SUBCUTANEOUS METHOTREXATE FOR PATIENTS WITH SEVERE CONDITIONS NOT RESPONDING TO ORAL MAXIMUM TOLERABLE DOSING

Submission to WHO Essential Medicine List

December 2022
Contents

1. TITLE PAGE ........................................................................................................................................... 4
2. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION ........ 5
3. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS .................................................................. 6
4. OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION ...................... 7
5. KEY INFORMATION FOR THE PROPOSED MEDICINE ....................................................................... 8
   5.1 International non-proprietary name (INN) of the proposed medicine(s) ......................................... 8
   5.2 Anatomical therapeutic chemical (ATC) code of the proposed medicine(s) ................................. 8
   5.3 Dosage form(s) and strength(s) of the proposed medicine(s) ....................................................... 8
   5.4 Indication(s) .................................................................................................................................. 9
6. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL
   CLASS / THERAPEUTIC GROUP ........................................................................................................... 10
7. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE .................................................. 11
8. TREATMENT DETAILS ......................................................................................................................... 15
   8.1 Dosage regimen and duration of treatment ..................................................................................... 15
   8.2 Pharmaceutical form(s) and strengths ............................................................................................ 16
   8.3 Requirements to ensure appropriate use of the medicine(s) .......................................................... 16
     8.3.1 Information to patients and carers ......................................................................................... 17
     8.3.2 Pregnancy and other special situations ................................................................................... 19
     8.3.3 Pharmacovigilance Activities & Risk Management Plans .................................................... 21
   8.4 Recommendations in existing WHO guidelines .............................................................................. 23
   8.5 Recommendations in other current clinical guidelines .................................................................. 23
9. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS .......... 24
   9.1 New medicine(s) / indication(s) .................................................................................................... 24
   9.2 Clinical Efficacy of MTX ............................................................................................................... 24
     9.2.1 Systematic Literature search .................................................................................................. 24
     9.2.2 Clinical Efficacy ..................................................................................................................... 29
   9.3 Bioequivalence of scMTX ............................................................................................................... 32
   9.4 Clinical Efficacy of scMTX ............................................................................................................... 35
   9.5 Safety ............................................................................................................................................ 38
     9.5.1 Contraindications and Cautions ............................................................................................. 39
     9.5.2 Drug interactions ...................................................................................................................... 40
   9.6 Stability .......................................................................................................................................... 42
   9.7 Recommendations for use .............................................................................................................. 43
     9.7.1 Rheumatoid Arthritis (RA) ..................................................................................................... 43
1. TITLE PAGE

SUBCUTANEOUS METHOTREXATE FOR PATIENTS
WITH SEVERE CONDITIONS NOT RESPONDING TO
ORAL MAXIMUM TOLERABLE DOSING

Contact information of responsible organization:

Laboratorios Gebro Pharma, S.A.
Av. del Tibidabo, 29
08022 Barcelona
Spain
2. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

Methotrexate (MTX) is included in WHO’s Essential Medicines List (EML) as a Cytotoxic Medicine (under chapter 8.2.1) as a tablet (5, 15 and 25 mg) and as a powder (3 mg/mL in 10 mL ampoule).

MTX is also included in the EML as a sodium salt 2.5 mg tablet as a Disease-modifying anti-rheumatic drugs (DMARDs) (chapter 29.2)

Subcutaneous Methotrexate (scMTX) should be included in the EML because:

- MTX is recommended by main guidelines to be part of the first treatment strategy unless not tolerated or contraindicated. Initiation or titration of methotrexate to a weekly dose of at least 15 mg within the first weeks of treatment is recommended for most indications in adults.
- scMTX has shown improved clinical efficacy, improved bioavailability, especially over 15 mg/wk, and improved treatment survival, when compared to oral MTX, without increases on side effects.
- it is effective alone or in combination with biologic DMARDs that are also in the EML, namely Adalimumab, while it decreases the formation of anti-drug antibodies.
- it is an effective drug in severe cases, as it allows a higher dosage than oral route, without the adverse side effects of the increased dosing.
- the scMTX in a prefilled pen or syringe does not require manipulation of the vial, thus requiring a healthcare professional and/or a healthcare facility where the drug can be manipulated and administered. As a prefilled syringe or pen, it reduces hazards to healthcare workers and the environment.
- the prefilled scMTX reduces the risks of manipulation and of infection of the intravenous route.
3. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

There have been no previous contacts with WHO regarding the potential inclusion of scMTX in the EML.
4. OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

Two companies have been contracted in order to support the preparation and presentation of this submission, namely:

**Company responsible for technical documentation preparation:**

**HITT**
Aragó 60, pral. 1a
08015 Barcelona
Spain

**Company responsible for the formal presentation to the WHO Expert Committee:**

**Asphalion, S.L.**
Carrer de Tarragona, 151-157, planta 10
08014 Barcelona
Spain

Letters of authorization for these companies are attached to the submission and at the end of this dossier.
5. KEY INFORMATION FOR THE PROPOSED MEDICINE

5.1 International non-proprietary name (INN) of the proposed medicine(s)

The INN for the proposed drug is Methotrexate

5.2 Anatomical therapeutic chemical (ATC) code of the proposed medicine(s)

The requested inclusion is the L04AX03

The ATC code for scMTX is L04AX03 as an immunosuppressant and L01BA01 as an antimetabolite.

5.3 Dosage form(s) and strength(s) of the proposed medicine(s)

Posology in adult patients with rheumatoid arthritis

The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. 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 in general not be exceeded. Doses exceeding 20 mg/week are associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4-8 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Posology in children and adolescents below 16 years with polyarthritic forms of juvenile idiopathic arthritis

The recommended dose is 10-15 mg/m² body surface area (BSA)/once weekly. In therapy-refractory cases the weekly dosage may be increased up to 20 mg/m² body surface area/once weekly.

Use in children less than 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population (see section 4.4).

Posology in patients with psoriasis vulgaris and psoriatic arthritis

It is recommended that a test dose of 5-10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone
marrow suppression. Response to treatment can generally be expected after approximately 2-6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

**Posology in Chron’s Disease**

The recommended dose is Induction with 25 mg/week sc and switching to 15 mg/week sc for maintenance.

**5.4 Indication(s)**

The inclusion of scMTX is requested for the following indications:

- Rheumatoid Arthritis (RA)
- Juvenile Idiopathic Arthritis (JIA)
- Psoriasis and Arthritic Psoriasis (PsA)
- Mild to moderate Crohn's disease (CD), alone or in combination with corticosteroids, in adult patients refractory or intolerant to thiopurines
6. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP

The inclusion of subcutaneous Methotrexate is proposed to the WHO Essential Drug List. This refers to an individual medicine.

The ATC code for the subcutaneous MTX is L04AX03

The ATC code for MTX is L04AX03 as an immunosuppressant and L01BA01 as an antimetabolite.

The WHO EML, recognises MTX for two indications

- As a cytostatic
- As an immunomodulating agent (disease modifying)

Despite most methotrexate-containing medicines have been authorised via national procedures, according to the European Medicines Agency (EMA), the indication of Methotrexate is as a cytostatic agent AND to treat inflammatory diseases.

- treatment of cancer for which the dosing frequency depends on the regimen and can involve daily administration of methotrexate;
- treatment of inflammatory diseases including rheumatoid arthritis, psoriasis and Crohn’s disease, which require once-weekly use of a low dose of methotrexate.

According to the Food and Drug Administration (FDA), oral and parenteral MTX is indicated for the same than EMA.

- Neoplastic Diseases
- Inflammatory diseases, such as Psoriasis or Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis, though no mention of Chron’s disease is made.

2 https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf
7. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

There are several arguments, supporting the inclusion of scMTX in the EML as per the public health arguments:

1. **The afore mentioned diseases are frequent and widespread in all geographic areas. The burden of this diseases is high, and there is no reason why severe cases should go untreated.**

   It is unlikely that control is achieved with oral doses in severe cases, thus the need to provide patients with a higher and safe alternative.

   In most of the globe, the incidence is unknown, but there are no good reasons to think the incidence and prevalence should be different than in known areas.

   The mean point prevalence of RA was 0.56% (SD 0.51), ranging from 0% to 2.70% based on studies from various countries between 1986 and 2014. The highest reported mean point prevalence was in North America (1.46%), followed by Africa (0.80%), Europe (0.53%), South America (0.46%), and Asia (0.34%) (Fig 1).

---

**Fig 1: Prevalence of RA**

---

---


[https://www.jrheum.org/content/48/5/669](https://www.jrheum.org/content/48/5/669)
Similarly, for psoriasis where the incidence of the disease varying from 31.4 per 100,000 person years in eastern Europe (Russia) to 521.1 per 100,000 person years in western Europe (Germany). (Fig 2)

**Fig 2: Prevalence of Psoriasis**

2. **MTX is a cytotoxic agent, that requires manipulation in a clean and safe environment.**

   The manipulation of MTX has to be done in a clinic with the appropriate equipment.

   The manipulation of intramuscular Methotrexate (imMTX) can lead to inappropriate management of this drug, leading to potential hazards, both to individuals and to the environment. The manipulation of drugs has also to be done under safe conditions for the personnel, and in this case it goes beyond the contagion of diseases but the contact with a cytotoxic agent.

   Furthermore, imMTX or intravenous Methotrexate (ivMTX) require not only high cost facilities for its appropriate management, but extensive highly trained personnel for its appropriate management.

---


It is unlikely that this is available across the globe, hence limiting the access to an effective treatment in large geographical areas of the world. The SmPC of the oral MTX indicate that tablets should not be split or crushed for administration and that carers should wear single-use gloves to handle methotrexate tablets; anyone handling the tablets should wash their hands immediately afterwards and skin or mucosa contact with methotrexate solution for injection should be avoided. Furthermore, pregnant people, including patients and carers, should avoid handling methotrexate.

3. **imMTX and ivMTX entail a risk of infection**

Because it is an intramuscular injection, the risk of infection is higher than with a subcutaneous injection.

The risks are far more obvious in the iv injection, where again trained personnel and expensive infrastructure are required.

The same goes for adalimumab, which requires an iv injection, making the access far less feasible in a large segment of the globe.

WHO recommends, via the Safe Injection Global Network (SIGN)\(^6\) to put special emphasis on the management of syringes, as there is risk of mismanagement in low-income countries, among other recommendations\(^7\).

4. **scMTX is stable at room temperature after 24 and 30 months**

The stability of the product grants its access in non-urban sites, without the requirement of expensive infrastructure and/or personnel.

It can be delivered at the point of care by non-health professionals without hazards to the individual.

5. **scMTX is convenient for the patient**

Given the low risk of infection and the drug stability, patients do not need to travel to the point-of-care for a bi-weekly treatment, meaning that access is significantly enhanced.

---


6. Appropriate management of drugs leads to better safety profile

A recent warning by EMA highlights the risk of mis-prescription of certain drugs. In particular they point that there should be more emphasis on MTX as they have seen risk of increased dosing.

The appropriate management of auto-dispensers may be harnessed by third parties, not having to rely on local healthcare personnel who may not be fully aware of the management of MTX in sits several indications.\(^8\)

8. TREATMENT DETAILS

8.1 Dosage regimen and duration of treatment

scMTX should be administered chronically or until a clinical decision to substitute by a different agent. Doses should be adjusted to diseases activity.

The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. Doses exceeding 20 mg per week can be associated with significant increase in toxicity, especially bone marrow suppression. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

In adult RA patients:

The recommended initial dose is 7.5 mg once weekly subcutaneously. 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 in general not be exceeded. Response to treatment can generally 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.

