

## **MEDICINES STANDARD A2: PRESCRIBING METHOTREXATE**

Methotrexate has been the subject of a National Patient Safety Agency, (NPSA) Safer Practice Notice “Reducing the harm caused by oral methotrexate (issued in July 2004 and June 2006) following a number of reports of serious medicines errors including fatalities. The NPSA recommended a series of actions to reduce risk associated with methotrexate prescribing and dispensing.

### **INITIATION OF METHOTREXATE IN SECONDARY CARE**

Methotrexate is an amber drug under the Dorset “traffic light system” and may be prescribed in primary care on a shared care basis after initiation and stabilisation of dose by secondary care.

Methotrexate tablets must be prescribed in multiples of 2.5 mg only. Prescriptions should list both the total weekly dose, *and* the number of 2.5 mg tablets per dose. Under no circumstances should instructions be written “as directed”.

All prescribers should be aware of the weekly dosing requirements of methotrexate prescribing and the necessary monitoring. Electronic prescribing systems should have suitable alerts to remind prescribers of the weekly requirements. This is a requirement of the NPSA patient safety alert.

The secondary care prescriber initiating the methotrexate must:

- Carry out baseline monitoring
- Provide an initial supply of medication until the treatment dose is stable
- Ensure that the patient is issued a patient held record book

The secondary care prescriber initiating the methotrexate must also counsel the patient regarding:

- The weekly dosing requirements
- Signs and symptoms of toxicity
- The use of 2.5 mg tablets only, and how to seek advice if the appearance of their tablets changes.

In the rare circumstance where a 10 mg methotrexate tablet is essential for patient compliance, e.g. children, then the prescriber should confirm this **IN WRITING** to the

pharmacy/dispensary. It is also strongly advised that the 10 mg tablets should be additionally flagged and/or set to non-formulary on GP computer systems where possible.

Injectable methotrexate must be prescribed as PRE-FILLED syringes only. Under no circumstances should vials be prescribed for use in a community setting. Licensed preparations of methotrexate in prefilled syringes are now available (Metoject<sup>®</sup> and Ebetrex<sup>®</sup>) and should be used whenever possible.

Injectable methotrexate should be prescribed as pre-filled injection pens wherever possible, see the summary of product characteristics for a full list of licensed indications. At the time of writing of this policy, Metoject pens were not licensed for use in Crohns disease, where pre-filled syringes remain the presentation of choice.

### **PRESCRIBING OF METHOTREXATE IN GP PRACTICES**

Repeat prescriptions should be retained separately for prescriber review prior to authorising. It may help to change the printer driver software so that it shades the prescription signature space on FP10 to alert the prescriber to this high-risk drug.

The patient held monitoring booklet should be completed after every blood test by the person responsible for prescribing and monitoring the drug.

A template SOP for local adaptation for the supply/administration of oral methotrexate can be found in [appendix 1](#).

Be aware of patients who attend with symptoms such as breathlessness, dry persistent cough, vomiting or diarrhoea, as these can be signs of methotrexate toxicity or intolerance.

### **SAFE DISPENSING OF METHOTREXATE**

Prior to dispensing methotrexate, the pharmacist must ask to see the patient's monitoring booklet and check if any dose changes have been made since the last prescription issue. All dose changes should be queried with the prescriber. Any patient who has not been issued with a monitoring booklet must be referred back to the prescriber.

Although 10 mg tablets are available, all pharmacies and dispensing practices are advised to stock only the 2.5 mg strength. No 10 mg tablets should be dispensed without separate written confirmation by the doctor and a check of the patients understanding. If 10 mg tablets are required in exceptional circumstances, e.g. compliance issues or for the treatment of malignant disease they should be stored separately from the 2.5 mg tablets, in a segregated area to avoid picking errors.

The strength of tablet supplied to the patient must stay consistent to prevent any confusion about the number of tablets they need to take, and the patient's monitoring document and Patient Medication Record should be checked to confirm the previous supply.

