance with the recommendations proposed by the clinical evaluator.

Response d. subcutaneous for psoriasis

The sponsor submitted three published reports which evaluated the efficacy and safety in patients with inflammatory disease, including some with psoriasis. These studies demonstrated that SC MTX has similar efficacy to IM MTX and oral cyclosporine. Jundt et al 1993 found that for low dose MTX mean absolute bioavailability is similar for oral tablets (0.85; 95%CI 0.77-0.93) and SC (0.97; 95%CI 0.83-1.12) compared to IM for low dose MTX, suggesting these routes of administration are interchangeable.[40] The SC route has tolerability and efficacy benefits over oral MTX particularly in the initial stages of treatment. Moreover, it is justified to extrapolate the pharmacokinetic data obtained in RA

[44] Harris JA et al., 2013 Determining best practices in early rheumatoid arthritis by comparing differences in treatment at sites in the Canadian Early Arthritis Cohort. *J Rheumatol* 2013; 40: 1823-1830
[45] Goodman SM et al., Outcomes Related to Methotrexate Dose and Route of Administration in Patients with Rheumatoid Arthritis: A Systematic Literature Review. *Clin Exp Rheumatol* 2015; 33: 272-278.
[46] Visser K, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. Ann Rheum Dis 2009; 68: 1086-1093.
[47] Scott et al. Retrospective evaluation of continuation rates following a switch to subcutaneous methotrexate in rheumatoid arthritis patients failing to respond to or tolerate oral methotrexate: the MENTOR study. *Scandinavian Journal of Rheumatology* 2014; 43: 470-476

patients and healthy volunteers also to psoriasis patients. The efficacy and safety of low dose MTX in psoriasis patients is well established.[24],[48]

Recently, another medac-sponsored PK study with the MTX 50 mg/mL formulation in a pre-filled pen has been undertaken in psoriasis patients (MC-MTX.12/PK).This medicinal product has meanwhile been approved for psoriasis and RA for SC administration by the EMA as well as FDA. This trial analysed the relative bioavailability of MTX 50 mg/mL administered SC by a prefilled pen compared with IM administration of MTX 25 mg/mL in patients with psoriasis. Relative bioavailability as measured by AUC_{0-t} and $AUC_{0-\infty}$ of MTX was equivalent following SC injection with the prefilled pen of MTX (30 mg) compared to administration of IM injection (30 mg) in patients with psoriasis. Similarly to the results obtained in trial MC-MTX.7/PH in healthy volunteers, C_{max} for MTX was approximately 25% lower following SC injection compared to IM injection in patients with psoriasis. The full study report is available on request.

Conclusions: The sponsor has provided sufficient data from clinical trials that support the IM and SC route of low-dose MTX administration of both formulations (10 and 50 mg/mL).

Delegates question 2

2. *Please discuss if there are differences in bioavailability in patients with BMI > 30*.

Sponsor's response:

The role of obesity on the pharmacokinetics of MTX has not been studied. However, a recently performed study by the sponsor addressed this question (MC-MTX.15/HF). This actual use study was planned to demonstrate that patients with RA can use a 50 mg/mL MTX formulation in a prefilled pen to self-administer MTX and to assess the pharmacokinetics (PK) of MTX across a range of body weights. The PK subset participants (n = 25) were stratified into three classifications of body weight: < 60 kg, 60 to 100 kg, and > 100 kg. Excessive body weight (more than 100 kg) significantly decreased both AUC and C_{max} of MTX when administered subcutaneously to the abdomen. Median T_{max} of MTX was similar in patients weighing up to 100 kg (ranging from 0.75 to 1.50 hours); however, median T_{max} was slightly delayed for patients weighing more than 100 kg (ranging from 1.78 to 2.25 hours). Data are summarized in Table 4.

Table 4: Geometric mean (CV) of PK parameters of MTX by body weight. Injection site: abdomen

Parameter		< 60 kg	60 – 100 kg	> 100 kg
n		4	5	4
AUC_{0-inf} (h x ng/mL)	Mean	2,697.90	2,803.99	1,599.23
	CV	31.1	21.0	39.7
Cmax (ng/mL)	Mean	619.14	512.19	256.87
	CV	36.6	16.6	26.6
Tmax (h)	Mean	1.33	0.75	1.78
	min, max	0.25 – 3.02	0.50 – 1.50	0.75 – 2.50
T1/2 (h)	Mean	3.47	4.05	3.44
	CV	21.3	27.1	23.4

However, such a big difference (especially with respect to AUC) could not be seen when MTX was administered into the thigh (Table 5).