In patients with JIA (< 16 years):

The recommended dose is 10 - 15 mg/m² body surface area (BSA) once weekly subcutaneously. In therapy-refractory cases the weekly dosage may be increased up to 20 mg/m² BSA once weekly.

In patients with psoriasis:

The recommended initial dose is 7.5 mg sc once weekly. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. 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.

In patients with CD:

- Induction treatment: 25 mg/week sc
- Maintenance treatment: 15 mg/week sc

Response to treatment can be expected after approximately 8 to 12 weeks.
There is not sufficient experience in the paediatric population to recommend scMTX for the treatment of Crohn's disease in this population.

**Maximum weekly dose**

The dose should be increased as necessary but should in general not exceed the maximum recommended weekly dose of 25 mg. 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 as toxicity will markedly increase.

### 8.2 Pharmaceutical form(s) and strengths

Some (non exhaustive) presentations available are:

- 1 pre-filled syringe or prefilled pen of 0.15 ml contains 7.5 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.20 ml contains 10 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.25 ml contains 12.5 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.30 ml contains 15 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.35 ml contains 17.5 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.40 ml contains 20 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.45 ml contains 22.5 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.50 ml contains 25 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.55 ml contains 27.5 mg methotrexate.
- 1 pre-filled syringe or prefilled pen of 0.60 ml contains 30 mg methotrexate.

The choice of the dosing will depend on a series of variables, including disease and severity.

### 8.3 Requirements to ensure appropriate use of the medicine(s)

In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease, **scMTX must only be used once a week**. Dosage errors in the use of scMTX can result in serious adverse reactions, including death.

Special effort should be put to the appropriate dosing of the drug.

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy. Patients must be educated and trained in the proper injection technique when self-administering methotrexate. The first
injection of scMTX should be performed under direct medical supervision. ScMTX is injected once weekly.

The patient must be explicitly informed about the fact that scMTX is administered once a week only. It is advisable to determine an appropriate fixed day of the week for the injection.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration.

**MTX has been linked to medication errors:**

On 22 August 2019 EMA\(^8\) recommended new measures to prevent serious and potentially fatal errors with the dosing of methotrexate for treating inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn’s disease. The recommendations result from a review of reports indicating that patients are using methotrexate incorrectly despite previous measures to prevent errors. The review found that the error in dosing frequency can occur at any step from prescribing the medicine to the patient taking it. The new measures to prevent errors include restricting who can prescribe these medicines, making warnings on the packaging more prominent and providing educational materials for patients and healthcare professionals. In addition, to help patients follow the once-weekly dosing, methotrexate tablets will be provided in blister packs and not in bottles (or tubes). The measures were agreed after consultation with patients and healthcare professionals.

In the UK, The National Patient Safety Association (NPSA) highlighted errors with incorrect MTX dosing for patients and overdose of MTX for non-cancer indications is still on the NHS Improvements Never Events List. The NPSA recommend families are advised of the dose and frequency, and given written information. Young people and families should be supplied with a MTX information sheet receive a blood monitoring booklet (either a local trust approved monitoring card or NPSA monitoring booklet) and an appropriate teaching package (if to be taught to self-administer).

**8.3.1 Information to patients and carers**

The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:

- Symptoms of chickenpox or contact with a person with chickenpox or shingles.
- Persistent cough, shortness of breath, or any other problems with breathing.
- Sore throat, mouth ulcers, high temperature, skin rash, swollen glands, or any other signs or symptoms of infection
- Signs or symptoms of liver problems, such as yellow skin or eyes (jaundice), itching all over, nausea or vomiting.
- Swelling of the hands, feet, or ankles
- Unexplained bleeding or bruising, black stools, or blood in the vomit or stools.
- Suspected or confirmed pregnancy.

The patient and/or carer should be advised:
- What shared care means for their treatment, what to expect, and their responsibilities under shared care.
- Methotrexate is taken once weekly and taking it more frequently can be dangerous. If a patient thinks they have taken too much methotrexate they should immediately seek advice from their prescriber.
- Which day or days they should take their folic acid, with emphasis that methotrexate and folic acid should not be taken on the same day.
- Moderate their alcohol intake to no more than 14 units per week while taking methotrexate. Taking alcohol and methotrexate together increases the risk of liver injury.
- Tell anyone who prescribes them a medicine that they are taking methotrexate. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe.
- Skin may be more sensitive to exposure to UV light while taking methotrexate. If this occurs use appropriate self-care: e.g. sun avoidance, protective clothing, avoiding tanning (including tanning beds) and to purchase and use a broad spectrum sunscreen (at least SPF30).
- To use effective contraception, and to take a pregnancy test if they think they could be pregnant. Patients should inform the specialist or GP immediately if they become pregnant. All patients, both men and women, should inform their specialist well in advance if they are planning a pregnancy so that changes can be made to their treatment regime.
- Not to drive or operate heavy machinery if methotrexate affects their ability to do so safely, e.g. due to fatigue or dizziness.
- That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended.
- For patients taking 20mg/week or more: to avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, contact the specialist for advice.

8.3.2 Pregnancy and other special situations

Pregnancy:

Methotrexate is contraindicated in pregnancy. It is cytotoxic and is used for termination of pregnancy and to treat ectopic pregnancy. Pregnancy should be excluded prior to starting treatment.

Patients of child bearing potential should use effective contraception during treatment and for 3 months afterwards. If a patient becomes pregnant within 3 months of treatment with methotrexate, folic acid 5 mg daily should be continued throughout the pregnancy. Those who wish to become pregnant should speak to their prescriber to discuss the possibility of switching to an alternative medicine.

Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.

- Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.

- Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected, in particular at doses commonly used in oncologic indications.

When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

Methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the drug is used during pregnancy or if the patient
becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the foetus.

If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).

**Breastfeeding:**

Methotrexate is excreted into breast milk. Breast-feeding must be stopped during treatment to avoid serious adverse reactions in breast-fed infants. If use during the lactation period should become necessary, breast feeding is to be stopped prior to treatment.

The manufacturers contraindicate use of methotrexate while breastfeeding. Breastfeeding should be avoided until at least 24 hours after a weekly dose not exceeding 25 mg. Infant blood counts should be monitored. Limited evidence indicates that small amounts are found in breast milk after weekly administration.

**Paternal exposure:**

It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

There are hypothetical risks of genetic abnormalities in sperm which could potentially affect offspring conceived during treatment. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less
than 30 mg/week). Where a couple wishes to attempt conception and the male partner’s condition is well-controlled with methotrexate, it is recommended an assessment and discussion of the potential benefits and risks of continuing paternal treatment vs. discontinuation. This should be undertaken by the specialist, using a shared decision-making approach. The risks to the foetus are theoretical rather than established.

**Contraception in males**

Paternal methotrexate use at the time of conception is not an indication for additional foetal monitoring. However, other risk factors may be present in individual cases which may independently increase the risk of adverse pregnancy outcome. Clinicians are reminded of the importance of consideration of such factors when performing case-specific risk assessments.

**Fertility:**

Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases.

Women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to therapy and men should seek advice about the possibility of sperm preservation before starting therapy as methotrexate can be genotoxic at higher doses.

**Effects on ability to drive and use machines**

Central nervous symptoms such as tiredness and dizziness can occur during treatment, therefore in isolated cases methotrexate can have minor or moderate influence on the ability to drive and use machines.

**8.3.3 Pharmacovigilance Activities & Risk Management Plans**

Regarding the management of potential safety hazards or adverse side effects, manufacturers should routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.
Routine Pharmacovigilance activities should be in place. A detailed assessment of each report as part of routine pharmacovigilance activities should be performed. All events reported to the company or published in the literature should be periodically assessed for trends and periodic safety update reports (PSURs) and should be provided to the relevant regulatory authorities in accordance with the relevant Directives.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
  - The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
  - The medicine’s legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

Spillage kits should be available for patients on subcutaneous methotrexate.

Safety concerns are summarised in Table 1:
Table 1: Summary of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Opportunistic infections (e.g. Pneumocystis jirovecii pneumonia)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lymphomas</td>
</tr>
<tr>
<td>Blood disorders</td>
<td></td>
</tr>
<tr>
<td>Leukocytopenia, thrombocytopenia, anaemia, pancytopenia, agranulocytosis</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Leukoencephalopathy, impaired vision</td>
<td></td>
</tr>
<tr>
<td>Interstitial alveolitis, pneumonitis, pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Elevated transaminases, hepatitis, cirrhosis and fibrosis, fatty degeneration of the liver</td>
</tr>
<tr>
<td>Skin ulcers</td>
<td></td>
</tr>
<tr>
<td>Stress fracture</td>
<td></td>
</tr>
<tr>
<td>Renal disorders</td>
<td>Renal impairment, renal failure, oliguria, anuria</td>
</tr>
<tr>
<td>Teratogenicity (Abortion and congenital disorders)</td>
<td></td>
</tr>
<tr>
<td>Effects on fertility</td>
<td></td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Potential for overdose</td>
</tr>
<tr>
<td>Missing information</td>
<td>Use in children less than 3 years of age</td>
</tr>
</tbody>
</table>

8.4 Recommendations in existing WHO guidelines

There are no current recommendations on WHO Guidelines

8.5 Recommendations in other current clinical guidelines

Section 9 includes a review of the recommendations by several CPG.
9. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

- The bioequivalence of scMTX is consistent with imMTX
- The efficacy of MTX is well established in several Guidelines
- The full effectiveness of MTX cannot be achieved in long term treatments because of adverse side effects and/or intolerance
- scMTX can be given at higher doses than oral MTX avoiding the Adverse Side Effects
- scMTX in a prefilled cartridge does not require manipulation

9.1 New medicine(s) / indication(s)

We are providing here a summary of the evidence that has been put forward by national and international organisations supporting the usage of MTX in the different indications of scMTX.

Most of the available evidence refers to oral MTX, and where available we are including the evidence referring to scMTX. However, it should be noted that according to the evidence provided in section 5 regarding clinical efficacy, bioequivalence and safety of MTX, the evidence on MTX is largely applicable to scMTX.

As stated in several parts of this document, there is limited evidence comparing oral MTX to scMTX, and in most of the literature both dosing are used interchangeably.

scMTX is in any case advisable where oral MTX dosing is either not tolerated or ineffective.

9.2 Clinical Efficacy of MTX⁹

9.2.1 Systematic Literature search

A broad search in PubMed has been performed using ("methotrexate"[MeSH Major Topic]) OR ("methotrexate/administration and dosage"[MeSH Major Topic]) Filters: Meta-Analysis, Review, Systematic Review] which yielded 1.449 articles.

---

⁹ SMPC
A more targeted searches (Box 1) returned 618 and 26 results respectively. Of the latter, after reading the title, 10 were selected for reading the abstract.