Tell the patient their dose in terms of quantity of tablets and weekly frequency. Give the patient a monitoring booklet if they have not already got one.

Be aware of patients who attend with symptoms such as breathlessness, dry persistent cough, vomiting or diarrhoea, as these can be signs of methotrexate toxicity or intolerance. You may need to refer them back to the prescriber.

Patients should be given a patient information leaflet with every dispensing of methotrexate.

It is good practice to maintain a record of any over-the-counter items supplied to the patient.

Assess the needs of the individual patient. For example, those patients who have reduced manual dexterity should be given larger containers or ribbed easy-to-grip lids as this could reduce the likelihood of them decanting the tablets into another container at home (Disability Discrimination Act applies).

As Methotrexate is not an emergency medicine, a new prescription must be received prior to supply or administration. Verbal dose changes for methotrexate should not be accepted. Written advice must accompany changes, with a new prescription following up these amendments.

Under no circumstances should pharmacies/GP dispensaries supply vials of methotrexate in the community. Prescriptions for vials should be returned to the prescriber to be amended to prefilled syringes.

Pharmacists should ensure that patients are aware of the safe storage of the drug, and the need to ensure thorough hand washing after handling the tablets. Pharmacists should ensure that the patient returns any unwanted Methotrexate to the pharmacy and is aware of the need to highlight that the waste contains Methotrexate.

### **SAFE ADMINISTRATION OF SUBCUTANEOUS METHOTREXATE**

Detailed guidance on administering subcutaneous methotrexate for inflammatory arthritis can be found in [appendix 3](#).

All surgeries who administer subcutaneous methotrexate must:

- Have standard operating procedures (SOPs) for the handling, administration and disposal of Methotrexate. A template SOP for local adaptation can be found in appendix 2.
- Have a cytotoxic spill kit available at all times
- Clearly label and segregate it from other products/waste at all times.
- Have arrangements in place for the disposal of cytotoxic waste.

Practices who have patients self-administering Methotrexate injections must ensure that:

- The patient is trained how to self-administer safely

- The patient is trained how to deal with any spills and is supplied with appropriate material to deal with a spill should it occur
- That the patient is supplied with an appropriate cytotoxic sharps bin

### **STORAGE OF METHOTREXATE PRE-FILLED SYRINGES**

Methotrexate is a clear yellowish solution and is generally stable if stored out of direct sunlight. Depending on individual suppliers' recommendations fridge storage (in temperatures between 2 to 8 degrees centigrade) may be required to minimise the potential for microbial colonisation.

Where patients are self-administering it is imperative the patient is counselled about correct storage. The storage of methotrexate pre-filled pens, needles, and cytotoxic waste bins should be out of reach and sight of children and pets.

Refer to the summary of product characteristics for guidance on storage specific to the methotrexate preparation. The sPC can be accessed at: [www.medicines.org.uk/EMC](http://www.medicines.org.uk/EMC)

### **SPILLAGE AND DISPOSAL**

Where methotrexate is stored or administered (including in a patient's home), adequate facilities for dealing with spillage and safe disposal should be available at all times. Practitioners are referred to [guidance](#) produced by the Royal College of Nursing for further details.

Detailed guidance on actions to take can be found in the [RCN guidance](#) on administration of subcutaneous methotrexate. COSHH risk assessments should be carried out for all areas where spillage may occur (including a patient's home). Both the injectable and tablet formulations are required to be disposed of as hazardous waste. For more details, refer to Medicines Statement B4: Waste Medicines.

### **INTERACTIONS WITH OTHER DRUGS**

The effects of methotrexate may be enhanced by concurrent administration of agents which can displace it from protein binding or decrease its renal excretion. Use with other hepatotoxic or nephrotoxic agents may increase the risk of toxicity; an increased incidence of cirrhosis has been reported in patients receiving methotrexate who have an excessive alcohol intake.