[48] Chiaravalloti A J et al. The Use of Self-Administered Subcutaneous Methotrexate for the Treatment of Psoriasis *J Drugs Dermatol* 2014; 13: 929-931.

Table 5: Geometric mean (CV) of PK parameters of MTX by body weight. Injection site: thigh

Parameter		< 60 kg	60 – 100 kg	> 100 kg
n		3	5	4
$AUC_{0\text{-}inf}$ (h x ng/mL)	Mean	2,391.13	2,092.53	2,584.80
	CV	10.8	23.4	17.7
Cmax (ng/mL)	Mean	444.00	354.68	319.89
	CV	10.6	23.6	22.1
Tmax (h)	Mean	1.50	1.50	2.25
	min, max	0.75 – 1.50	1.00 – 3.00	1.55 – 4.00
T1/2 (h)	Mean	6.27	7.17	5.80
	CV	10.8	23.4	17.7

Therefore, patients with a body weight > 100 kg should inject MTX into the thigh. The full study report is available on request. This is now adequately considered in the Trexject/Trexject IN PI and CMI.

Delegates question 3

Please provide a justification for the different maximum doses for the requested indications. Please provide an overview of the evidence for the use of doses of MTX > 25 mg weekly in either of the proposed indications.

Sponsor's response:

For RA patients, a weekly SC dose of 7.5 to 25 mg MTX is usually recommended, depending on response and tolerability. A weekly dose of 25 mg should in general not be exceeded. Response to treatment can be expected after approximately 4 to 8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose. 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. In addition, large inter-individual variations are encountered. The most common dose range used today in maintenance therapy is 15 to 20 mg/week. The British Society for Rheumatology recommends 7.5 to 25 mg once weekly; starting dose may vary depending on the severity of the condition and patient characteristics such as age, renal function and other comorbid conditions. The initial dose may be 5 to 10 mg once weekly, increasing by 2.5 to 5mg every 2 to 6 weeks until disease stabilized. Rarely, the maximum dose can be 30 mg/week. Lower doses should be considered for frail elderly patients who often have poor renal function. If maximum oral dose is not effective or causes intolerance, consider IM or SC route of administration before discontinuation of the drug.[49]

Visser et al. (2009)[46] reviewed systematically the available literature on the optimal dosage and route of administration of MTX in patients with RA, as an evidence base for generating clinical practice recommendations. A start dose of 15 mg/week orally, escalating with 5 mg/month to 25 to 30 mg/week or the highest tolerable dose, with a subsequent switch to subcutaneous administration in the case of an insufficient response, seems to be the optimal evidence-based dosing and routing strategy for MTX in RA. This conclusion was incorporated as one of the recommendations of the 3E Initiative for the use of MTX in rheumatic diseases.[50] Please note that the recommendation for the highest dose 30 mg refers to oral administration of MTX. For SC use the maximum dose should be 25 mg because of the better bioavailability.

[49] Chakravarty, K. et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* (Oxford), 2008; 47: 924–925.
[50] Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti rheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.

Of the 10 published studies presented to support the psoriasis indication in this application, only one used a weekly dose in excess of 25 mg. Montaudié et al. systematically reviewed the literature regarding treatment modalities with MTX in psoriasis patients.[24] Based on expert experience, the starting dose of MTX is between 5 and 10 mg/week for the first week. Fast dose escalation is recommended in order to obtain a therapeutic target dose of 15 to 25 mg/week. The maximum recommended dose is 25 mg/week. For both indications, there is currently no evidence to use a higher subcutaneous weekly dose than 25 mg. We therefore propose to change the PI accordingly:

> "Dosage of Trexject (Trexject IN) in patients with psoriasis vulgaris:
>
> A weekly dose of 7.5 to 25 mg is recommended, depending on response and tolerability…"

This is now adequately considered in the Trexject/Trexject IN PI.

Delegates question 4

Please indicate how the prescriber should dose-adjust when changing from oral to SC and between parenteral routes of administration for example IM to SC or IV to SC given the differences.