**Box 1: Targeted literature review for efficacy of scMTX**

((("methotrexate"[MeSH Major Topic]) OR ("methotrexate/administration and dosage"[MeSH Major Topic]))) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter]) AND ((("rheumatic diseases"[MeSH Major Topic]) OR ("psoriasis"[MeSH Major Topic]) OR ("arthritic psoriasis"[MeSH Major Topic])) OR ("juvenile idiopathic arthritis"[All Fields]) OR ("Infantile Inflammatory Arthritis"[All Fields]) OR ("Crohn's Disease"[All Fields]) OR ("Inflammatory bowel disease"[All Fields]) OR (inflammatory[MeSH Major Topic]))

((("methotrexate"[MeSH Major Topic]) OR ("methotrexate/administration and dosage"[MeSH Major Topic]))) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter]) AND ((("rheumatic diseases"[MeSH Major Topic]) OR ("psoriasis"[MeSH Major Topic]) OR ("arthritic psoriasis"[MeSH Major Topic])) OR ("juvenile idiopathic arthritis"[All Fields]) OR ("Infantile Inflammatory Arthritis"[All Fields]) OR ("Crohn's Disease"[All Fields]) OR ("Inflammatory bowel disease"[All Fields]) OR (inflammatory[MeSH Major Topic])) AND ("subcutaneous"[All Fields]) AND (("subcutaneous"[All Fields]) OR ("subcutaneous injection"[All Fields]))

*No additional filters*

We present here a summary of the findings of these 10 papers (Table 2).

**Table 2: summary of findings on the selected publications**

<table>
<thead>
<tr>
<th>Reference &amp; Type of study</th>
<th>Short summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szczerkowska-Dobosz A. (2016)</td>
<td>Article in Polish not available</td>
</tr>
</tbody>
</table>

Bianchi, G. et al. (2016)\textsuperscript{11}. The authors suggested that the parenteral route of administration should always be considered before determining a patient’s overall failure on or intolerance to MTX. In other words, failure of MTX therapy should only be declared in case of lack of efficacy of or intolerance to MTX SC. MTX SC seems to ensure better tolerability and safety profiles, mainly with less gastrointestinal discomfort for patients, compared with MTX OR.

Yadlapati, S. et al (2016)\textsuperscript{12}. Efficacy: SC MTX appears to surmount the problems coupled with oral administration. Several studies demonstrated better clinical response among patients receiving SC MTX when compared to those receiving oral MTX. In patients non-responsive to oral MTX, substitution of SC MTX may impede the necessity for therapy with biologics or other non-biologic combinations and provide considerable savings.

Patient preference for prefilled pen was 75% ($p < 0.0001$), and their preference was in regard to use, acceptability, and satisfaction [27]. Health personnel and investigator preferences were also assessed which revealed the same.

ASE: The most commonly reported adverse effect of MTX therapy is gastrointestinal (GI) disturbances. Alleviation of GI symptoms is one among the many benefits of switching from oral to SC MTX.

Li, D (2016)\textsuperscript{13}. Efficacy: Two articles reported ACR20, ACR50, ACR70 24 weeks after first MTX treatment. The ACR20 (OR=1.68; 95%CI, 1.09 to 2.61) and ACR70 (OR=1.52; 95%CI, 1.02 to 2.26) in SC group showed better results compared with oral group. While the ACR50 in the two groups had no significant difference (OR=1.68; 95%CI, 0.64 to 4.44). Two works VAS score and the results showed the SC group had a better pain control (MD=−0.65; 95%CI, -0.93 to -0.37). Three articles presented the clinical failure and there was no significant difference between two groups (OR=1.20; 95%CI 0.85 to 1.71).

ASE: Three studies presented headache, but no significant difference was found between SC group and oral group (OR=0.69; 95%CI, 0.39 to 1.24, Fig 4). Three studies showed nausea and the SC group had a lower occurrence rate (OR=0.53; 95%CI, 0.28 to 0.97, Fig 4). Two works reported vomiting (OR=0.55; 95%CI, 0.26 to 1.18) and dyspepsia (OR=0.67; 95%CI, 0.37 to 1.19) and the difference had no statistical significance. Two studies showed diarrhea and the occurrence rate was lower in SC group than oral group (OR=0.43; 95%CI, 0.20 to 0.95).

Sharma, P et al (2015)\textsuperscript{14}. Subcutaneous methotrexate should be routinely considered in patients with active rheumatoid arthritis, prior to using biological therapy.


Administering MTX by the subcutaneous or intramuscular (IM) route provides reliable absorption into the systemic circulation most likely explaining the improved efficacy described for scMTX. Recent studies performed to assess new proprietary MTX auto-injector formulations have replicated the demonstration of increased bioavailability of scMTX vs. oral, measuring area under the curve (AUC) and maximum concentration. While the AUC of oral dose MTX plateaued at 15 mgs, the AUC for the sc dose continued to increase in a dose dependent fashion. GI effects were greater with the oral drug.

Moderate evidence suggesting superior efficacy of subcutaneous injections, due to the ease of oral administration and similar bioavailability at typical starting doses

Switching from OR-MTX to SC-MTX in patients with active RA (DAS 43 which is considered as an index of low/moderate activity) resulted in a substantial change in the concentration of metabolites of MTX in erythrocytes, with increased proportions of the long-chain polyglutamates; a significant clinical improvement was observed in these patients. Although the increase in such metabolites was associated with a better clinical response, as evaluated by using the Disease Activity Score in 28 joints (DAS28) in this cohort of patients, their clinical utility as a predictor of good clinical response requires further study.

Concerning the route of administration of MTX, the greater effectiveness of the parenteral route is consistent with pharmacokinetic data. In dosages higher than 25 mg/week, mean bioavailability with the oral route is 0.64 [0.21–0.96] compared to the subcutaneous route [35]. Tolerance seemed better with parenteral administration in the studies selected for this review, most notably in terms of gastrointestinal events. Thus, parenteral administration may deserve consideration for MTX initiation in selected patients and should be tried in patients with unresponsiveness or intolerance to oral MTX before switching to another drug.

Starting on methotrexate 15 mg/week orally, escalating with 5 mg/month to 25–30 mg/week, or the highest tolerable dose, with a subsequent switch to subcutaneous administration in the case

---

16 Schiff MH, Jaffe JS, Freundlich B Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration *Annals of the Rheumatic Diseases* 2014;73:1549-1551.
of an insufficient response, seems to be the optimal evidence-based dosing and routing recommendation for methotrexate in RA.

SLR: Systematic Literature Review; ASE: Adverse Side Effects; RCT: Randomised Clinical Trial

In summary, we believe there is good evidence showing the increased efficacy of scMTX at high doses reducing the adverse side effects.

Through indirect searches 3 more recent publications were found, that allegedly are leading to the same type of conclusion than the previous publications:

<table>
<thead>
<tr>
<th>Reference &amp; Type of study</th>
<th>Short summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanaka Y et al (2022)²⁰</td>
<td>Efficacy: At Week 12, the ACR20 response rate (primary end point) was numerically higher for MJK101 (59.6%) than for oral MTX (51.0%). For ACR20 at Weeks 4 and 8 as well as ACR50 and ACR70 responses at Weeks 4, 8, and 12 of Part 1, the proportion of responders in the MJK101 treatment group was comparable to the oral group. The change in DAS28-ESR score from the baseline to Weeks 4, 8, and 12 was also comparable [Week 12: −1.49 (MJK101) vs. −1.62 (oral MTX)]. There were no significant differences in the proportion of patients achieving remission after 12 weeks (MJK101: 19.2%; oral MTX: 14.3%). All other secondary end points in Part 1, such as CDAI, SDAI, including the respective individual disease activity categories, HAQ-DI score, or mean CRP, were comparable between both groups. ASE: AEs occurred in 57.7% of patients treated with MJK101, which was lower than 72.0% of patients with AEs receiving oral MTX. The majority of patients had AEs of only mild intensity (MJK101: 50.0%; oral MTX: 58.0%).</td>
</tr>
<tr>
<td>Vena GA et al (2018)²¹</td>
<td>A limited number of trials have compared oral and SC formulations of MTX in patients with Rheumatoid Arthritis or Juvenile Idiopathic Arthritis, and most of them were open-label observational studies. Various studies have assessed the response to MTX following a switch to SC treatment in RA or JIA patients with inadequate response to oral MTX. These studies were generally retrospective analyses. There are very few data concerning SC MTX treatment in psoriatic disease. Moreover, no study has compared SC and oral routes of administration for the management of psoriasis. It should be stressed that the study design of many studies does not allow a direct comparison of the efficacy and tolerability profiles between oral and SC formulations of MTX. Moreover, the</td>
</tr>
</tbody>
</table>


majority of comparative studies were open labelled, and most of the studies examining patients who were changed from oral to SC MTX were retrospective. Preliminary data suggest the possibility of high persistence rates and optimal adherence with SC MTX. This may minimize or delay the need to start more expensive alternative therapies, having a considerable economic impact. Therefore, in RA patients refractory to oral MTX, switching to parenteral administration has been recommended as a useful strategy before introducing other therapies.

The effectiveness and safety of SC MTX have mostly been assessed in rheumatological settings, especially in patients with RA. There are only a limited number of data on SC MTX in juvenile idiopathic arthritis and even fewer in psoriatic disease. Various clinical experiences have suggested that SC MTX is more effective than oral MTX and may provide significant benefit even in patients in whom oral MTX proved to be inadequate. The increased efficacy of SC MTX resulting from higher drug exposure compared with oral MTX has been associated with a similar safety profile and in various reports even with a lower frequency of gastrointestinal complaints.

9.2.2 Clinical Efficacy

The use of MTX has been approved in several diseases (namely, Rheumatoid Arthritis, Psoriasis and Arthritic Psoriasis, Juvenile Idiopathic Arthritis and Chron’s Disease).

In Rheumatoid arthritis and psoriatic arthritis MTX is the first-choice disease-modifying anti-rheumatic drug (DMARD) due to low costs, efficacy and an acceptable safety profile. Serious adverse effects such as pulmonary toxicity, hepatotoxicity and bone marrow suppression are rare or transient if MTX is stopped. In contrast, gastrointestinal adverse effects are common, affecting as many as 66% of patients. Due to these adverse effects, up to 12% of RA and PsA patients discontinue MTX after 6 months to 2 years of treatment.

Rheumatoid Arthritis:

- Despite the development of several new agents whose efficacy is directed against specific RA-related targets such as cytokines (TNFα, interleukins), B cell antigens, or T-cell adhesion molecules, MTX remains the standard backbone of treatment of patients with RA.
- According to clinical practice, the recently published European guidelines verify the importance of MTX for second- and third-line treatments. When first-line treatment results insufficient for patients, adding a bDMARD or a tsDMARD is recommended.

---

Therefore, the EULAR Task Force continues to advocate the continuation of MTX (or other csDMARDs) when treatment with bDMARDs or JAKi is planned.

Psoriasis:
- MTX is an effective anti-psoriatic agent and has been widely used to treat severe psoriasis and psoriatic arthritis since the 1960s, although scientific evidence from randomised clinical trials is rather scarce. Nevertheless it possesses a very high benefit-to-toxicity ratio compared with other therapies and immunosuppressive agents used in this disorder. The most important evidence-based guidelines published to date recommend the use of traditional DMARD as a first step for the treatment of patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extraarticular manifestations). The drugs suggested in these earlier stages are sulfasalazine, MTX, Leflunomide and Cyclosporine. Only leflunomide is not included in WHO’s EML.
- In the last decade, MTX has gained importance because of its use in combination with biologics, either to increase the efficacy of these products or in an attempt to diminish the development of antidrug antibodies. The concomitant use of MTX with biologics is nowadays almost the standard of care in rheumatologic patients who are refractor to conventional disease-modifying drugs. MTX is the suggested first-line DMARD in PsA, but neither EULAR nor GRAPPA120 currently recommend its use in combination with TNFi, owing to insufficient data (though accepting the lack of data is due to historical factors). Despite this, the use of MTX in combination with TNFi in PsA is not uncommon.
- Long-term (e.g., >10 years) methotrexate therapy can be effective for many patients with moderate-to-severe psoriasis 18; however, only an estimated 50–60% of patients who tolerate oral methotrexate doses of 15–20 mg/week will achieve marked improvement, leaving 40–50% of patients without an effective therapy23

Juvenile Idiopathic Arthritis (JIA):
- Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease.
- MTX remains the most widely used conventional DMARD in the management of JIA

---

MTX may exhibit a disease-modifying effect as the radiologic damage progression rate was decreased in two small uncontrolled series. In JIA, methotrexate (MTX) is the cornerstone treatment, due to its efficacy and safety. MTX is also a part of a consensus treatment plan for new-onset systemic JIA.