The following drugs should be used with caution or avoided in patients receiving methotrexate (this list is not intended to be exhaustive and further information should be sought prior to co-prescribing methotrexate with other drugs):

- Anaesthetics (nitrous oxide)
- Nonsteroidal anti-inflammatory drugs
- Antibacterials – co-trimoxazole, trimethoprim\*, sulphonamides, penicillins.
- Antiepileptics – Phenytoin
- Antimalarials – pyrimethamine

- Ciclosporin
- Corticosteroids
- Retinoids – Acitretin
- Uricosurics – Probenecid
- \*Particular attention should be paid to patients on methotrexate being prescribed trimethoprim in primary care, the combination requires extreme caution in use due to the potential for haematological toxicity and is best avoided where possible.

An exception is use of low-dose co-trimoxazole as PCP prophylaxis in patients having high-dose methotrexate as part of a chemotherapy regimen as these patients should be having routine blood tests.

If co-administration of methotrexate with interacting drugs is unavoidable, ensure the patient's full blood count (FBC) is closely monitored. Patients should be counselled to be alert for signs of bone marrow suppression such as a sore throat, increased bruising and bleeding.

Please refer to the current BNF and summary of product characteristics (SPC) for full details of interactions. Both of these resources can be accessed via the pan-Dorset formulary available at [www.dorsetformulary.nhs.uk](http://www.dorsetformulary.nhs.uk).

#### **LIAISON WITH SECONDARY CARE PRESCRIBERS**

A shared care guideline published by the Dorset Medicines Advisory Group is available, which sets out the prescribing and monitoring responsibilities where prescribing is undertaken in primary care on a shared care basis.

Prior to transfer of prescribing from secondary care the shared care guideline should be received and agreed upon and the dose of methotrexate confirmed in writing.

#### **DUTIES/RESPONSIBILITIES AND ACCOUNTABILITY**

All practitioners should ensure that they are familiar with the NPSA alert documents related to methotrexate, and local policies, COSHH assessments and local standard operating procedures (SOPs).

All registered nurses responsible for medicines administration should be familiar with the additional precautions necessary when administering the drug in tablet form and by injection. The Royal College of Nursing (RCN) has produced [guidance](#) for nurses in administering the drug subcutaneously. In addition to this national guidance, the local policy on the administration of subcutaneous methotrexate should be followed (see Appendices [1](#) and [2](#) Standard Operating Procedure templates).

Managers are responsible for ensuring that the CCG policy is followed and that the premises have COSHH assessments, waste disposal facilities and standard operating procedures in place for all handling of methotrexate.

Where nurses are required to administer the injectable form of the drug, Managers are responsible for ensuring that they have access to the RCN and local guidance documents outlining the safety issues.

Community Pharmacists are responsible for ensuring that this policy is followed, and communicated to all staff and locums and that the pharmacy SOPs reflect CCG guidance. As part of the clinical governance responsibilities, pharmacists are advised by the CCG to challenge methotrexate prescriptions which are:

- Requesting 10 mg tablets
- Requesting dispensing of methotrexate vials (rather than pre-filled syringes)
- Unclear, or contain instruction "As Directed"

Prescribers are responsible for ensuring that prescribing systems and formularies reflect CCG guidance and that appropriate checking mechanisms are in place for repeat prescribing and monitoring of patients.

All prescribers and dispensers should be aware of the NPSA Patient safety alerts and able to recognise signs of methotrexate toxicity.

Pharmacies and GP dispensaries should have a SOP in place for Methotrexate dispensing and ensure that all staff and locums are aware of the SOP. The SOP should include advice about handling for staff and avoiding contact if pregnant (particularly in the first trimester) or trying to conceive.

## **PATIENT/RELATIVE/VISITOR/CONTRACTOR COMMUNICATION AND SUPPORT**

Patients should receive adequate information (verbal and written) to enable them to make an informed decision about methotrexate therapy.

Patients should be adequately counselled and educated to ensure understanding of the dose of methotrexate to be taken, that it is a weekly dose and the potential risks associated with methotrexate, including common side effects and contra-indications. In addition they should be advised of the requirement for regular blood checks and additional monitoring.

