**DRUG:**

**METHOTREXATE (Adults)**

**Introduction:**
- Rheumatoid Arthritis, Psoriatic Arthritis, undifferentiated inflammatory arthritis, spondyloarthropathies, connective tissue disorders, vasculitis, Inflammatory Bowel Diseases, Psoriasis, Diffuse lupus, some connective tissue disease with dermatological involvement, cutaneous sarcoidosis, uveitis and scleritis and rarely other rare inflammatory conditions (see consultant handover letter for specific indications for individual patients),

**Licensing Information:**
Varies for different manufacturers – includes severe, uncontrolled psoriasis, rheumatoid arthritis, and psoriatic arthritis.

**Formulations:**
- **Oral yellow tablets:** 2.5mg and 10mg strengths.
  - It is requested, for patient safety, that only **2.5mg tablets** are prescribed.

**Subcutaneous injections:**
- The subcutaneous route is used to try and increase control of disease / or reduce side effects before switching to biologics
  - There are 3 formulations of methotrexate available and to avoid confusion it should be prescribed by brand name

  **Nordimet prefilled pen 25mg/mL**
  - Doses available in 2.5mg dose intervals from: 7.5mg (in 0.3mL) to 25mg (in 1mL).

  **Metoject prefilled pen 50mg/mL**
Doses available in 2.5mg dose intervals from: 7.5mg (in 0.15mL) to 30mg (in 0.60mL).

**Zlatal prefilled syringe  25mg/mL**
Doses available in 2.5mg dose intervals from: 7.5mg (in 0.3mL) to 25mg (in 1mL). This preparation may be used by patients who find the Metoject or Nordimet device unsuitable.

**Prescribing:**
Methotrexate should **ALWAYS** be prescribed as a **ONCE WEEKLY** dose.

Folic acid is indicated to minimise gastrointestinal and haematological side effects. The recommended dose will be provided in the clinic letter.

It is recommended that repeat prescriptions for methotrexate be reviewed separately from standard repeat GP prescriptions by the primary care prescriber to ensure blood monitoring is satisfactory.

**Please note:**
Methotrexate will be discontinued for ALL patients on admission for ANY reason to any site within the York Hospitals NHS Foundation Trust. This is to avoid inappropriate and potentially harmful prescribing. It may be appropriate for this to be re-initiated during admission and this should be done by the appropriate consultant team (for sites served by acute trust doctors) or by a GP (for sites served by one or more GPs). Please see guidance below.

**Dosage & administration:**
For all indications doses may vary from 2.5mg to 30mg **ONCE WEEKLY**. Doses may be oral or subcutaneous.

**Contraindications & Warnings:**
- Pregnancy and breastfeeding. Both males and females to avoid conception for at least 3 months of stopping methotrexate (National Teratology Service advise 6 months for paternal exposure).
- Renal impairment: Renal function should be closely monitored throughout treatment. If there is any deterioration in renal function methotrexate must be discontinued and discussed with the consultant who started treatment.
  - Contraindicated if GFR <10mL/min.
  - GFR 10-50mL/min reduce dose by 50%, seek advice from initiating consultant.
- Hepatic impairment, bilirubin levels > 85.5µmol/L
- Severe anaemia, leucopenia or thrombocytopenia
- Serious acute or chronic infections (e.g. Chickenpox/shingles, tuberculosis, HIV or other immunodeficiency syndromes)
- Live attenuated vaccines should be avoided. There may be a reduced response to other vaccines given.
- Trimethoprim and co-trimoxazole can cause folate deficiency which can potentiate methotrexate toxicity and so should be avoided.
- Methotrexate therapy should be stopped in acute infective episodes requiring antibiotic treatment (see below).
- Caution in underlying chest disease/smoker/history of alcohol excess
Interactions:

- **Antibiotics** may increase the risk of toxicity with methotrexate.
- **NSAIDs and salicylates**: May increase the plasma levels of methotrexate. They may be continued in certain rheumatology patients where appropriate.
- **Drugs that may reduce excretion of methotrexate**: Diuretics, theophylline, phenytoin and oral hypoglycaemics.
- **Vitamin preparations containing folic acid**
- **Acitretin**—severe hepatitis reported when combined with methotrexate.

For full list see SPC at [www.medicines.org.uk/EMC](http://www.medicines.org.uk/EMC) and BNF.

Adverse Effects:

In general, the side effects are considered to be dose related and most will resolve on reduction of methotrexate dose or on cessation of treatment.

**Common**

Nausea, diarrhoea, mild stomatitis, increased hair loss.

To improve nausea the following can be advised: taking the dose with food; taking the dose at night; using a ginger supplement (this can be purchased by the patient); ensuring the folic acid dose is 5mg six times weekly (every day except day of methotrexate) or use of anti-emetics (for gastroenterology patients please seek specialist advice before prescribing). If nausea still problematic after trying the above please contact specialist for advice.