Serious adverse effects such as hepatotoxicity and bone marrow suppression occur rarely\(^2^4\). In contrast, MTX-related gastrointestinal adverse effects, such as nausea, abdominal pain and vomiting, occur frequently. Folic acid supplementation is an accepted strategy to prevent and treat these adverse effects. Despite folic acid use, many JIA patients experience gastrointestinal adverse effects after MTX intake. Notably, MTX intolerance occurs in up to half of JIA patients on MTX, and can negatively affect their quality of life. Moreover, over three-quarters of intolerant patients reluctantly used or even refused MTX, which, besides leading to non-compliance, could lead to premature discontinuation of MTX, and even replacement by biologics.

Weekly low-dose MTX is associated with strikingly few documented long-term side effects. MTX for the paediatric rheumatic disorders seems to be associated with less frequent physician visits, lower total costs, improved function, and fewer late reconstructive surgeries.

**Chron’s Disease**\(^2^5\):

- The first description of MTX use in CD dates back to 1989\(^2^6\). Since then, MTX has been included in international therapeutic guidelines\(^2^7,2^8\).
- MTX was superior to placebo in maintaining clinical remission of CD\(^2^9\)

---


- The use of MTX is supported by randomized clinical trials only in steroid-dependent CD, with similar outcomes to thiopurines. Combination therapy with biologics can optimize the immunogenic profile of the biological drug, but the impact on long-term clinical outcomes is described only in small series with anti-TNFα. Other off-label uses, such as fistulizing disease, mucosal healing, postoperative prevention and extraintestinal manifestations, are described in small uncontrolled series.
- The best performance in most indications was shown by parenteral MTX, favouring higher doses (25 mg/week) in the induction phase.
- Regarding Adverse Side Effects, a meta-analysis\(^{30}\) on CD studies showed a significantly higher risk of AEs (defined as MTX withdrawal because of AEs) in three studies investigating induction of remission (RR = 6.40; 95% CI 1.52–27.03; \(I^2 = 0\%\)), but no statistical differences in two studies investigating maintenance of clinical remission (RR = 2.95; 95% CI 0.31–28.19; \(I^2 = 0\%\)) when comparing the risk of AEs in the MTX group versus placebo.

### 9.3 Bioequivalence of scMTX

To substantiate the appropriateness of scMTX, the bioequivalence of this route of administration needs to be documented.

In the original approval of scMTX, a clinical study to evaluate the pharmacokinetic characteristics and the rate and extent of absorption of 16.5 mg MTX disodium salt as an aqueous solution corresponding to 15.0 mg MTX following subcutaneous (SC) compared to intramuscular (IM) administration was performed in healthy male subjects.

AUC\(_{0-\text{inf}}\) and AUC\(_{0-t}\) were found equivalent for both routes of administration. \(C_{\text{max}}\) following SC administration was about 60% of that for IM administration. The average (geometric mean) concentration time profiles revealed that IM administration leads to higher maximum concentrations at earlier time points. From 2 – 12 hours p.a., MTX concentrations were higher after SC compared to IM administration\(^{31}\).

The bioequivalence of IM and scMTX have also been proven elsewhere\(^{32}\).

---


\(^{31}\) Medac_Clinical Overview on Methotrexate 10 (50) mg/ml. 2018

Prior PK studies comparing oral to parenteral MTX mostly tested MTX dosed in mg/m2 and never clearly established a continuum of bioavailability over the range of commonly used oral doses (Fig 3A-B). This study compared bioavailability across commonly prescribed doses of oral and scMTX, showing that there is no advantage to increasing the oral MTX dose above 15 mg/week, a common clinical practice. Subcutaneous MTX exhibited a linear, dose-proportional increase in exposure with no plateau. At each dose level, SC administration achieved higher MTX exposure than the comparable oral dose and continued to increase through doses of 25 mg/week. Potential confounders of the comparison of dosage forms were minimised by the random sequence crossover design. No increases in AEs were observed with scMTX.

Fig 3A-B: Studies showing better bioavailability

![Graph showing bioavailability comparison between oral and subcutaneous MTX](https://pubmed.ncbi.nlm.nih.gov/2302272/)

Figure 1: Mean±SEM AUC by MTX dose. Mean oral MTX exposure plateaus at doses ≥15 mg/week. AUC, area under the concentration versus time curve; MTX, methotrexate; SC, subcutaneous; SEM, SE of the mean.
The bioavailability of MTX when administered via oral route leads to highly heterogenous bioavailability. Pharmacokinetic studies in adult patients with RA show comparable bioavailability of oral and parenteral MTX in doses up to 25 mg weekly. In these studies the mean relative bioavailability of oral MTX, compared to intramuscular administration, ranged from 0.85 to 1.0. In other studies, using 15 mg MTX and 10 mg/m2 MTX, bioavailability of oral compared to intravenous MTX was 0.67 and 0.70, respectively. In a comparison of 25 mg MTX, the mean bioavailability after oral administration was 73% compared to the intravenous route. Bioavailability of a higher oral dose of MTX in adult patients with RA is highly variable, and on average two-thirds that of the subcutaneous administration. To improve efficacy of MTX at dosages of 25 mg weekly or more, a change to parenteral administration should be considered.

Multiple studies have shown that bioavailability variations of MTX are dose-dependent, with greater variability and reduced absorptions at the higher doses sometimes required to manage RA. This variability in oral MTX bioavailability is attributed to saturation of gastrointestinal (GI) transport processes and the absorption mechanism, and forms the basis of the confounding and inconsistent relationship between dose of oral MTX and treatment response.

Additionally, treatment with oral MTX tablets is commonly associated with GI disorders, such as abdominal pain, anorexia, stomatitis, nausea, vomiting, diarrhoea, and constipation. The frequency of these GI side effects in patients using oral MTX tablets often warrants a switch to parenterally administered MTX or another therapy.

A bioavailability study comparing autoinjectors with oral administration showed that plasma concentrations (Cmax) and area under the plasma-concentration curves (AUC0-t), was generally higher with the SC MTX pen compared with oral administration for all dose groups. AUC0-t ratios increased with ascending doses; after a single dose administration, Cmax ratios did not increase, but unlike the AUC0-t profile of oral MTX, which began to plateau above 22.5 mg, the AUC0-t of the SC MTX pen never reached a plateau and maintained linearity at all doses tested. Higher mean Cmax values were observed after SC MTX pen administration compared with oral MTX tablet for all dose groups except for the 7.5-mg dose group, where no difference was observed. AUC0-t ratios for the SC MTX pen/oral MTX tablet increased with ascending doses, whereas the Cmax ratios for the SC MTX pen/ oral MTX tablet did not increase with ascending doses (Fig. 2b). The variability of AUC0-t was higher after oral MTX tablet administration for all doses except for the 22.5-mg dose

A total of 80 AEs were reported in 35/62 subjects; none were severe. Differences in the safety profiles were related to the route of administration. Single administrations with the MTX pen were well tolerated at the injection site.

9.4 Clinical Efficacy of scMTX

MTX, when given orally reaches a plateau. In patients needing higher doses of MTX, toxicity may be a limiting factor. Treatment with oral MTX tablets is commonly associated with GI disorders, such as abdominal pain, anorexia, stomatitis, nausea, vomiting, diarrhoea, and constipation. The frequency of these GI side effects in patients using oral MTX tablets often warrants a switch to parenterally administered MTX or another therapy.

Gastrointestinal (GI) tract absorption limitations may compromise the bioavailability of higher oral doses. This variability in oral MTX bioavailability is attributed to saturation of gastrointestinal (GI) transport processes and the absorption mechanism, and forms the basis of

the confounding and inconsistent relationship between dose of oral MTX and treatment response.

Studies have shown that the bioavailability of oral MTX varies widely among patients and decreases with increasing dose. The GI side effects of oral MTX, such as nausea and vomiting, also limit optimal use. Doses greater than 15 mg/week are frequently used to control disease activity, but may be only partially effective in some patients and poorly tolerated by others (see clinical efficacy section for details). A study\(^{35}\) of oral and scMTX in patients with RA suggested that limitations in systemic exposure of oral administration may affect efficacy. In that trial, clinical responses were significantly better in patients given scMTX.

**Rheumatoid Arthritis:**

A review of the evidence\(^ {11}\) shows the appropriateness of scMTX when compared to oral MTX. At the same dose level, bioavailability of scMTX is significantly higher and less variable than that of oral MTX. This difference is even more pronounced for medium-to-high dosages (i.e., >15 mg/week).

With regard to clinical response (Disease Activity Score-28, American College of Rheumatology Criteria), randomized, double-blind studies and retrospective or longitudinal analyses in real-life settings showed that scMTX is more effective than oral MTX. This is true both in MTX-naive patients with early RA, and in patients who switch from oral MTX OR to scMTX due to previous treatment failure, lack of efficacy and/or adverse events.

scMTX has a better tolerability profile than oral MTX, with fewer gastroenterological side effects. Delaying the use of more expensive biological therapies by switching from MTX OR to MTX SC in non-responders might provide cost savings, with relevant implications in the management of patients with RA.

Unlike oral MTX, the systemic exposure of SC MTX did not plateau over the doses studied, particularly at doses ≥15 mg/week\(^ {36}\). Therefore, since a rapid escalation to 25 mg weekly doses is recommended by current guidelines, subcutaneous MTX is widely used as a first-line treatment in RA.


Psoriasis:

There are very few data concerning scMTX treatment in psoriatic disease.

The METOP study\(^ {37}\), in MTX-naive patients compared scMTX to placebo, showing increased efficacy (PASI75) at week 16 (41% vs 10%, RR 3.93, 95% CI 1.31–11.81; \(P=0.0026\)). Response rates increased with continuous MTX treatment. The dropout rate over 52 weeks in patients treated with SC MTX in the METOP study was 39% (n=35/91), with 8 patients discontinuing because of poor efficacy and 19 due to AEs. During the placebo-controlled study phase, gastrointestinal AEs (especially nausea or vomiting) and increases in hepatic enzymes were more common in the MTX group than in the placebo group. Gastrointestinal AEs were usually mild or moderate and led to permanent discontinuation of study drug in 3% of patients who received MTX during the entire study period. Over 52 weeks, elevation of hepatic enzymes was reported in 23% of patients started on MTX, with 12% permanently discontinuing treatment.

Other prospective\(^ {38,39}\) and retrospective\(^ {40}\) studies confirm the good results also when switching from oral MTX.

The British Association of Dermatology guideline\(^ {41}\), recommends to switch to subcutaneous administration or another treatment, in case of clinical inefficacy of oral MTX. Several authors recommend to start with scMTX\(^ {42}\)

Psoriatic Arthritis:

There is very limited evidence on the benefit of scMTX on PsA. However, a Cochrane review\(^ {43}\) states that low-dose oral methotrexate may be more effective than placebo when taken for six months in terms of disease response (PsARC), function, pain, and patient and physician global

---


assessments of disease activity. And equally suggests a dose-dependent efficacy at higher than 15mg weekly dosing when administered subcutaneously.

