NHS
Salisbury
NHS Foundation Trust

Methotrexate Subcutaneous Injection for Adults in Rheumatology

Methotrexate Subcutaneous Injection for adults Shared Care Guidelines: For use in Rheumatology

Subcutaneous methotrexate is prescribed for patients who are not tolerating or responding to oral methotrexate. The same monitoring is use for subcutaneous and oral methotrexate. Patients will need to be educated and trained by 'the specialist' in safe handling, self-injection and disposal of methotrexate

See shared care monitoring of DMARDS document for further information:

Licensed Indications:

Metoject® (methotrexate prefilled pen 50mg/ml) is licensed for the following Rheumatological conditions:

- Adults with moderate to severe rheumatoid arthritis (RA) unresponsive or intolerant to conventional therapy (i.e. oral methotrexate).
- Polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.

Unlicensed Rheumatological indications:

- Connective tissue disease (SLE, myositis and vasculitis), Felty's syndrome, dermatomyositis.

RESPONSIBILITIES and ROLES

Hospital Clinician / Specialist responsibilities
Also see shared care monitoring of DMARDS document for further information
1. The specialist will do baseline assessment blood tests as listed on page 3 and in the DMARD shared care agreement (link above).
2. The specialist will provide an initial supply of sc MTX (usually 6 weeks) and monitor treatment until the patient reaches a stable dose. Once the patient has reached a stable dose, the specialist will provide a further 4 week supply to allow sufficient supplies for prescribing & monitoring to move to the GP.
3. The specialist will be responsible for training the patient on self- administration and safe disposal of the syringes.
4. Ensure the patient is aware that Metoject® prefilled pen contain an air bubble which should NOT be removed before administration.

5. Ensure the patient is given a purple lidded cytotoxic waste bin
6. If the patient requires doses in excess of 25mg per week prescribing responsibility must be retained by the specialist.
7. Ensure the patient has a NPSA methotrexate monitoring handbook

General Practitioner responsibilities
Also see shared care monitoring of DMARDS document for further information
1. Prescribe cytotoxic sharps containers – IL Sharpsafe® - see additional info on page 4
2. Remind patient to contact the council for collection of sharps waste (contact details on page 4).
3. Continue to prescribe sc MTX injection (Metoject®) once the patient is on a stable dose
4. Undertake blood monitoring as specified on page 3/as in the DMARD shared care agreement (link above), or as advised by the specialist to monitor for toxicity.

Patient's role
1. Put used syringes and needles in purple lidded cytotoxic sharps box provided by the GP on prescription.
2. Contact council for disposal of sharps waste.
3. Put any unopened syringes in cytotoxic sharps bins for disposal safely.
4. Report any side-effects or problems to your GP or specialist.
5. To bring the NPSA methotrexate monitoring booklet to any GP/Hospital appointment along with a printout of latest blood results.
6. Present NPSA methotrexate monitoring booklet to the Pharmacist dispensing the methotrexate.

SUPPORTING INFORMATION

Treatment Schedule (including dosage and administration)

Rheumatology

- Usual starting sub-cutaneous dose 7.5mg ONCE a week, rapidly titrating by 2.5mg per week. Doses exceeding 20mg/week are associated with a significant increase in toxicity. A weekly dose of 25mg should in general not be exceeded except in a few exceptional cases where a maximum dose of 30mg per week can be used.

All indications

- The lowest possible effective dose should be used.
- Elderly patients should be given a smaller test dose and titrated at a slower rate.
- Oral folic acid (usually 10mg dose) ONCE WEEKLY (not on day of methotrexate) may help reduce side effects

Contra-indications and precautions for use

- Patients receiving anti-folate drugs e.g trimethoprim, sulphonamides.
- Severe or significant renal impairment
- Significant hepatic impairment, or liver disease including fibrosis, cirrhosis, recent active hepatitis
- Active localised or systemic infectious disease e.g tuberculosis, hepatitis A, B C
- Overt or laboratory evidence of immunodeficiency syndrome(s)
- Serious cases of anaemia, leucopenia, or thrombocytopenia
- Pregnancy. Women of childbearing potential should use effective contraception during treatment. A pregnancy test should be done to rule out pregnancy prior to initiating treatment.
- As methotrexate can be genotoxic, this should be discussed with patients prior to initiation as per SPC.
- Breast-feeding
- Patients with a known allergic hypersensitivity to methotrexate or excipients of the formulation

Adverse effects

Patients must urgently report mouth ulcers, sore throat, fever, epistaxis, jaundice, unexpected bruising or bleeding, any unexplained illness/infection and should be seen urgently for clinical assessment, FBC and LFT.