Patients should be advised that their dose should be taken on the same day each week. If they miss a dose, they may take it one or two days late. However they should be advised that they should not take the dose if it is three or more days late, but should just take the usual dose on the correct day the following week.

Patients should be advised to consult their doctor/pharmacist prior to taking over the counter medicines.

Patients may choose to self administer methotrexate injections (or elect a carer), provided they undertake the necessary training.

**REFERENCES**

[Royal College of Nursing Guidelines on the administration of subcutaneous Methotrexate](#)  
(April 2013)

[Electronic Medicines Compendium](#) (for Summary of product characteristics for UK medicines)

[Improving compliance with oral methotrexate guidelines](#) (NPSA, June 2006)

[The 'NEVER EVENTS' list for 2015/16](#)

**APPENDIX 1                      STANDARD OPERATING PROCEDURE FOR SUPPLY/  
ADMINISTRATION OF METHOTREXATE TABLETS**

**Standard Operating Procedure for Supply/Administration of Methotrexate tablets in  
...*insert practice/pharmacy***

**Note this is a template for pharmacies/practices to use for modification to their operational area. It is not exhaustive, and managers should ensure that they complete the SOP, filling in the areas in italics prior to use.**

**OBJECTIVES**

This procedure outlines the safety precautions and arrangements for the safe administration/supply of Methotrexate tablets.

**SCOPE**

This procedure covers the activities surrounding methotrexate administration/supply in...*practice/pharmacy*.

**THE STAGES OF THE PROCESS**

**Prescribing:** *Insert here the prescribing mechanisms for methotrexate tablets in your practice/pharmacy taking into account the trust protocol.*

**Patient information:** *Insert here the patient information systems available in your area taking into account the trust protocol, e.g. who issues the patient held record card, who fills it in, who informs patient of changes etc. blood test info and regularity may also be added.*

**Supply:** *Insert here how methotrexate tablets are supplied in your area e.g. Pharmacy, wholesaler, specials supplier, acute trust, etc. Add how to order and any additional information needed.*

**COSHH/Risk Assessment:** *Insert here where the COSHH/risk assessment for persons working with MTX can be found.*

**Storage:** *Where and how are the tablets stored?*

**Protection/safety facilities for administration:** *Gloves, counting trays, etc what is available, where?*

**Administration:** Methotrexate is potentially teratogenic (may cause birth defects), mutagenic and carcinogenic. Female pharmacy or clinical staff who are pregnant or trying to conceive should not be involved with the dispensing or administration of methotrexate.

A 'no touch' or 'minimum touch' technique should be used when counting tablets/capsules and a dedicated cytotoxic tablet triangle should be used. Gloves should be provided if direct contact cannot be avoided. Do not inhale dust if any is present. Take care not to damage containers.

Provided normal procedures, general safety notes and good pharmaceutical practices are observed, the procedures, which these substances normally undergo within the pharmacy (e.g. dispensing or labelling), should not represent any hazard to health.

**Training:** *Insert here what training staff should have received in order to be able to administer/dispense and details of staff training resources/updates on Methotrexate*

**Waste disposal:** *Insert here the waste disposal facilities for cytotoxic/hazardous waste in your area and any additional precautions necessary for hazardous waste if necessary.*

*Spillage information: Insert here any additional spill info such as where kits are located, where they can be reordered, AIRS reporting of spills etc.*

**Emergency procedures:** If a spill occurs ensure that all staff are aware of the spill and do not enter the affected area. Close doors and windows to prevent drafts from spreading any powder.

- Put on disposable apron, mask, goggles, PVC gloves and carefully transfer any spilled powder/tablets and glass (use forceps) into a hazardous waste disposal bin.
- Wash all contaminated surfaces with plenty of water using a disposable cloth or paper tissue and dry surfaces well.
- Dispose of protective clothing and cleaning materials in a hazardous waste bin. If a hazardous waste bin is not available, use a normal sharps bin and label with 'Cytotoxic waste – incineration', and consult your waste policy/ waste contractor for advice on collection and destruction.