Sponsor's response:

The proposed PI for Trexject/Trexject IN describes that "*if changing the oral application to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.*" However, an exact dose adjustment schedule was not provided for the following reasons:

- In most cases patients switch from oral to SC administration because of insufficient disease control. Using the same SC dose as the former PO dose will increase treatment efficacy due to the better and reliable bioavailability.
- The bioavailability varies widely after oral MTX administration and can therefore not always be predicted with certainty for an individual patient.
- Changes in the response to treatment can be expected after approximately 4 to 8 weeks. Upon achieving the therapeutically desired result, the dose can be reduced gradually to the lowest possible effective maintenance dose, that is, the same procedure can be used as with the start of MTX treatment.

When switching from IM to SC administration the same dose should be used. This is justified because studies MC-MTX.7/PH and MC-MTX.9/PH have clearly shown that both routes of administration result in a comparable total exposure as indicated by the AUC comparison. An increase of dose after switch to SC route to compensate for the slightly lower C_{max} values after this route of administration is not justified because this would result in an increase of total exposure. This is now adequately considered in the Trexject/Trexject IN PI.

Delegates question 5

Please indicate the reason the PI does not contain a mention of the potential interaction with nitric oxide, and does not include the list of incompatibilities included in the PIs of other methotrexate products in Australia.

Sponsor's response:

Worldwide methotrexate has been in use for several decades and its safety profile is meanwhile well established, both in high and low dose treatment schemes. There are a few publications from the 1980ies/1990ies that discuss the risk of a potential interaction of methotrexate with nitric oxide when methotrexate is used in oncological/

haematological indications. [51; 52; 53; 54] In oncology/haematology methotrexate dosing is significantly higher than in rheumatic diseases and the dose may play a role as to the clinical significance of this potential interaction. Whilst Australian PIs of other methotrexate products seem to mention this potential interaction, in general it is not commonly included in relevant documents used in other countries and regions of the world (EU, USA). If there is mention of this interaction in the relevant labelling documents then it is for those methotrexate products that have been authorised in oncological/haematological indications. This interaction is also not necessarily found in known drug information databases (for example Micromedex). In terms of the incompatibilities, the product that the application refers to, is a ready-to use product (pre-filled syringe) and does not require any further preparation. Hence mentioning of incompatibilities included in the PIs of other methotrexate products in Australia does not seem relevant to this product.

Delegates question 6

Please discuss the safety of self-administration of SC MTX outside the clinic setting and include the following:

> *The sponsor has proposed instruction in the Dosage and Administration section that personnel handling methotrexate injection should wear disposable gloves and masks. Given this medication is a cytotoxic agent how does the sponsor propose patients dispose of used syringes and waste from any spills?*

Sponsor's response:

Self-administration of SC MTX outside the clinic setting has been successfully performed for many years and in many countries, incl. the above discussed clinical studies performed by the applicant. Arthur AM et al. taught 40 patients with RA or psoriatic arthritis to self-administer parenteral gold (n = 20) or MTX (n = 17) or both compounds (n = 3).[14] 65% of patients performed self-injection and 35% received injections at home from a partner. Side effects in the self-injection patients were similar to those observed in clinic patients receiving drug by nurse administration. MTX treated patients continued self-injection after a mean of 34 months. Patients surveyed for satisfaction identified time saving and convenience as major benefits.

SC self-injection can be easily learned by the patient or a family member as has been shown by several educational programs that have especially been established in UK.[55],[56] Lindsay et., 2000; Royal College of Nursing, 2013). The Royal College of Nursing (RNC) guideline describes that "*in light of emerging evidence that the cytotoxic risk relating to the low dosages of subcutaneous methotrexate used in the treatment of inflammatory arthritis is small (Wong et al., 2009), this guidance suggests that aprons, goggles, masks or armlets, no longer need to be worn by practitioners when administering pre-filled subcutaneous methotrexate injections. …* "Best practice recommends that practitioners and carers should use gloves, but this is not required for patients who self-administer." (Royal College of Nursing, 2013). Wong et al. (2009)[57] investigated whether the risk of MTX exposure through skin contamination using parenteral doses of 25 mg warrants special oncology