**Chron’s Disease:**

Similarly to PsA, the evidence for scMTX is limited\(^44\). Several retrospective\(^45,46\) and prospective\(^47,48\) studies have shown improved efficacy with the usage of scMTX.

**9.5 Safety**

scMTX has been studied in the past to show that it is as safe as oral MTX but has significant better tolerability, leading to less discontinuation and adverse side effects.

West et al.\(^49\) conducted a meta-analysis on safety of MTX in patients with PsA, RA, CD, palmoplantar psoriasis, as well as sero-negative spondyl-arthritis. They identified 34 studies describing MTX administration for at least 3 months. Results are shown in the following table (Table 3). Data shown include AEs reported in at least three independent studies with >200 total patient safety years and with a weighted incidence of > 0.1%.

According to the British Rheumatology Society\(^50\), in patients with autoimmune rheumatic disease, the incidence of malignancy is increased although the absolute risk remains low. There is considerable evidence that this risk may relate to the underlying disease although any additional role of immunosuppression and treatment remains unclear.


Equally, they state that the blood monitoring schedule can be less frequent than advised in most guidelines as they believe there is not enough evidence to do so. Their recommended schedule is:

- Full blood count and liver function tests (ALT/AST).
- Check every two weeks for the first month after starting methotrexate treatment or after changing the dose of methotrexate.
  - If stable at one month check monthly for three months.
  - Thereafter check every three months.
- Inflammatory markers to check response and disease activity: ESR, CRP.
- Check creatinine clearance and urinalysis once every six months.

### 9.5.1 Contraindications and Cautions

**Contraindications:**

- Hypersensitivity to methotrexate or any excipients.
- Significant hepatic impairment.
- Ascites or pleural effusion: drain prior to treatment to reduce the risk of methotrexate accumulation.
- Significant renal impairment – creatinine clearance (CrCl) less than 30 mL/min.
- Severe infections (acute or chronic) or immunodeficiency syndromes.
- Known active peptic ulceration.
- Pregnancy and breast-feeding.
- Vaccination with live vaccines during treatment with methotrexate at immunosuppressive doses.
- Concomitant use of medicines with anti-folate properties, e.g. trimethoprim, co-trimoxazole.

**Cautions:**
- Renal impairment: dose reduction required.
- Alcohol dependence.
- Hepatic impairment, particularly if due to alcohol use.
- Pre-existing blood dyscrasias or disorders, including bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia.
- Respiratory disease.
- Concomitant use with hepatotoxic or haematotoxin medicines.
- History of ulcers of the oral cavity, ulcerative stomatitis, gastrointestinal ulcers or ulcerative colitis.
- History of chronic or recurrent infection (e.g. frequent infective COPD exacerbations, or recurrent urinary tract infection).
- Frail or elderly – consider reduced dose.
- Conditions which increase the risk of dehydration (e.g. vomiting) may increase the risk of toxicity. Consider interrupting treatment until symptoms cease.

**9.5.2 Drug interactions**

Methotrexate is associated with a large number of interactions\(^\text{51}\), some of which are significant enough to contraindicate concurrent use, require dose adjustment and/or additional

monitoring. Additional interactions which become relevant at higher doses (e.g. those used in oncology) are not included.

- Co-administration of medicinal products which cause folate deficiency (e.g. trimethoprim and co-trimoxazole) can lead to increased methotrexate toxicity and is contraindicated (see section 4). Particular caution should therefore also be exercised in the presence of existing folic acid deficiency.
- Leflunomide: increased risk of bone marrow and liver toxicity; increased monitoring and vigilance required.
- Ciclosporin: increased risk of nephrotoxicity and methotrexate toxicity.
- Azathioprine and mercaptopurine: not advised due to increased risk of toxicity.
- Sulfasalazine: may increase risk of bone marrow and liver toxicity. However, this combination is used in clinical practice without incident. Be aware of trends in monitoring parameters.
- Drugs with hepatotoxic, haematotoxic or nephrotoxic effects: Increased frequency of monitoring may be recommended.
- Live vaccines (e.g. oral polio, oral typhoid, MMR, BCG, Zostavax®) are advised in line with the national schedule for all patients, unless the patient is taking a dose of methotrexate or other immunosuppressive drug that exceeds those specified in the Green Book. Doses below this level are not considered sufficiently immunosuppressive and these patients can receive live vaccines. Clinician discretion is advised. Please refer to the Green Book Chapter 6 for current advice.
- Avoid concomitant use of cytotoxic, clozapine, and olanzapine: increased risk of agranulocytosis.
- Retinoids: increased risk of hepatotoxicity, and may increase plasma levels of methotrexate.
- Levetiracetam: may increase plasma levels of methotrexate.
- Nitrous oxide and pyrimethamine: increased antifolate effect of methotrexate.
- Lomitapide: increased risk of hepatotoxicity.
- Probenecid: excretion of methotrexate reduced.
- Phenytoin: possible increased methotrexate toxicity, and decreased phenytoin effect.
- NSAIDs, COX-2 inhibitors, aspirin: may reduce excretion of methotrexate, increasing risk of toxicity. These drugs are frequently used with methotrexate without incident, and aspirin at antiplatelet doses is unlikely to interact to a significant degree. Be aware of trends in monitoring parameters.
- Antibiotics may alter methotrexate levels. Methotrexate should be interrupted during periods of acute infection (see section 10).
- Theophylline and other methylxanthines: may reduce methotrexate efficacy. Methotrexate may reduce theophylline clearance.
- Anticonvulsants: may reduce methotrexate levels.
- Cholestyramine: may increase elimination of methotrexate.
- Alcohol: consumption of alcohol increases the risk of hepatotoxicity. Patients should moderate their alcohol intake to no more than 14 units per week.

9.6 Stability

Finally, in order to include scMTX in the EML it is important to show that the prefilled scMTX pen is stable at a wide range of environments, granting its use and shelf life in a wide range of potential access conditions, and making it appropriate for patients to access it in non-conventional healthcare settings.

As per the SmPC, the stability data obtained with the production batches demonstrate, as expected, a similar stability profile at all storage conditions for both drug source materials. After 24 months there are no differences between the syringes with embedded needle and the syringes without embedded needle. The stability data for the additional pack sizes does not differ from the previously gained stability data for the other fill volumes for the available time points. The values all lie well within the specification limits. Therefore the pack sizes with 12.5 mg; 17.5 mg; 22.5 mg and 27.5 mg are considered similar with respect to stability and the approved shelf life of 24 months remains unchanged.

Based on the results obtained a shelf life of 24 months is proved. As the medicinal product contains no preservatives it is dedicated for single dose only. Any unused solution should be discarded. The product should not be stored above 25 °C and protected from light.

\[52\] 3.2.P.8 section. Methotrexate 50 mg/ml, solution for injection dossier
9.7 Recommendations for use

9.7.1 Rheumatoid Arthritis (RA)

- The European Alliance of Associations for Rheumatology (EULAR) states that MTX is indicated as first choice DMARD in RA, with or without glucocorticoids.
  - Initially, MTX plus GCs is recommended and on insufficient response to this therapy within 3–6 months, treatment should be based on stratification according to risk factors; With poor prognostic factors (presence of autoantibodies, high disease activity, early erosions or failure of two csDMARDs), any bDMARD should be added to the csDMARD;
  - In the presence of sufficient folic acid supplementation, MTX can be rapidly escalated to about 25 mg once weekly.
  - The EULAR Task Force continues to advocate the continuation of MTX (or other csDMARDs) when treatment with bDMARDs or JAKi is planned.
  - When a patient is in sustained remission without glucocorticoids, there is also compelling evidence that stopping bDMARDs and/or csDMARDs will ultimately lead to flares in most patients. Therefore, the Task force felt that either dose reduction or interval increase (‘spacing’) is preferred, but completely stopping may not be advisable.

- According to the American College Rheumatology (ACR),
  - Methotrexate is strongly recommended over hydroxychloroquine or sulfasalazine for DMARD-naive patients with moderate-to-high disease activity.
  - Methotrexate monotherapy is strongly recommended over bDMARD or csDMARD monotherapy for DMARD-naive patients with moderate-to-high disease activity.
  - Methotrexate monotherapy is conditionally recommended over methotrexate plus a tumour necrosis factor (TNF) inhibitor for DMARD-naive patients with moderate-to-high disease activity.
    - The recommendation is conditional because some patients, especially those with poor prognostic factors, may prioritize more rapid onset of action and greater chance of improvement associated with combination therapy over the

53 https://ard.bmj.com/content/early/2022/11/10/ard-2022-223356
54 https://www.rheumatology.org/Portals/0/Files/2021-ACR-Guideline-for-Treatment-Rheumatoid-Arthritis-Early-View.pdf
additional risks and costs associated with initial use of methotrexate in combination with a TNF inhibitor.

- Methotrexate monotherapy is strongly recommended over methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD for DMARD-naïve patients with moderate-to-high disease activity
- Switching to subcutaneous methotrexate is conditionally recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target
  - there are no data comparing outcomes in patients who switch to subcutaneous methotrexate versus another treatment strategy that includes other DMARDs.
  - The recommendation is conditional because patient
    - preferences and the magnitude of previous response to methotrexate play an important role in this decision.
- moderate evidence suggesting superior efficacy of subcutaneous injections, due to the ease of oral administration and similar bioavailability at typical starting doses.

Regarding the route of administration (Fig 4 A&B):

- According to a preference systematic review on the route of administration, in 3 of the 5 studies examining patients’ preferred route of delivery, more patients preferred subcutaneous (SC) over intravenous (IV) therapy, although 2 of these found that 22% and 21% of patients expressed no preference. The final study found preferences to be split (50%) between SC and IV.
- With intravenous dosing, blood concentrations show a high peak post-infusion, subsequently falling as biopharmaceutical distributes into tissues and extracellular space. With subcutaneous dosing, blood concentrations reach a steady state with less peak-to-trough variation.

There is no robust published evidence of a causal association between the presence of ADAβ and injection-site reactions with subcutaneously administered

---

56 https://www.jrheum.org/content/47/2/176.long
biopharmaceuticals. The task force considers such an association unlikely and advises against measurement of ADAb under these circumstances.

**Fig 4 A&B: Summary of recommendations EULAR recommendations**

<table>
<thead>
<tr>
<th>Table 3. Methotrexate administration*</th>
<th>Certainty of evidence</th>
<th>Based on the evidence report(s) of the following PICO(s)</th>
<th>Evidence table(s) in Supp. App. 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate.</td>
<td>Moderate</td>
<td>PICO 9</td>
<td>p. 181</td>
</tr>
<tr>
<td>Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is conditionally recommended over initiation/titration to a weekly dose of &lt;15 mg.</td>
<td>Moderate/ very low†</td>
<td>PICO 10,1,1-C3</td>
<td>p. 184-5</td>
</tr>
<tr>
<td>A split dose of oral methotrexate over 24 hours or subcutaneous injections, and/or an increased dose of folate/folic acid, is conditionally recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate.</td>
<td>Very low</td>
<td>PICO 16 and PICO 15</td>
<td>p. 206-10</td>
</tr>
<tr>
<td>Switching to subcutaneous methotrexate is conditionally recommended over the addition of switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target.</td>
<td>Very low</td>
<td>PICO 18</td>
<td>p. 235</td>
</tr>
</tbody>
</table>

† This recommendation refers only to the initial prescribing of methotrexate and is not meant to limit further dose escalation, which often provides additional efficacy.
‡ The first certainty of evidence applies to the first listed option; the second certainty of evidence applies to the second option.