New onset of shortness of breath should also be reported.

The incidence and severity of adverse effects are considered to be dose related

Commonly these include: nausea, stomach pains, mucositis / stomatitis mouth ulcers, hair loss

Rarely these include: vomiting, diarrhoea, loss of appetite, headache, tiredness, dizziness, blurred vision, eye irritation, fever, chills, joint / muscle pain, allergic reaction, rash, acne, mood changes.

Serious adverse effects include:

Blood	Bone marrow depression – leucopenia, thrombocytopenia and anaemia
Skin	Stevens-Johnson Syndrome, epidermal necrolysis, erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary, changes, alopecia, ecchymosis, telangiectasia,, furunculosis
Lungs	Acute or chronic interstitial pneumonitis, acute pulmonary oedema, pulmonary fibrosis
Liver	Hepatic toxicity / significant elevations in LFTs (> 2-3 times ULN), fibrosis or cirrhosis
Kidney	Severe Renal failure and uraemia
Neurological	Aphasia, paresis, hemiparesis, and convulsions
Other	Malignant lymphomas

Immunization

Influenza vaccination is recommended PRIOR to the first dose of methotrexate and then annually (due to immunosuppression). A pneumococcal vaccine may also be recommended. Passive immunisation should be carried out using Varicella Zoster Immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles. A list of safe vaccinations prior to travel is also available via the following links:

http://www.bad.org.uk/for-the-public/patient-information-leaflets/immunisation/?showmore=1&returnlink=http%3a%2f%2fwww.bad.org.uk%2ffor-the-public%2fpatient-information-leaflets

http://www.bad.org.uk/for-the-public/patient-information-leaflets/methotrexate/?showmore=1&returnlink=http%3a%2f%2fwww.bad.org.uk%2ffor-the-public%2fpatient-information-leaflets%3fl%3d0%26group%3d00016001000200010003

Pregnancy and Lactation

Because methotrexate is both abortifacient and teratogenic it is strictly contraindicated in pregnancy and during breastfeeding. Adequate contraceptive measures must be taken by women of childbearing potential during methotrexate therapy, and for at least **3 months** after treatment discontinued. Although methotrexate is not mutagenic, the drug may affect spermatogenesis. It is customary to advise men to avoid fathering children during therapy and for at least **3 months** after stopping

Interactions

Methotrexate is extensively protein-bound and may be displaced by other protein-bound drugs (e.g. diuretics, salicylates, hypoglycaemics), with a potential for increased toxicity. Concomitant use of other drugs with nephrotoxic or hepatotoxic potential (including alcohol) should be avoided.

- Always avoid trimethoprim, co-trimoxazole and sulphonamides (increases anti-folate effect) risk of pancytopenia
- Avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
- Live vaccines should not be administered (may cause strong antigenic reaction)
- Avoid aspirin (but low-dose regular aspirin is acceptable)

- NSAIDs can be prescribed, but patients will need to be carefully monitored for any side effects, particularly at higher methotrexate doses.
- Phenytoin can increase the antifolate effect of methotrexate.
- Excretion of methotrexate possibly reduced by ciprofloxacin, penicillins
- Increased risk of toxicity when given with doxycycline, ciclosporin, probenecid, and lefluomide

- Avoid concomitant use of acitretin

Monitoring – Also see shared care monitoring of DMARDS document for further information