**Contact/Contamination:** Contamination of the eye must be dealt with IMMEDIATELY. Rinse the eye with large quantities of gently flowing water or eyewash for at least 10 minutes. Ensure the water reaches the eyeball by gently prising the eyelids open and keeping them apart until the treatment is complete. Seek medical attention. Spills on the skin should be washed off with copious quantities of water. Seek medical advice.

*Insert here the facilities available in your location, and any additional info such as AIRS/NPSA reporting, Occupational Health procedure etc. that may be unique to your area.*

**Transport:** Transportation of methotrexate should be in sealed containers or bags and clearly labelled as cytotoxic. *Insert here the transport arrangements specific to your area.*

## RESPONSIBILITY

All staff involved in methotrexate prescribing/dispensing/administration must be familiar with the NPSA safety alerts of July 2004 and June 2006, and the "Never Event" list.

It is the responsibility of the manager to ensure that appropriate training has been undertaken for staff who are expected to work with methotrexate.

The Manager is responsible for ensuring that there are appropriate facilities for disposal, spillage, transportation of methotrexate.

*Insert here any additional information including:*

*Who is responsible for carrying out each stage of the process in your area?*

*- under normal operating conditions*

*- in different circumstances e.g. when staff are sick/on holiday*

*Insert here the required qualifications/training of those undertaking any of the above tasks.*

## **RECORD KEEPING**

*Who checks the results of the blood test are acceptable before releasing a prescription for a further supply?*

*Who updates the methotrexate patient held record?*

## **OTHER USEFUL INFORMATION**

NMC Guidance for handling methotrexate can be found: *insert location in your area.*

Medicines policy can be found: *insert location in your area*

*Insert here any other information you think could usefully be included in the procedure?*

*Mechanisms for audit of methotrexate policy in your area:*

## **REVIEW**

This SOP will be subject to review on a yearly basis or sooner in the light of new local or national guidance.

*How are you going to ensure that the procedure continues to be relevant, useful and up to date?*

Date of preparation	
Review date	

Author name	
Author signature	
Authorising manager Name (PRINT)	
Authorising manager signature	

I have read and understood the SOP for [insert subject]

Name (PRINT)	Sign	Date

**APPENDIX 2                      STANDARD OPERATING PROCEDURE FOR SUPPLY/  
ADMINISTRATION OF INJECTABLE METHOTREXATE**

**Standard Operating Procedure for Supply/Administration of Methotrexate tablets in  
...insert practice/pharmacy**

**Note this is a template for pharmacies/practices to use for modification to their operational area. It is not exhaustive, and managers should ensure that they complete the SOP, filling in the areas in italics prior to use.**

**OBJECTIVES**

This procedure outlines the safety precautions and arrangements for the safe administration/ supply of injectable Methotrexate.

**SCOPE**

This procedure covers the activities surrounding methotrexate administration/supply in... *practice/pharmacy.*

**THE STAGES OF THE PROCESS**

**Prescribing:** *Insert here the prescribing mechanisms for Methotrexate injectable in your practice/pharmacy taking into account the trust protocol.*

**Patient information:** *Insert here the patient information systems available in your area taking into account the trust protocol, e.g. who issues the patient held record booklet, who fills it in, who informs patient of changes etc? Blood test info and regularity may also be added.*

**Supply:** *Insert here how methotrexate injectable is supplied in your area e.g. specials supplier, acute trust, etc. Add how to order and any additional information needed.*

**COSHH/Risk Assessment:** Insert here where the COSHH/risk assessment for persons working with methotrexate injectables can be found.

**Storage:** *Where and how are the pre-filled syringes stored?*

**Protection/safety facilities for administration:** As a minimum, gloves (ideally latex free, nitrile) should be worn by healthcare professionals when administering the injection. Upon disposal of the syringe this should be placed in a sharps bin suitable for hazardous waste and clearly identified as cytotoxic waste.