**Comparison 1: SC MTX versus Oral MTX. Data based on direct RCT evidence.**

**Overall certainty of evidence: Moderate**

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>100/188 (53.1%)</th>
<th>144/187 (77.0%)</th>
<th>RR 1.11 (1.00 to 1.22)</th>
<th>≤5 more per 1,000 (From 0 fewer to 159 more)</th>
<th>CRITICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC MTX</td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Oral MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Activity (Follow up: 4 months, assessed with ACR 20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (1) randomized trials</td>
<td>not serious∗</td>
<td>not serious√</td>
<td>not serious*</td>
<td>none</td>
<td>100/188 (53.1%)</td>
</tr>
<tr>
<td>CI: Confidence interval; RR: Risk ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MTX should not be discontinued in patients already using the drug.

In a recent meta-analysis, it was shown that withdrawing MTX slightly increases the RA disease activity in patients treated at target with bDMARDs/tsDMARDs plus MTX and has limited effects for patients with deep remission.

Six articles were included for qualitative and quantitative analysis, all of which were noninferior RCTs involving 1430 patients (734 in the withdrawal group and 696 in the continuation group). Compared with continuing combination therapy, tapering off or discontinuing MTX increased DAS28 by 0.20 (95% CI 0.09, 0.32, I² = 0%) and decreased the percentage of patients with LDA.

---

assessed by DAS28 to <3.2 [risk ratio (RR) 0.88 (0.80, 0.97), I² = 0%]. However, MTX withdrawal did not decrease remission rates assessed by DAS28, SDAI, CDAI or ACR/EULAR Boolean remission [RR 0.90 (0.81, 1.01), 0.93 (0.77, 1.11), 0.90 (0.74, 1.11), 0.95 (0.70, 1.29), respectively].

9.7.2 Psoriasis

- As per the Joint American Academy of Dermatology (JAAD)⁵⁹,
  - Methotrexate was FDA approved in 1972 at a time when randomized clinical trials were not required for regulatory approval. As such, there were few large, high-quality studies analysing the safety and efficacy of methotrexate. Nonetheless, several studies have demonstrated the benefit of methotrexate in psoriasis.
  - A large randomized clinical trial comparing methotrexate to adalimumab and placebo showed MTX performed significantly better than placebo but was less effective than adalimumab.
  - Combination therapy with methotrexate and tumour necrosis factor inhibitors results in improved efficacy over methotrexate monotherapy for the treatment of psoriasis

- NICE⁶⁰ recommends MTX
  - Methotrexate is a low-cost intervention that is effective in an important proportion of patients

- The European Academy of Dermatology and Venereology (EADV)
  - From a safety and efficacy perspective⁶¹ in elderly psoriasis patients, we recommend the following biological drugs adalimumab, certolizumab pegol, etanercept and infliximab; brodalumab, ixekizumab and secukinumab; ustekinumab, guselkumab, risankizumab, tildrakizumab and, the synthetic drug, apremilast. We also

---


recommend the conventional drugs, methotrexate, cyclosporine, and fumarates and acitretin are used to treat patients (greater than 65 years) with psoriasis.

- Methotrexate (MTX) should be preferentially given subcutaneously\(^2\) once weekly for increased safety (oral intake has higher risk for overdosing as patients are more likely to take tablets daily instead of once weekly) and improved bioavailability (MTX is a prodrug that is polyglutaminated into its active in vivo moiety). The recommended initial and maintenance dose is usually 15 mg MTX once weekly. In case of insufficient response, the dose can be increased up to 20 mg MTX once weekly. A further increase up to 25 mg MTX is only beneficial for a small subgroup of patients. S.c. dosing is recommended in patients with suboptimal response to oral treatment and may be considered as the starting route of administration in high need patients.

9.7.3 Psoriatic Arthritis (PsA)

- The EULAR Recommends\(^3\)
  - The day-to-day management of patients with PsA includes non-pharmacological as well as pharmacological interventions. The number of disease-modifying antirheumatic drugs (DMARDs) indicated for PsA has increased during the last decade. The armamentarium now includes not only conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX), sulfasalazine and leflunomide and tumour necrosis factor inhibitors (TNFi), but also other targeted biological agents (bDMARDs) aimed at different cytokines, such as TNF, interleukin (IL)-12/23 and IL-17A, as well as targeted synthetic DMARDs (tsDMARDs) that inhibit phosphodiesterase-4 (PDE4) or Janus kinases (JAKs).
  - In patients with polyarthritis, a csDMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement.


the SEAM-PsA study, which was part of the SLR and has meanwhile been published in full, revealed that MTX has similar efficacy in joint counts, skin involvement, enthesitis, dactylitis and physical function as etanercept or even etanercept plus MTX. Given this similarity of effectiveness, and the differences in costs, this study further supports the taskforce’s decision to place MTX and other csDMARDs at the top of the therapeutic algorithm.

- In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered.

- The ACR recommends
  - MTX is recommended over NSAIDs in treatment-naive patients with active PsA. Very low evidence to recommend to treat with MTX over NSAIDs (PICO 9) Very low (67) Conditional recommendation based on very-low-quality evidence; may consider NSAIDs before starting MTX in patients with less active disease, after careful consideration of cardiovascular risks and renal risks of NSAIDs.
  - Adding MTX in active PsA despite treatment with an IL-17i biologic agent as monotherapy. All recommendations for patients with active PsA despite IL-17i biologic treatment are conditional based on very-low-quality evidence. MTX may be added to the current IL-17i regimen instead of switching to a TNFi or IL-12/23i biologic in patients who have had a partial response to the current IL-17i biologic.
  - The quality of the evidence suggesting IL-17 is preferred over MTX is of low or very low quality.

- The Cochrane review recommends:
  - In terms of reaching PASI 90, anti-IL17 treatments (secukinumab, ixekizumab, brodalumab, and bimekizumab) were more effective than placebo (risk ratio at class level (RR) 30.68, 95% confidence interval (CI) 22.96 to 41.00). These findings were also confirmed for anti-IL23 (guselkumab, tildrakizumab, risankizumab, and mirikizumab) (class-level RR 20.23, 95% CI 14.76 to 27.73); anti-IL12/23 (ustekinumab) (RR 19.77, 95% CI 13.25 to 29.52); anti-TNF alpha (infliximab, etanercept, adalimumab, and certolizumab) (class-level RR 13.65, 95% CI 10.71 to 17.40); and small molecules (apremilast, tofacitinib, and oral

---

tyrosine kinase 2 (TYK2) inhibitor) (class-level RR 7.09, 95% CI 5.05 to 9.95). Both infliximab and adalimumab were more effective than methotrexate (respectively: RR 2.86, 95% CI 2.15 to 3.80; and RR 3.73, 95% CI 2.25 to 6.19) (low quality of evidence) (Fig 5 A&B)

Fig 5 A&B: a: League table of the relative effects of psoriasis treatments; b: comparison of biologic vs non biologic treatments

Figure 7. Relative effects of the intervention as estimated from the network meta-analysis model for Psoriasis Area and Severity Index (PASI) 90 and serious adverse events (AEs). Outcomes were all measured at the induction phase (assessment from 8 to 24 weeks after randomisation). Drugs are reported in order of primary benefit ranking. Each cell contains the risk ratio (RR) and 95% confidence interval for the two primary outcomes (PASI 90 and SAEs) of the intervention in the respective column versus the comparator in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 for the upper triangle favour the treatment on the left. Certainty of evidence was assessed for each comparison using CINeMA and classified in high (highlighted in green), moderate (in blue), low (in yellow) and very-low (in red). AC: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MIRI: mirikizumab; MTX: methotrexate; PBO: placebo; RI: ranibizumab; SECU: secukinumab; TILDRA: tildrakizumab; TOFA: tofacitinib; TYK2: Oral Tyrosine kinase 2 inhibitor; USK: ustekinumab
Juvenile Idiopathic Arthritis (JIA)

- The ACR recommends:
  - Methotrexate is conditionally recommended as a preferred agent over leflunomide, sulfasalazine, or hydroxychloroquine (in that order). Despite an absence of comparator trials, methotrexate is the preferred agent, given the preponderance of evidence showing its long-term safety and efficacy in children (22–24).
  - With regard to the route of administration of methotrexate, the 2019 JIA guidelines conditionally recommended subcutaneous over oral administration for polyarthritis. This recommendation was conditional because the supporting evidence was of very low quality and patient preferences may guide choice of route of administration. There is little reason to suggest that methotrexate should be used differently in oligoarthritis than in polyarthritis.
  - Biologic DMARDs or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors.
Other EU recommendations:

- First-line pharmacological interventions are based on non-steroidal anti-inflammatory drugs and intra-articular corticosteroids. Patients who are refractory to these therapies are candidates to receive disease-modifying anti-rheumatic medications, namely methotrexate or, in case of enthesitis-related arthritis, sulfasalazine. If therapeutic response is inadequate or suboptimal, the introduction of a biologic response modifier is considered.

### 9.7.5 Chron’s Disease

- The American College of Gastroenterology (ACG) recommends:
  - Azathioprine, 6-mercaptopurine, or methotrexate (15 mg once weekly) may be used in treatment of active CD and as adjunctive therapy for reducing immunogenicity against biologic therapy.
  - Methotrexate (up to 25 mg once weekly IM or SC) is effective and should be considered for use in alleviating signs and symptoms in patients with steroid-dependent Crohn’s disease and for maintaining remission.
  - In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, the thiopurine analogues (6-mercaptopurine and azathioprine) may be used. Mercaptopurine, and its prodrug, azathioprine, are effective steroid-sparing agents in CD. Methotrexate, when given subcutaneously (SC) or intramuscularly (IM), is also effective as a steroid-sparing agent.
  - The use of methotrexate in combination with steroids is effective for treatment of moderately active steroid-dependent/resistant CD.
  - Azathioprine (at maximal doses of 1.5–2.5 mg/kg/day), 6-mercaptopurine (at maximal doses of 0.75–1.5 mg/kg/day), or methotrexate (15–25 mg SC/IM once weekly) may be used in treatment of active CD.
  - Once remission is induced with corticosteroids, a thiopurine or methotrexate should be considered.

---


67 Lichtenstein, Gary R MD, FACG; Loftus, Edward V MD, FACG; Isaacs, Kim L MD, PhD, FACG; Regueiro, Miguel D MD, FACG4; Gerson, Lauren B MD, MSc, MACG (GRADE Methodologist)5; Sanders, Bruce E MD, MS, FACG6. ACG Clinical Guideline: Management of Crohn’s Disease in Adults. American Journal of Gastroenterology: April 2018 - Volume 113 - Issue 4 - p 481-517 doi: 10.1038/ajg.2018.27
Anti-TNF monotherapy is effective at maintaining anti-TNF-induced remission, but because of the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered (strong recommendation, moderate level of evidence).

Parenterally (SC or IM) administered methotrexate at a dose of 25 mg per week is effective for maintenance of remission in CD after steroid induction (285). If steroid-free remission is maintained with parenteral methotrexate at 25 mg per week for 4 months, the dose of methotrexate may be lowered to 15 mg per week (204). Data demonstrating efficacy of the use of oral methotrexate for maintenance of remission in patients with CD are lacking.