Regular monitoring during treatment is essential to detect adverse reactions at an early stage and patients should be counselled about the risk factors and to report all signs and symptoms of toxicity. Carry out full blood count (FBC) and renal and liver function tests (including ALT and/or AST and albumin) before starting treatment and repeat every 2 weeks until patient is on stable dose for 6 weeks. Once on stable dose carry out monthly FBC, renal and liver function tests for 3 months. Thereafter carry out FBC, renal and liver function tests at least every 12 weeks. If there is a dose increase or unstable bloods repeat monitoring every 2 weeks until dose of methotrexate and monitoring stable for 6 weeks. Threshold laboratory values and symptoms that need discussion with the specialist are: wbc $<3.5x10^9$/l, neutrophils $<1.6x10^9$/l, platelets $<140x10^9$/l, ALT &/or AST>100u/L, unexplained fall in albumin, rash or oral ulceration, new or increasing dyspnoea or cough. Also rapid fall or consistent downward trend in haematological values should prompt caution and extra vigilance.

Administration of subcutaneous syringe

Patients and Carers: The specialist will decide which patients are suitable to receive SC methotrexate. Patients will be assessed by the clinic nurses taking into account:

- The patient is compliant
- The patient has hand function adequate for self administration
- The patient has a good understanding of:
    - Information on injection technique – self administration
    - Awareness of contact numbers
    - Awareness of the storage requirements
    - Understanding of disposal requirements

With the final decision taken by the hospital staff in conjunction with the patient. Patients will be trained by the clinic nurses who will document that training has occurred. The training will start by the nurse demonstrating how to give the injection, and then the patient self administering while supervised by the nurse. Details of who to contact in case of difficulties to be provided by the clinic.

Where the patient cannot self-administer consideration should be given to training a carer.

Nurse administration: Should a nurse administer subcutaneous methotrexate, then it is advised they follow accepted good practice as described by the RCN guidance (see ref below). Gloves and apron should be worn and methotrexate should NOT be administered by anyone who is, or suspects they may be pregnant.

Cost - Metoject® (50mg/ml) (March 2016)

Strength	Cost per Syringe	Annual drug cost
7.5mg/0.15ml	£14.85	£772.20

10mg/0.2ml	£15.29	£795.08
12.5mg/0.25ml	£16.50	£858.00
15mg/0.3ml	£16.57	£861.64
17.5mg/0.4ml	£17.50	£910.00
20mg/0.4ml	£17.84	£927.68
22.5mg/0.45ml	£18.45	£959.40
25mg/0.5ml (hospital only)	£18.48	£960.96
27.5mg/0.55ml (hospital only)	£18.89	£982.28
30mg/0.6ml (hospital only)	£18.95	£985.40

Cytotoxic Bins – A range of sizes are now available on FP10, such as:

1L bin Sharpsafe© - cytotoxic bin purple lid. Should fit one month's worth of sharps.

5L bin Sharpsguard®- cytotoxic bin purple lid may be appropriate for patients as will cover 3-4 months rather than only 1 month.

Sharps
http://www.daniels.co.uk/catalog/browse.php?id=5 http://www.sharpsafe.co.uk/p/23/1_Litre.html

Area	Disposal of cytotoxic waste details	Telephone No.
Wilts	Contact Council for waste disposal http://www.wiltshire.gov.uk/rubbish-and-recycling/hazardous-clinical-waste	0300 456 0102 or Martin Litherland Waste and recycling manager 01225 718524

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References

- National Guidelines for the Monitoring of Second Line Drugs. British Society for Rheumatology. July 2008
- National Patient Safety Agency. www.npsa.nhs.uk Patient Safety Alert Number 13 June 2006 and June 2004
- RCN guidance on the administration of subcutaneous methotrexate for inflammatory arthritis

https://www.rcn.org.uk/professional-development/publications/pub-005564

- Wyeth Pharmaceuticals. Methotrexate sodium tablets 2.5 mg. Summary of Product Characteristics 2003.
- Patient held booklet NPSA http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800
- Methotrexate treatment books available from www.nhsforms.co.uk SEE BNF for details
- British National Formulary Sept 2015-March 2016
- Summary of Product Characteristics: Metoject - http://www.medicines.org.uk/emc/medicine/28982

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