**Administration:** Administration of methotrexate injections should only be by appropriately trained staff with the appropriate safety measures in place. The pre-filled syringes should be removed from any packaging and checked for any leaks or breakages. Under no

circumstances should the bag be opened if a leak has occurred and the procedure in section 5 relating to spills should be followed.

Methotrexate is potentially teratogenic (may cause birth defects), mutagenic and carcinogenic. Female pharmacy or GP practice staff who are pregnant, or trying to conceive should not be involved with the dispensing or administration of methotrexate.

Provided normal procedures, general safety notes and good pharmaceutical practices are observed the procedures, which these substances normally undergo within the pharmacy (e.g. dispensing or labelling) should not represent any hazard to health.

**Under no circumstances should practice staff or patients/carers be drawing up methotrexate for injection from vials.** All methotrexate injections should be supplied to a practice/patient via a local acute Trust pharmacy department or Community Pharmacy (or Doctors Dispensary) in pre-filled syringes containing the appropriate dose. These syringes should be sealed to minimise spillage if breakage occurs and clearly labelled as cytotoxic.

**Training:** *Insert here what training nurses should have received in order to be able to administer/details of staff training resources/updates on Methotrexate (RCN Guidance etc)*

**Waste disposal:** *insert here the waste disposal facilities for cytotoxic waste in your area and any additional precautions necessary for hazardous waste if necessary.*

**Spillage information:** *Insert here any additional spill info such as where kits are located, where they can be reordered, AIRS reporting of spills etc.*

**Emergency procedures:** If a spill occurs ensure that all staff are aware of the spill and do not enter the affected area. Close doors and windows to prevent drafts from spreading any powder/liquid:

- Put on disposable apron, mask, goggles, PVC gloves and disposable armlets (available pre-packed in the 'Cyttox Special' packs).
- Carefully transfer any spilled powder/liquid and glass (use forceps) into a sharps bin suitable for the disposal of hazardous/cytotoxic waste.
- Wash all contaminated surfaces with plenty of water using a disposable cloth or paper tissue and dry surfaces well.
- Dispose of protective clothing and cleaning materials in a yellow bag. Double bag the sharps box and yellow bag in a second yellow bag and seal. Label with 'Cytotoxic waste – incineration' label.

**Transport:** Transportation of methotrexate should be in sealed containers or bags and clearly labelled as cytotoxic. *Insert here the transport arrangements specific to your area.*

**Contact/Contamination:** Contamination of the eye must be dealt with IMMEDIATELY. Rinse the eye with large quantities of gently flowing water or eyewash for at least 10 minutes. Ensure the water reaches the eyeball by gently prising the eyelids open and keeping them apart until the treatment is complete. Seek medical attention. Spills on the skin should be washed off with copious quantities of water. Seek medical advice.

*Insert here the facilities available in your location, and any additional info such as adverse incident / NPSA reporting, Occupational Health procedure etc. that may be unique to your area.*

## RESPONSIBILITY

All staff involved in methotrexate prescribing/dispensing/administration must be familiar with the NPSA safety alerts of July 2004 and June 2006.

It is the responsibility of the manager to ensure that appropriate training has been undertaken for staff who are expected to work with methotrexate.

The Manager is responsible for ensuring that there are appropriate facilities for disposal, spillage, and transportation of injectable methotrexate.

*Insert here any additional information including:*

*Who is responsible for carrying out each stage of the process in your area?*

- under normal operating conditions
- in different circumstances e.g. when staff are sick/on holiday

*Insert here the required qualifications/training of those undertaking any of the above tasks.*

## OTHER USEFUL INFORMATION

NMC Guidance for handling methotrexate can be found: *insert location in your area.*

Medicines policy can be found: *insert location in your area*

*Insert here any other information you think could usefully be included in the procedure?*

*Mechanisms for audit of methotrexate policy in your area:*

## REVIEW

This SOP will be subject to review on a yearly basis or sooner in the light of new local or national guidance.