[51] Goldhirsch, et al., 1992 For the full details of this reference please contact the sponsor
[52] Goldhirsch, A et al. Methotrexate/nitrous-oxide toxic interaction in perioperative chemotherapy for early breast cancer. *Lancet* 1987; 2: 151-
[53] Ludwig Breast Cancer Group. Toxic effects of early adjuvant chemotherapy for breast cancer. *Lancet* 1983; 322: 542-544.
[54] Ludwig Breast Cancer Group 1988 For the full details of this reference please contact the sponsor
[55] Garrick V, et al. Successful implementation of nurse led teaching programme to independently administer sc methotrexate. *Aliment Pharmacol Ther*, 2008; 29: 90-96.
[56] Lindsay G, et al. Self administration of sub-cutaneous methotrexate (SC MTX: A survey of patient benefit and convenience). *Rheumatology* 2000; 39, 88.
[57] Wong et al 2009 For the full details of this reference please contact the sponsor

handling precautions during administration. Six human volunteers deliberately exposed to an entire dose of 25 mg MTX solution on their skin for 30 min were included into this trial. Serum levels of MTX were measured at baseline, 2, 4, 8, 12 and 24 h as well as serum homocysteine at baseline and 24 h after clinical exposure. Twenty-four-hour urinary excretion of MTX and possible local or systemic signs of toxicity were also recorded. All MTX serum concentrations were less than 0.02 µM within the 24-h period. This is 500 times below the recommended serum concentration for which folinic acid supplementation is recommended. There was also no significant increase in homocysteine level to suggest MTX toxicity. The only adverse effects were mild local dermal reactions in three female volunteers. The authors conclude that precautions to prevent contact with MTX designed for oncology protocols are unnecessary for rheumatology patients or their carers using these much lower immunosuppressant doses for autoimmune diseases. The proposed PI for Trexject/Trexject IN contains the following information:

- Instructions to patients: "Patients and caregivers should be instructed in the correct technique and importance of proper disposal of the pre-filled syringe and be cautioned against reuse of the pre-filled syringe."
- Instructions for handling: "Personnel handling methotrexate injection should wear disposable gloves. All items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for disposal in a cytotoxic waste bin."

With basic instruction and close supervision, self-injection of MTX 50 mg/mL prefilled syringe is safe in many patients. Self-injection reduces utilisation of health care services, is convenient and time and cost-saving to the patient. The PI/ CMI were updated accordingly.

Delegates question 7

How does the sponsor ensure the complete dose is expelled from the syringe? Is there any information the patient/health professional should be aware of for example small air bubble or small residual volume in the syringe. How will this be conveyed to the clinician providing instruction to the patient?

Sponsor's response:

In the CMI under the section Instructions for handling was updated to clearly describe how the complete dose is expelled from the syringe: "*Insert the needle fully into the fold of skin. Slowly push the plunger down completely to inject the liquid underneath your skin*." Further assurance for a complete dose expelling is given by the information in the CMI such as: "*The doctor may decide that you can administer the injection yourself under the skin (subcutaneously). If you will be self-administering Trexject, your doctor or nurse will give you detailed instructions on how to do this…"* The CMI was updated accordingly. If the plunger is completely pushed down, the complete volume is expelled from the syringe. Furthermore, volume of injection is tested at release of the drug product which assures that the patient receives the complete dose. Until today, in EU and worldwide countries no safety or efficacy concerns related to the incomplete release of the dose from the syringe have been reported.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Trexject and Trexject IN solution for injection, pre-filled syringe containing 7.5mg/0.15 mL, 10 mg/0.2 mL, 12.5mg/0.25 mL, 15 mg/0.3

mL, 17.5 mg/0.35 mL, 20 mg/0.4 mL, 22.5 mg/0.45 mL, and 25 mg/0.5 mL of methotrexate to have an overall positive benefit–risk profile for the indication

> ***Rheumatoid arthritis chemotherapy***
>
> *Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.*
>
> *Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.*
>
> *Steroids may be reduced gradually in patients who respond to methotrexate.*
>
> *Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine or cytotoxic agents has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.*
>
> ***Psoriasis chemotherapy***
>
> *Methotrexate may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.*

In making this recommendation the ACPM

- noted the sponsor had withdrawn the request for the intravenous route of administration.
- noted the sponsor has agreed to amend the maximum dose of subcutaneous methotrexate in the PI to 25 mg per week.