**Less common**

Reduced libido, impotence and menstrual dysfunction (may persist for some time after cessation of methotrexate therapy).

**Potentially serious**

- **Blood dyscrasias** - See monitoring information below
- **Raised transaminases** - See monitoring information below
- **Interstitial Pneumonitis** (sudden unexplained SOB & dry cough) - can occur at any time and can be life threatening. URGENT ADVICE from initial prescriber required or admission to hospital and STOP methotrexate.

Also see section below on ‘Responsibilities of the Prescriber’

For full list see SPC at [www.medicines.org.uk/EMC](http://www.medicines.org.uk/EMC) and BNF.

Responsibilities of the specialist initiating treatment:

**General:**

- To assess the suitability of the patient for treatment.
- As per national, regional and local guidelines, to ensure that the patient/carer has received counselling and understands the therapy, its benefits, limitations, continued monitoring (where applicable), adverse effects, and is aware of actions to take if adverse effects are suspected.
- Go through patient information leaflet with patient.
- Inform patients of the long term monitoring requirements.
- If injections are prescribed: ensure patient is trained to self-inject as per RCN Guidance prior to hand over to the primary care prescriber and supply the first cytotoxic sharps bin.
- Inform the primary care prescriber of the information provided to the patient.
To review the patient at agreed intervals and copy any relevant results to the primary care prescriber

Carry out disease and initial drug monitoring as listed below.

Formally hand over to primary care prescriber by letter and patient informed - send a copy (either electronically or paper copy) of the Shared Care Guideline to the primary care prescriber and ask whether they are willing to participate in shared care.

Prescribing – on initiation:

- Issue all prescriptions for 8 weeks minimum until patient is safely established on methotrexate and specialist team are satisfied that it is appropriate to share care.
- Prescribe adjuvant folic acid (until care formally handed over to primary care prescriber) and titrate dose according to clinical need. Advise the primary care prescriber of the doses of both methotrexate and folic acid.

Prescribing on re-initiation during hospital admission:

- It may be appropriate to re-start certain rehabilitation inpatients back on treatment once they are clinically stable. On Trust sites served by Acute Trust clinicians, the patient should be reviewed by a specialist of the appropriate speciality before this occurs.
- Bloods tests should be checked and be in line with the tables below. There should be no active infection requiring antibiotic treatment.
- The notes and drug chart should be signed by the clinician with a message stating ‘Rheumatology/Gastroenterology/Dermatology reviewed and approved’ as appropriate

Disease & drug monitoring (on initiation):

- Consider pre-treatment pregnancy test.
- All patients should have a pre-treatment chest X-ray and consider Pulmonary function tests (in RA). Where TLCO less than 70% or clinical concern a baseline HRCT chest may be advisable (lung toxicity is increased when fibrosis is present).

- Monitor bloods according to schedule:

<table>
<thead>
<tr>
<th>FBC</th>
<th>LFTs</th>
<th>U&amp;Es</th>
<th>On initiation of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 weekly for first 8 weeks whilst under secondary care</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Then as advised by specialist team.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(See responsibilities of other prescribers- monitoring)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FBC</th>
<th>LFTs</th>
<th>U&amp;Es</th>
<th>On dose increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>week 2,4,8 and then resume previous monitoring regime, at which point the patient can be transferred back to their GP.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIIINP*</th>
<th>(Dermatology patients only)</th>
<th>Pre-treatment then every 3 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(See responsibilities of other prescribers – monitoring)</td>
</tr>
</tbody>
</table>
*PllNP: pro-collagen III amino terminal peptide. May indicate potential liver damage. Should not be measured in any patients with inflammatory arthritis due to the risk of false positive test results.

- Discuss shared care arrangement with patient.
- Support and advise primary care prescribers as required.
- Assess response to treatment and initiate any dose changes as clinically appropriate including discontinuation of treatment