*How are you going to ensure that the procedure continues to be relevant, useful and up to date?*

Date of preparation	
Review date	

NHS Dorset Clinical Commissioning Group

Author name	
Author signature	
Authorising manager Name (PRINT)	
Authorising manager signature	

**I have read and understood the SOP for [insert subject]**

<b>Name (PRINT)</b>	<b>Sign</b>	<b>Date</b>

## APPENDIX 3                      GUIDANCE FOR ADMINISTERING SUBCUTANEOUS METHOTREXATE FOR INFLAMMATORY ARTHRITIS

Guidance for administering subcutaneous methotrexate for inflammatory arthritis in  
*[...insert practice]*

**Note this is a template for pharmacies/practices to use for modification to their operational area. It is not exhaustive, and managers should ensure that they complete the document, filling in the areas in italics prior to use.**

### INTRODUCTION

The information is only a summary. For more comprehensive details (e.g. of side effects/ drug interactions), please consult the summary of product characteristics or the British National Formulary (BNF).

Please ensure you have read this in its entirety before prescribing or administering parenteral methotrexate.

For further information, see the Royal College of Nursing's (RCN) guidance for nurses on administering subcutaneous methotrexate for inflammatory arthritis.

Nurses who are required to administer methotrexate by this route should have documented evidence of having read and understood the RCN guidance and local SOP. In addition evidence of competence to administer should be maintained in continuing development portfolio or similar. Practices and line managers may wish to keep records of those staff competent to administer.

### INDICATIONS

Methotrexate is an anti-metabolite cytotoxic agent that has an immunosuppressive action. It is widely used in patients with active inflammatory arthritis – particularly rheumatoid and psoriatic arthritis. It can be used as a sole therapy or in combination with other second line drugs (particularly sulfasalazine and hydroxychloroquine) or anti-TNF therapy.

### CAUTIONS

Methotrexate is contraindicated for those patients with severe renal or hepatic impairment, blood dyscrasias, immunodeficiency syndromes and alcoholism.

On account of teratogenic effects, methotrexate is contraindicated in conception, pregnancy and breastfeeding. Contraception is therefore mandatory in both men and women of childbearing age and must be continued for at least 6 months after stopping treatment.

A number of drugs have the potential to interact with methotrexate. Drug interactions can enhance the action of methotrexate resulting in an increased risk of methotrexate toxicity. Some of these drugs include ciclosporin, salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs), phenytoin, sulphonamides (such as co-trimoxazole), folate antagonists or drugs with anti-folate properties (e.g. trimethoprim).

Regular doses of NSAIDs in addition to treatment with methotrexate for the management of inflammatory joint disease are not contraindicated. However, patients should be advised to avoid self-medication with over the counter (OTC) aspirin or ibuprofen.

**Live** vaccines are contraindicated for patients taking methotrexate. Inactive vaccines can be given and an annual influenza vaccination should be given.

Patients on methotrexate should be advised that excess alcohol should be avoided.

### **TYPICAL DOSE REGIME**

Oral therapy is the traditional route of administration for methotrexate in inflammatory joint disease. However, subcutaneous and intramuscular administration is increasingly being used.

The rationale for considering administration using parenteral routes is usually based on the need to increase the therapeutic dose ensuring maximum bioavailability and reduce side effects experienced with oral administration.

Subcutaneous is a less painful route for parental administration and therefore should be preferred over the intramuscular route.

Initially, the dose is 7.5 mg subcutaneously each week, increasing to 10 mg after 4 weeks (4 doses). Any further dose increments will be advised by the rheumatologist. Lower doses should be used in the elderly or those with mild to moderate renal impairment. Whenever possible, dose increments will be in line with the available licensed pre-filled syringes.