Proposed conditions of registration

The ACPM agreed with the delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Include information regarding the small AUC difference between the 50 mg/mL and the 10 mg/mL formulations observed following IM dosing.
- Under instructions for handling, more specific advice on glove use and apply the advice to carers when appropriate.
- Guidance on how to adjust the dose if changing from oral to subcutaneous or intramuscular route if an equivalent parenteral dose needs to be maintained.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *The proposed methotrexate parenteral product has a concentration of 50 mg/mL. The PK studies have identified the following:*
   - *A difference in C_{max} between formulations with a MTX concentration of 50 mg/mL and 10 mg/mL*
   - *A difference in AUC and C_{max} between SC and IM administration.*

Could the committee please comment on the potential clinical significance of these findings?

The ACPM advised that the differences in the C_{max} and AUC highlighted above are small and expected and are not likely to be of clinical significance. The ACPM considered that extensive clinical experience with the 25 mg/mL solution supported this conclusion.

2. *Does the committee consider that the PK differences between the 10 mg/mL solution and the 50 mg/mL solution allow the findings of study MC-MTX.6/RH to be extrapolated to the proposed methotrexate product?*

The ACPM noted that the 50 mg/mL and 10 mg/mL formulations were bioequivalent in terms of extent of methotrexate exposure (based on comparative AUC results) following SC dosing. The ACPM advised that inclusion of information in the PI regarding the small AUC difference between the 50 mg/mL and the 10 mg/mL formulations observed following IM dosing should be sufficient to alleviate any concern.

3. *Has the sponsor provided sufficient evidence to support (a) the intravenous and (b) the intramuscular routes of administration of methotrexate for the proposed RA indication?*

The ACPM noted that the sponsor advised in its pre-ACPM response that it is withdrawing the request for the IV route of administration as this route is no longer used by rheumatologists, who prefer the oral, IM and SC routes. The ACPM noted that the efficacy data for IM administration were limited to the published literature and were comparable for IM and SC use. The ACPM advised that although the SC route is more popular, use of the less common IM route should be acceptable.

4. *Can the RA and PK study data for the 10 mg/mL formulation be extrapolated for the SC use in psoriasis patients?*

The ACPM advised that given the comparability of the PK of the 10 mg/mL and 50 mg/mL solutions and the efficacy of the former in psoriasis, extrapolation of subcutaneous use in psoriasis patients is reasonable.

5. *Has the safety of patient self-injection been sufficiently addressed in the submission?*

The ACPM advised that Studies MC-MTX.10/RH and MC-MTX.5/RH demonstrated acceptability and tolerability of SC administration. Serious adverse events were infrequent in MC-MTX.5/RH and MC-MTX.10/RH and appeared not to be study drug related. The ACPM advised that advice regarding disposable gloves should apply to both patient and carers and be included in the CMI as well. The ACPM noted that the PI/CMI under instructions for handling, advises on glove disposal but not on glove use (apart from the instruction to wear disposable gloves) and that instructions should be more explicit.

6. *The sponsor has proposed advice on the monitoring of liver functions tests for the PI in the precautions section under the heading 'Recommended examinations and safety measures before and during use' that differs from the PIs of other methotrexate products. Please comment on the appropriateness of the advice in the Australian clinical context.*

The ACPM noted that the Pfizer PI for methotrexate injection recommends '*during therapy for psoriasis, monitoring of liver and renal function every one to two months.*' The ACPM considered that an interval of two months is generally reasonable for clinical practice. The ACPM advised that the sponsor should be invited to justify why a three monthly interval for monitoring liver function after the initial six month period is recommended.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Trexject and Trexject IN methotrexate (as sodium) solution for injection pre-filled syringe, indicated for:

> *'Psoriosis therapy (see WARNING box)*
>
> *TREXJECT IN/ TREXJECT may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, OS by biopsy and/or after dermatologic consultation.*
>
> *Rheumatoid arthritis therapy (see WARNING box)*
>
> *Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.*
>
> *Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.*
>
> *Steroids may be reduced gradually in patients who respond to methotrexate.*
>
> *Combined use of methotrexate with gold or penicillamine, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued."*

Specific conditions of registration applying to these goods

- The methotrexate METOJECT EU-Risk Management Plan (EU-RMP), version 2, dated 1 February 2013 (data lock point 1 February 2013), with Australian Specific Annex dated January 2015, included with submission PM-2014-01.050-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The following studies must be submitted to the TGA for evaluation as a Category 1 submission, within three months of registration:
  - MC-MTX.12/PK
  - MC-MTX.14/PK
  - MC-MTX.15/PK

Attachment 1. Product Information

The PIs for Trexject and Trexject IN approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PIs, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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