### Responsibilities of other prescribers (GP):

- To reply to the request for shared care within 2 weeks of receipt of the Consultant letter.
- Monitor and prescribe as recommended by the specialist. Ensure continued prescribing of methotrexate remains clinically appropriate at dose advised by initiating team.
- The primary care prescribers will be asked to take up the monitoring and prescribing of methotrexate around 8 weeks after it has been initiated.
- For patients prescribed methotrexate injections: prescribe a sharps bin (for cytotoxic waste) upon request by patient. This should be prescribed on FP10 as “sharpsguard 1 litre” and include the instructions “purple lid”.
- Notify Consultant if treatment with methotrexate is discontinued.
- Ensure there are no drug interactions with any other medications initiated in primary care.
- **Live vaccines** – avoid. Polio and typhoid are available in killed inactivated form but may not be as effective
- **Other vaccinations**-
  - Annual influenza vaccine and pneumococcal vaccine every 5 years should be offered unless otherwise advised by the initiating specialist.
  - Varicella zoster vaccine should be offered to patients who are over the age of 70 and:
    - Are on doses of methotrexate 20mg/week or less and
    - in the past 3 months have NOT received short term high-dose corticosteroids (>40mg prednisolone per day for more than 1 week), or long term lower dose corticosteroids (>20mg prednisolone per day for more than 14 days)
  - Individuals who have not been vaccinated or pre-existing immunity cannot be verified, the need for
    - Varicella immunoglobulin (VZIG) should be considered if there has been significant exposure to chicken pox or shingles.
    - Normal Human Immunoglobulin (HNIG)) should be considered if there has been significant exposure to measles.

### General and Prescribing:

- Discuss shared care arrangement with patient.
- Support and advise primary care prescribers as required.
- Assess response to treatment and initiate any dose changes as clinically appropriate including discontinuation of treatment

### Prescribing on re-initiation during hospital admission:

- To reply to the request for shared care within 2 weeks of receipt of the Consultant letter.
- Monitor and prescribe as recommended by the specialist. Ensure continued prescribing of methotrexate remains clinically appropriate at dose advised by initiating team.
- The primary care prescribers will be asked to take up the monitoring and prescribing of methotrexate around 8 weeks after it has been initiated.
- For patients prescribed methotrexate injections: prescribe a sharps bin (for cytotoxic waste) upon request by patient. This should be prescribed on FP10 as “sharpsguard 1 litre” and include the instructions “purple lid”.
- Notify Consultant if treatment with methotrexate is discontinued.
- Ensure there are no drug interactions with any other medications initiated in primary care.
- **Live vaccines** – avoid. Polio and typhoid are available in killed inactivated form but may not be as effective
- **Other vaccinations**-
  - Annual influenza vaccine and pneumococcal vaccine every 5 years should be offered unless otherwise advised by the initiating specialist.
  - Varicella zoster vaccine should be offered to patients who are over the age of 70 and:
    - Are on doses of methotrexate 20mg/week or less and
    - in the past 3 months have NOT received short term high-dose corticosteroids (>40mg prednisolone per day for more than 1 week), or long term lower dose corticosteroids (>20mg prednisolone per day for more than 14 days)
  - Individuals who have not been vaccinated or pre-existing immunity cannot be verified, the need for
    - Varicella immunoglobulin (VZIG) should be considered if there has been significant exposure to chicken pox or shingles.
    - Normal Human Immunoglobulin (HNIG)) should be considered if there has been significant exposure to measles.
- It may be appropriate to re-start certain rehabilitation inpatients back on treatment once they are clinically stable. On Trust sites served by GPs, the patient should be reviewed by the GP before this occurs.
- Bloods tests should be checked and be in line with the tables below. There should be no active infection requiring antibiotic treatment.
- The notes and drug chart should be signed by the clinician with a message stating 'GP reviewed and approved'.

### Disease & drug monitoring:
- Carry out drug monitoring as listed – and communicate abnormal results to the Specialist.
- Urgent drug discontinuation/ referral to specialist as clinically appropriate
- To stop treatment on the advice of the specialist.
- To refer back to the specialist if the patient’s condition deteriorates.
- Identify adverse effects to methotrexate and report these to the specialist and where appropriate to the Commission on Human Medicines/MHRA (Yellow card scheme).

Unless otherwise stated by the secondary care specialist, apply the following monitoring frequencies following handover from secondary care:

<table>
<thead>
<tr>
<th>FBC</th>
<th>LFTs</th>
<th>U&amp;Es</th>
<th>After handover from the specialist:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Every 2 weeks if handover is during the first 8 weeks of treatment (but this should be in exceptional cases), then, Monthly for 4 months then every 3 months (Unless dose changed then see below)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>See below for abnormal blood results</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FBC</th>
<th>LFTs</th>
<th>U&amp;Es</th>
<th>On dose increase by hospital:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>The specialist will organise for patients to have any additional monitoring necessary after a dose increase and will transfer responsibility back to their GP once the patient is back on their previous monitoring regimen.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIIINP* (Dermatology patients only)</th>
<th>Every 3 months after handover from specialist</th>
</tr>
</thead>
</table>

| At consultations | Ask about oral ulceration, unexplained bruising/bleeding, rash, sore throat, shortness of breath or dry cough |

*PIIINP: pro-collagen III amino terminal peptide. May indicate potential liver damage. Should not be measured in any patients with inflammatory arthritis due to the risk of false positive test results.