### **METHOD OF SUBCUTANEOUS ADMINISTRATION**

Subcutaneous methotrexate should be administered using a 26 gauge (brown) needle, length 8 mm or 3/8 inch.

- The skin does not need to be swabbed prior to injection if it is visibly clean.
- Insert the needle at a 90° angle combined with the use of the skin pinch.
- Administer the injection into subcutaneous tissue.
- There is no need to aspirate prior to injection.
- Injection sites should be rotated.

#### **Note:**

Co-administration of subcutaneous biologic therapies can be undertaken provided appropriate site rotation is adhered to.

## CYTOTOXIC ISSUES AND RISK MANAGEMENT

It is widely acknowledged that cytotoxic therapies should be recognized and managed as an occupational hazard to all staff, patients and carers involved in the preparation and administration of therapies. There is no evidence that methotrexate at a low dose fails to act as a cytotoxic agent. Therefore practitioners should practice on the basis that methotrexate is a cytotoxic agent with teratogenic properties and irritant effects to the skin.

**For this reason the following precautions should be adhered to:**

- Pre-filled syringes with a luer lock system clearly labelled for subcutaneous use should be used. **Under no circumstances should methotrexate be drawn up and administered from vials.** Details of suppliers of pre-dosed, pre-filled syringes can be provided on request by the medicines team.
- Storage will vary depending on the product used but all prefilled syringes should be stored in a secure system.
- Protective water resistant aprons and powder free gloves should be worn when administering the treatment. Ideally nitrile gloves should be used – as these are more chemically resistant.
- Practitioners should have access to a spillage kit and first aid equipment as set out in COSHH regulations (2002).
- Used syringes and needles should be disposed of as cytotoxic waste, in a designated container, as per Medicines Code Chapter 18: Waste Medicines.

## ONGOING MONITORING

Ensure that the practice has a system in place to recall the patient for monitoring blood tests where appropriate, unless the GP is assured by the secondary care team that a recall system is already in place.

Blood monitoring incorporating FBC, LFTs and ESR/CRP should be performed fortnightly for the first 8 weeks of treatment or until the maximum dose recommended by the specialist has been achieved. Thereafter, blood monitoring can be performed monthly. In the case of a subsequent increase in dose, a blood test should be performed after 2 weeks. Providing this is satisfactory, monthly blood tests can be resumed thereafter. Where patients are stable on treatment and monitoring results have been satisfactory for 12 months, FBC, LFTs and ESR/CRP can be performed every 2-3 months. U&Es should be monitored every 3/6 months.

In addition to the above monitoring requirements, due to mounting evidence of an increased incidence and/or prevalence of ischaemic cardiac pathologies (such as myocardial infarction, congestive cardiac failure and coronary death) in rheumatology patients, it is

suggested that annual checks are performed on fasting lipids and blood pressure is measured regularly.

All patients on methotrexate will have a patient held monitoring record in accordance with the National Patient Safety Agency guidelines. This should be completed after every blood test by the person responsible for prescribing and/or monitoring the drug.

## TOXICITY

Abnormal bruising, sore throat, fever or severe mouth ulcers may indicate neutropenia. FBC should be performed immediately and methotrexate stopped until the result is available. Any patient presenting with new or increasing dyspnoea, cough or fever should have a further chest x-ray and advice sought from the rheumatologist as this may indicate pulmonary toxicity.

In the instance of deterioration in the patient's renal function, the methotrexate dose should be reduced and renal function rechecked.

Haematological / biochemical values	Action to be taken
WBC $<4.0 \times 10^9 / L$	Withhold until discussed with rheumatologist
MCV $>105 fL$	Withhold until discussed with rheumatologist
Platelets $<150 \times 10^9 / L$	Withhold until discussed with rheumatologist
Neutrophils $<2.0 \times 10^9 / L$	Withhold until discussed with rheumatologist
$>2$ -fold rise in AST */ ALT from upper limit of reference range	Withhold until discussed with rheumatologist
Unexplained fall in albumin	Withhold until discussed with rheumatologist