The European Chron’s and Colitis Organisation (ECCO) Guideline recommends

There is limited good quality evidence on the use of MTX monotherapy versus placebo to induce remission. Based on the current evidence, agreement on a recommendation for the use of MTX for inducing clinical remission in patients with CD could not be reached. However, MTX may be considered as an option for steroid-dependent patients with moderate-to-severe disease when alternative options [including surgery] cannot be used.

Methotrexate is recommended administered parenterally for the maintenance of remission in patients with steroid-dependent Crohn’s disease. There were no differences in severe AEs in the MTX as compared with the placebo group.

---

9.7.6 Oral vs Subcutaneous

- A SRE\(^{69}\) reviewing a total of 38 publications showed that starting on methotrexate 15 mg/week orally, escalating with 5 mg/month to 25–30 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 recommendation for methotrexate in RA.

  - Although oral methotrexate is widely preferred, because of patients’ preferences and low costs, the bioavailability of parenteral methotrexate is higher with increasing doses. Whether this leads to increased efficacy is addressed in only one RCT, which suggests that methotrexate 15 mg/week subcutaneously is indeed associated with a better response compared with 15 mg/week orally. However, escalating the oral dose to 25 mg/week might also have increased clinical efficacy in this trial. This is supported by data from observational studies, in which patients switching from parenteral to oral methotrexate at an equal dose showed disease exacerbations, but not if the oral dose was 2.5–5 mg/week higher. In contrast, in longstanding RA patients who failed 15–20 mg/week oral methotrexate plus other DMARD, neither a switch to 15 mg/week intramuscularly, nor subsequent intramuscular dose escalation resulted in increased efficacy. However, for this selected population not responding well to conventional DMARD, therapy with biologicals is currently indicated.\(^{29}\) The evidence on toxicity associated with the parenteral use of methotrexate is inconsistent. Whereas more withdrawal due to toxicity, but similar adverse events were seen in the RCT from Braun et al\(^ {70}\), observational data suggest a decrease in (gastrointestinal) side effects administering methotrexate parenterally. **Therefore, in summary, the preferred route of methotrexate seems to be oral, but a switch to subcutaneous is suggested in the case of an insufficient response at the highest tolerable oral dose.**

---

\(^{69}\) [https://ard.bmj.com/content/68/7/1094](https://ard.bmj.com/content/68/7/1094) Visser K, van der Heijde D Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature Annals of the Rheumatic Diseases 2009;68:1094-1099.

In RA, a Meta-analysis showed that SC MTX can significantly increase the AUC\textsubscript{0−t} (area under plasma concentration curve from administration to last observed concentration at time t)\textsuperscript{71}. SC route of MTX at high doses made better performance on improving the bioavailability and clinical efficacy, reducing the GI disorders, but it cannot decrease the treatment failure when compared with oral administration of MTX.

In patients with IJA failing oral medication a study suggests\textsuperscript{72} that for patients failing oral MTX either because of inefficacy or toxicity, the use of SC MTX has a high likelihood of success with more than 70% of patients achieving clinically significant improvement, without clinically significant toxicity.

9.7.7 Paediatric indication

The British Society Rheumatology\textsuperscript{73} recommends:

- **Indications for drug:** Methotrexate is available in a variety of forms (tablets, oral liquid, subcutaneous injection, intravenous injection). Although all forms are used to treat rheumatological conditions in children of all ages, only the oral 2mg/ml methotrexate liquid (e.g. JylamvoTM or Rosemont brand) and the subcutaneous prefilled pens or syringes have a licence for use in children and only for children with polyarticular JIA aged three years and older.

- **Not licensed but widely used:** Methotrextate is a useful DMARD for many paediatric and adolescent rheumatological conditions including juvenile idiopathic arthritis; juvenile dermatomyositis; vasculitis; uveitis; systemic lupus erythematosus; localised scleroderma; sarcoidosis as well as having a variety of non-rheumatological indications.


\textsuperscript{72} [https://www.jrheum.org/content/31/1/179.short](https://www.jrheum.org/content/31/1/179.short) Khayriah Alsufyani, Oliva Ortiz-Alvarez, David A Cabral, Lori B Tucker, Ross E Petty, Peter N Malleson The role of subcutaneous administration of methotrexate in children with juvenile idiopathic arthritis who have failed oral methotrexate. The Journal of Rheumatology Jan 2004, 31 (1) 179-182;

Several authors claim the importance of MTX in paediatric indications.\textsuperscript{74}

9.7.8 Orphan indications

EMA and FDA has recognised a number of orphan indications\textsuperscript{75,76,77}, including (but not limited to)

- Alkaptonuria
- Vitreoretinopathy (Retinal Detachment)
- Acute Lymphoblastic Leukaemia
- Osteosarcoma
- Myasthenia gravis

These are not the focus of this submission.

9.8 Summary of available evidence for comparative effectiveness

In the preceding section we have collected the abundant evidence regarding the efficacy and effectiveness of MTX and the usage of scMTX in specific indications.

The usage of scMTX is widely validated and recommended in several major well recognised clinical practice guidelines. The endorsement of MTX is clearly not in any indication and in any treatment positioning, but it is clear that it is recommended both as monotherapy and in conjunction to other bDMARDs. The usage of scMTX should be evaluated individually according to the patients’ capacity to tolerate maximum doses of oral MTX.

We have provided evidence showing that scMTX, is appropriate in a number of positionings in the diseases where it is indicated. And more importantly there is evidence that the usage of scMTX is preferred by patients and when oral dosing is not possible or ineffective, before switching to a combination therapy.

\textsuperscript{75} https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=metotrexate
\textsuperscript{76} https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=25029
\textsuperscript{77} https://www.accessdata.fda.gov/scripts/opdlisting/opd/listResult.cfm
In summary,

**For Rheumatoid Arthritis:**

- Methotrexate monotherapy is strongly recommended over bDMARD or tsDMARD monotherapy for DMARD-naïve patients with moderate-to-high disease activity.
- Switching to subcutaneous methotrexate is recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target.

**For Psoriasis:**

- Several studies have demonstrated the benefit of methotrexate in psoriasis.
- Methotrexate is a low-cost intervention that is effective in an important proportion of patients.
- Methotrexate (MTX) should be preferentially given subcutaneously once weekly for increased safety (oral intake has higher risk for overdosing as patients are more likely to take tablets daily instead of once weekly) and improved bioavailability.

**For Psoriatic Arthritis:**

- MTX is recommended over NSAIDs in treatment-naïve patients with active PsA.
- In patients with polyarthritis, a csDMARD should be initiated rapidly, with methotrexate preferred in those with relevant skin involvement.

**For Juvenile Idiopathic Arthritis:**

- Methotrexate is recommended as a preferred agent over leflunomide, sulfasalazine, or hydroxychloroquine (in that order).
- With regard to the route of administration of methotrexate, the 2019 JIA guidelines conditionally recommended subcutaneous over oral administration for polyarthritis.

**For Chron’s Disease:**

- Methotrexate (up to 25 mg once weekly IM or SC) is effective and should be considered for use in alleviating signs and symptoms in patients with steroid-dependent Crohn’s disease and for maintaining remission.
In patients with moderate-to-severe CD who remain symptomatic despite current or prior corticosteroid therapy, the thiopurine analogues (6-mercaptopurine and azathioprine) may be used. Mercaptopurine, and its prodrug, azathioprine, are effective steroid-sparing agents in CD. Methotrexate, when given subcutaneously (SC) or intramuscularly (IM), is also effective as a steroid-sparing agent.

9.9 Assessment of applicability of the available evidence across diverse populations and settings

We have provided in the previous sections evidence to support the usage of scMTX in different diseases and across a wide range of populations.

We have also tried to be precise in the positioning of the treatment, although some clinical practice guidelines recommend the usage of scMTX in all patients when indicated, given the higher acceptance of the treatment and the potential to provide higher dosing without the adverse side effects.

As referred in section 7, we believe the subcutaneous indication is preferable to the other parenteral alternatives in all potential settings, given the many hazards linked to the manipulation of the drug and the cost implications of the appropriate management of the vial.

Therefore, **where oral administration is not possible or ineffective, the subcutaneous route should be preferred, at least in the indications for which the drug has been approved.**
10. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY

Section 9 provides information about comparative safety of scMTX to oral MTX.

10.1 Exposure

The following amount of low dose MTX has been sold worldwide cumulatively (until 31/10/2018, latest data available): 3,043,368,876 mg.

For autoimmune indications the applied average dose for a patient is 2.5 mg MTX/day = 17.5 mg/week. The patient exposure is therefore calculated to:

Patient exposure (patient-years) = 3,043,368,876 mg / [(2.5 mg) x 365] = 3,335,199

10.2 NEW MEDICINE(S) / INDICATION(S)

10.2.1 Systematic Literature search (SLR)

As in the previous section a systematic literature search is not the appropriate tool to find the relevant evidence. The search engine does not allow a segregation of the different indications, and we would still be faced with the problem of the many indications for which does not allow.

We have performed a broad search in PubMed using ["methotrexate/adverse effects"[MeSH Major Topic] Filters: Meta-Analysis, Review, Systematic Review] which yielded 355 articles.

A more targeted searches (Box 2) returned 153 and 4 results respectively, which was not as useful as the many well documented and referenced reviews or the clinical practice guidelines on which this proposal is based on. None of the publications here mentioned are referring to a comparative analysis of oral MTX versus scMTX.

Furthermore, the whole purpose of this submission is to reinforce the idea that the adverse side profile is the same in type but less frequent.

The publications on the Adverse Side Effects for the scMTX administration are scarce, and we have made our best effort to publish them. As per the SLR strategy, no systematic reviews or meta-analyses, and the reviews do not compare subcutaneous versus oral administration.
Box 2: Targeted literature review for adverse side effects

("methotrexate/adverse effects"[MeSH Major Topic]) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter]) AND ("rheumatic diseases"[MeSH Major Topic]) OR ("psoriasis"[MeSH Major Topic]) OR ("arthritic psoriasis"[MeSH Major Topic]) OR ("juvenile idiopathic arthritis"[All Fields]) OR ("Infantile Inflammatory Arthritis"[All Fields]) OR ("Crohn's Disease"[All Fields]) OR ("Inflammatory bowel disease"[All Fields]) OR (inflammatory[MeSH Major Topic])

("methotrexate/adverse effects"[MeSH Major Topic]) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter]) AND ("rheumatic diseases"[MeSH Major Topic]) OR ("psoriasis"[MeSH Major Topic]) OR ("arthritic psoriasis"[MeSH Major Topic]) OR ("juvenile idiopathic arthritis"[All Fields]) OR ("Infantile Inflammatory Arthritis"[All Fields]) OR ("Crohn's Disease"[All Fields]) OR ("Inflammatory bowel disease"[All Fields]) OR (inflammatory[MeSH Major Topic]) AND ("subcutaneous"[All Fields] OR (subcut*) OR ("subcutaneous injection"[All Fields]))

No additional filters

10.2.2 Clinical Safety

In what precedes we have tried to establish that scMTX is as effective as oral MTX without many of the adverse side effects which limit its adherence and effectiveness.

The comparator of scMTX should only be oral MTX, as this is the proposed indication being sought in this dossier. Therefore, the comparison to other potential DMARDs is not appropriate.