Discontinue methotrexate and seek advice from initiating team if:

| WCC (x10^9/L): | <3.5 |
| Neutrophils (x10^9/L): | <2.0 |
| Platelets (x10^9/L): | <150 |
| AST or ALT (U/L): | >3 times the normal range |
| PIIINP* (Dermatology patients only): | 4.2-8.0 micrograms/L on 3 occasions within a 12 month period or two consecutive results >8.0 micrograms/L |
| GFR | Renal function should be closely monitored throughout treatment. If there is any deterioration in renal function methotrexate must be discontinued and discussed with |
the consultant who started treatment. Contraindicated if GFR < 10mL/min

<table>
<thead>
<tr>
<th>Dry cough &amp; shortness of breath – seek urgent specialist advice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Oral or throat ulceration</td>
</tr>
<tr>
<td>Unexplained bruising, bleeding or rash</td>
</tr>
<tr>
<td>Fever, nausea, vomiting or diarrhoea</td>
</tr>
<tr>
<td>Diffuse alopecia</td>
</tr>
</tbody>
</table>

- Discontinue methotrexate for a minimum of two doses during acute infective episodes requiring antibiotic therapy.

Responsibilities of the Patient / Carer:

**General:**
- Report any possible side effects to their primary care prescriber, in particular potential signs and symptoms of bone marrow suppression (e.g. unexplained bruising, bleeding, sore throat, infection etc.) and any fever, unexplained shortness of breath or dry cough.
- Ensure they have adequate supply of medication.
- If using methotrexate injections, contact local council to arrange for disposal of cytotoxic waste contained in sharps bin.
- Attend appointments and take along monitoring book.
- Ensure adequate contraception is used (for both males and females taking methotrexate).
- Avoid breastfeeding.
- Inform primary care prescriber if unexpected pregnancy is suspected (females on methotrexate or when the male is taking methotrexate).
- Limit alcohol intake to within current national guidelines.

**Disease & drug monitoring:**
As above – contact primary care prescriber or initiating team if side effects develop (see adverse effects) and attend appointments including those for routine blood tests/investigations.

**Communication:**

**Specialist to Primary Care Prescriber:**
The specialist will inform the primary care prescriber when they have initiated methotrexate and when there are any subsequent changes in treatment – standard clinic letter
Send a copy (either electronically or paper copy) of the Shared Care Guideline to the primary care prescriber and ask whether they are willing to participate in shared care
Inform the primary care prescriber of the information provided to the patient

**Primary Care Prescriber to Specialist:**
- To reply to the request for shared care within 2 weeks of receipt of the consultant letter
- Irrespective of whether you accept prescribing responsibility or not, you should inform the consultant of relevant medical information regarding the patient and changes to the patient’s medication regime, irrespective of the indication.
- Notify consultant if treatment with methotrexate is discontinued

Contact names & details:
If you have any concerns regarding individual patients, see clinic letter for details of consultant and contact via switchboard
York: 01904 631313
Scarborough: 01723 368111

Alternatively contact one of the following:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone / Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatology advice line (York)</td>
<td>01904 721854</td>
</tr>
<tr>
<td>Rheumatology advice line (Scarborough)</td>
<td>01723 385058</td>
</tr>
<tr>
<td>York inflammatory bowel disease nurse specialists</td>
<td>01904 726154</td>
</tr>
<tr>
<td>Dermatology Specialist Nurse (York)</td>
<td>01904 726048</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Consultant/ Secretary via switchboard</td>
</tr>
</tbody>
</table>

**Cost:**

**Drug tariff June 2017:** Methotrexate 2.5mg x28 = £1.74
Sharpsguard (sharps container) = 85p

**Mims July 2017:** Metoject £14.85- £18.95 per pen
Zlatal and Nordimet £13.37 – £16.64 per syringe/ pen

**References:**
- BNF 71
- Metoject SPC accessed on 10th September 2016
- Matrex SPC accessed on 10th September 2016
- NPSA alert: Towards the safer use of oral methotrexate 2004
- BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists Guidelines 2008 and 2017
- Toxbase- maternal and paternal exposure to methotrexate- accessed 8th August 2017
- September 2016
- Renal Drug Database- accessed 8th August 2017

**Other information:**

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.

The original Microsoft Word file of this document is located on:
York Teaching Hospital NHS Foundation Trust Pharmacy Department X:\MEDICINES INFORMATION\Shared Care Guidelines\Approved Shared Care Guidelines\METHOTREXATE Shared Care Guideline V2

Shared Care Guidelines are also available electronically via [http://www.yorkandscarboroughformulary.nhs.uk/](http://www.yorkandscarboroughformulary.nhs.uk/)

Prepared by: Katie Dore
Checked by: Jane Crewe
Version: 2
Date of Issue / Review: August 2017
Date for next Review: August 2019
Approved by: York and Scarborough Medicines Commissioning Committee