It is not the intention of this dossier to substitute other DMARDs. There is no available evidence to do so, and it would be extremely challenging, given the exiting evidence, to try to produce indirect comparisons with other potential treatments, as the evidence is old and scarce (as it has been repeatedly been pointed out throughout this document).
11. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

11.1 Oral MTX, imMTX or ivMTX versus scMTX
There is limited evidence on the cost-effectiveness of scMTX when compared to imMTX or ivMTX. However, it should be highlighted that given the hazards and administration costs of imMTX and ivMTX it is very likely that the costs are compensated with the costs of a scMTX injection.

Furthermore, in severe patients, where oral MTX cannot be administered any longer (either because of toxicity, lack of effectiveness or both), scMTX offers an increased efficacy that would compensate for the extra costs of oral MTX.

11.2 scMTX versus adalimumab
An important aspect is whether scMTX should be an alternative to adalimumab, which is also in the WHO EML. Again, the evidence is limited, and we will need to refer to indirect comparisons to build an answer. We have not been able to find evidence from low-income countries, where the cost of adalimumab may be significantly lower than in high-income countries, nor there are studies showing the cost-effectiveness of biosimilar adalimumab compared to MTX.

Before we do that, we must bear in mind that Adalimumab is on WHO’s EML as an iv medication, therefore all the aspects of access, safety and cost that would apply to imMTX and ivMTX would also apply here.

11.3 NEW MEDICINE(S) / INDICATION(S)
11.3.1 Rheumatoid Arthritis
The NICE Recommendations\(^{78}\) on the usage of MTX state that it should be used in combination with bDMARDs under certain circumstances. More precisely the recommendations state:

\(^{78}\) NICE_Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (TA375)_NICE_2016
- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
  - disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
  - disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs) and
  - the companies provide certolizumab pegol, golimumab, abatacept and tocilizumab as agreed in their patient access schemes.
- The results of the Assessment Group's systematic review indicated that, in people who had previously had DMARD therapy, many biological DMARDs had incremental cost-effectiveness ratios (ICERs) close to £30,000 per quality-adjusted life year (QALY) gained in both directions, and that the ICERs were often higher for those people not previously treated with DMARDs. No individual biological DMARD was seen to be consistently more cost effective than any other biological DMARD.

In summary, they recommend adding bDMARDs to highest tolerable dose of MTX, which may be obtained by scMTX.

Several publications show that adalimumab, which is on the EML as an iv medication, are on the range of the 30.000 €/QALY, thus suggesting that adalimumab could be an efficient therapy either added or as a substitution to MTX. This information further supports the idea of introducing scMTX as it is more effective than oral MTX and far less expensive than adalimumab, even in its biosimilar form.

Chen\textsuperscript{79} analysed the ICER of adalimumab when added or as an alternative to MTX, and found that the cost (in €) per QALY was higher than 34.000 when provided as an alternative, and up to 41.000 when added to MTX.

At the licensed dose, the numbers needed to treat (NNTs) (95% CI) required to produce an American College for Rheumatology (ACR) response compared with placebo were: ACR20: adalimumab 3.6 (3.1 to 4.2), etanercept 2.1 (1.9 to 2.4), infliximab 3.2 (2.7 to 4.0); ACR50: adalimumab 4.2 (3.7 to 5.0), etanercept 3.1 (2.7 to 3.6), infliximab 5.0 (3.8 to 6.7); and ACR70: adalimumab 7.7 (5.9 to 11.1), etanercept 7.7 (6.3 to 10.0), infliximab 11.1 (7.7 to 20.0). In patients who were naïve to methotrexate, or who had not previously failed methotrexate

treatment, a TNF inhibitor combined with methotrexate was significantly more effective than methotrexate alone. (Fig 6)

**Fig 6: Incremental Cost-Effectiveness ratio of Adalimumab versus MTX**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>Study</th>
<th>Date</th>
<th>Time-horizon</th>
<th>ICER (€/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>DMARD sequence</td>
<td>Bansback</td>
<td>2005</td>
<td>Lifetime</td>
<td>ACR50/DAS28 good:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€34,167 per QALY (MTX)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€34,922 per QALY (MTX) from pooled analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€41,561 per QALY (monotherapy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anakinra</td>
<td>2004</td>
<td>1 year</td>
<td>ACR20/DAS28 moderate:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€40,875 per QALY (MTX)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chiu</td>
<td></td>
<td></td>
<td>€44,018 per QALY (MTX) from pooled analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>€65,499 per QALY (monotherapy)</td>
</tr>
<tr>
<td></td>
<td>Adalimumab alone dominated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adalimumab + MTX dominated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Similarly, an earlier study (2004) showed that the ICER if adalimumab monotherapy was in the same range (40,000 €/QALY) for the ACR50 but much higher for the ACR20 (65,000 €/QALY).

In the ACR50 analysis, adalimumab plus methotrexate shows the greatest number of QALYs gained (equal to 2.3 and 2.1). The etanercept plus methotrexate strategy shows QALY gains similar to the pooled adalimumab results. Figure 2 shows the incremental cost effectiveness analyses in comparison with DMARDs. The results for all comparisons are concentrated between €35,000 and €50,000. (Fig 7).

The results are consistent with a more recent paper.

In comparison with MTX alone, the most cost-effective strategy from the payer (societal) viewpoint was to use TOC with the incremental cost-utility ratio (ICUR) of €17,057 (€17,091) and €18,957 (€18,991) per QALY gained based on the wholesale price and retail price of TOC, respectively. In comparison with ETAN, the ICURs of retail-priced TOC were €6089 (€2762), while

---


the wholesale-priced TOC dominated ETAN. Treatment with ETAN was more cost-effective (dominating) than treatment with ADAL. The CEEF, average expected results, and ICURs are presented from the payer perspective and using the retail price for TOC. (Fig 8)

Fig 7: ICER of adalimumab compared to other DMARDs

Fig 8: ICER of adalimumab compared to other DMARDs
Interestingly, it has been shown\textsuperscript{82} that the typical incremental cost per QALY of bDMARDs compared with cDMARDs alone for those with severe RA is > £40,000. This increases for those who cannot tolerate MTX (£50,000) and is > £60,000 per QALY when bDMARDs were used prior to cDMARDs. Values for individuals with moderate to severe RA were higher than those with severe RA. Results produced using EULAR and ACR data were similar. (Fig 9)

Fig 9: ICER of adalimumab compared to other DMARDS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>Study</th>
<th>Price year</th>
<th>Time horizon</th>
<th>Previous treatments</th>
<th>ICER (per QALY gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>MTX</td>
<td>Sparkling and Hoy, 2006\textsuperscript{90}</td>
<td>2005</td>
<td>Lifetime</td>
<td>None</td>
<td>US$64,000</td>
</tr>
<tr>
<td>cDMARDs</td>
<td>Chen et al., 2006\textsuperscript{133}</td>
<td>2004</td>
<td>Lifetime</td>
<td>None</td>
<td>£53,000</td>
<td></td>
</tr>
</tbody>
</table>

There have been recent systematic reviews of this matter. In MTX-naive RA participants\textsuperscript{83}, it was found that there was moderate-quality evidence that, compared with MTX alone, biologics with MTX was associated with absolute and relative clinically meaningful benefits in three of the efficacy outcomes (ACR50, HAQ scores, and RA remission rates). A benefit regarding less radiographic progression with biologics with MTX was not evident (low-quality evidence). Moderate- to low-quality evidence was found that biologic therapy with MTX was not associated with any higher risk of serious adverse events compared with MTX, but results were inconclusive for withdrawals due to adverse events and cancer to 24 months. TNF biologic monotherapy did not differ statistically significantly or clinically meaningfully from MTX for any of the outcomes (moderate-quality evidence), and no data were available for non-TNF biologic monotherapy. We conclude that biologic with MTX use in MTX-naive populations is beneficial and that there is little/inconclusive evidence of harms. More data are needed for tofacitinib, radiographic progression and harms in this patient population to fully assess comparative efficacy and safety.


6b. There was no evidence to indicate an effect of biologics without MTX compared to MTX, for achieving an ACR50 response, with an OR 0.92 (95% CI 0.61 to 1.38), absolute difference of -2% (95% CI -11% to 7%) with an I² of 49% indicating moderate heterogeneity (moderate-quality evidence). (Fig 10)

Fig 10: ICER of adalimumab compared to other DMARDs

Finally, the economic impact of intensive treatment with csDMARDs was also analysed, showing that RA medical cost increases in line with patients’ disability levels. Delaying disability by controlling disease activity is economically beneficial and can be achieved with the use of the low-cost csDMARDs by further delaying the need for biologic therapies. The BeSt study reported better Health-Related Quality of Life (HRQoL) improvement with initial combination treatment of INF (group d). However, when the analysis was restricted to healthcare cost alone, initial combination-therapy with csDMARDs (group c) was preferable.

11.3.2 Psoriasis & PsA

Adalimumab has similar or better cost-effectiveness than other biologics, but is less efficient than methotrexate and cyclosporine.\(^{85}\)

Studies indicate that it is highly efficacious both in moderate-to-severe plaque type psoriasis and in severe PsA with significant improvements within 4 weeks. A recent meta-analysis indicated that adalimumab is superior to cyclosporine, efalizumab, and etanercept in the treatment of chronic plaque-type psoriasis. Based on published trials, infliximab leads to higher response rates than adalimumab within 12 to 16 weeks of treatment. However, a loss of efficacy over time has been observed in patients receiving infliximab, but does not appear to be an issue for adalimumab based on published data. One head-to-head study suggested that adalimumab is at least similarly efficacious and possibly more efficacious than MTX in the short-term treatment of moderate-to-severe plaque-type psoriasis.

12. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

Regulatory status of the proposed medicine(s)

scMTX is approved for commercialisation in most high and middle income countries.

Market availability of the proposed medicine(s)

Parenteral scMTX is marketed in most high and middle income countries in different strengths.

The list includes (non exhaustive) (Fig 11):

Argentina, Australia, Austria, Azerbajan, Bangladesh, Belgium, Bolivia, Brasil, Bulgaria, Canada, Chile, China, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, Egypt, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, India, Indonesia, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malasya, Mexico, Netherlands , New Zeland, Norway, Panama, Peru, Philipines, Poland, Portugal, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Sweden, Switzerland, Taiwan, Turkey, UAE (United Arab Emirates), Ukraine, United Kingdom, United States of America, Vietnam.

Pharmacopeial standards

- USP monograph for Methotrexate Injection. Official date May 1, 2019.
LETTER OF AUTHORIZATION

To whom it may concern

We
Laboratorios Gebro Pharma, S.A.
Av. del Tibidabo, 29
08022 Barcelona
Spain

hereby authorize
HITT
Aragó 60, pral. 1a
08015 Barcelona
Spain

to use Laboratorios Gebro Pharma’s documentation and knowledge to prepare
the technical documentation for the submissions for inclusion of Methotrexate
subcutaneous (SC) on the List of Essential Medicines (EML) to the WHO Expert
Committee.

Barcelona, 14th December 2022

Laboratorios Gebro Pharma, S.A.

_____________________
Meritxell Cortés
Medical, Quality & Market Access Director
LETTER OF AUTHORIZATION

To whom it may concern

We

Laboratorios Gebro Pharma, S.A.
Av. del Tibidabo, 29
08022 Barcelona
Spain

hereby authorize

Asphalion, S.L.
Carrer de Tarragona, 151-157, planta 10
08014 Barcelona
Spain

to perform the formal presentation to the WHO Expert Committee of the submissions for inclusion of Methotrexate subcutaneous (SC) on the List of Essential Medicines (EML).

Barcelona, 14th December 2022

Laboratorios Gebro Pharma, S.A.

_____________________
Meritxell Cortés
Medical, Quality & Market Access Director