Methotrexate Sub Cut Injection *(TLS amber)* (Adults)

Shared Care Guidelines: For use in rheumatology patients only

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of medicine name and indication shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients with the condition are under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

RESPONSIBILITIES and ROLES

	Hospital Clinician / Specialist responsibilities
In addition to the responsibilities in the document Summary of shared care guidelines for DMARDs March 2019 (link above):	
1	Provide a prescription for initiating methotrexate treatment (at least 4 weeks) & train the patient on self-administration
2	Ensure the patient is aware that Metoject© prefilled pens and Zlatal prefilled syringes contain an air bubble which should NOT be removed before administration.
3	Ensure the patient is given a cytotoxic waste bin and a cytotoxic spillage kit
4	If the patient requires doses in excess of 25mg per week prescribing responsibility must revert to the specialist.

	General Practitioner responsibilities
1	Prescribe cytotoxic sharps containers – IL Sharpsafe© or 1LSharpsguard© - see additional information on final page.
2	Advise patient to contact local authority for collection of sharps waste - see additional information on final page.

	Patient's role
1	Put used syringes, pens 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	Attend all appointments with GP and specialist including appointments for blood tests and other monitoring.
5	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
6	Share any concerns in relation to treatment with medicine.
7	Inform specialist or GP of any other medication being taken, including over-the-counter products.
8	Report any adverse effects to the specialist or GP whilst taking the medicine.

BACK-UP ADVICE AND SUPPORT (GWH)

Contact details: Telephone No.	**Email address:**
01793 604314/7/8	gwh.rheumatologysecretaries@nhs.net

In most patients, subcutaneous methotrexate will replace current oral methotrexate. The same monitoring is used for subcutaneous and oral methotrexate. Patients will need to be educated and trained by 'the specialist' in safe handling, self-injection and how to dispose of injectable methotrexate.

SUPPORTING INFORMATION

Treatment Schedule (including dosage and administration)

Licensed Indications:

Metoject® (methotrexate prefilled pen 50mg/ml) and Zlatal® (methotrexate prefilled syringe 25mg/ml) are licensed for:

- Adults with active rheumatoid arthritis (RA).
- Polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate.
- Moderate to severe psoriasis in adult patients who are candidates for systemic therapy, and severe psoriatic arthritis in adults (not included in this SCA)
- Mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines (not included in this SCA).

Unlicensed indications:

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

Use in Rheumatology

- From the SPC, 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.
- Maximum licensed injectable dose of Metoject for Rheumatoid Arthritis is 30mg ONCE a week (specialist only).
- The lowest possible effective dose should be used.
- Elderly patients should be given a smaller test dose and titrated at a slower rate.
- Folic acid ONCE WEEKLY (not on day of methotrexate) may help reduce side effects.

Contra-indications and precautions for use

- hypersensitivity to the active substance or to any of the excipients
- severe liver impairment
- alcohol abuse
- severe renal impairment (creatinine clearance less than 30 ml/min.)
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- serious, acute or chronic infections such as tuberculosis, HIV or other immunodeficiency syndromes,
- ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- pregnancy (following administration to a man or woman) should be avoided for at least 3 months before conception (see section entitled 'pregnancy')
- Breast-feeding
- concurrent vaccination with live vaccines. Patients receiving anti-folate drugs e.g trimethoprim, sulphonamides (glibenclamide, tolbutamide etc)

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 – leucopoenia, 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 pneumovax II vaccination 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 link (p3): (http://www.bad.org.uk/shared/get-

file.ashx?id=4021&itemtype=document)

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 during the period of its administration – but this appears to be reversible on discontinuing therapy. It doesn't affect all men but contraception must be used as they will still be fertile.

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.

NOTE: Methotrexate is used in combination with leflunomide sometimes and requires close monitoring as there is potential for hepatotoxicity.

- 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 – See https://prescribing.bswccg.nhs.uk/shared-care-agreements and find: BSW Summary of Shared Care Guidelines and Monitoring of Disease Modifying Drugs (DMARDs) in Adults Nov 2020 Rheumatology, Dermatology & Gastroenterology.

Administration of subcutaneous or intramuscular 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:

- Compliance
- The patient's hand function for self-administration
- The patient's 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 or by using the IM route.

Nurse administration: Should a practice nurse administer subcutaneous methotrexate, then it is advised they follow accepted good practice as described by the RCN guidance (see ref below), then it is advised they follow accepted good practice as described in the guidance. 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) (Drug Tariff June 2020)

Strength	Cost per Pen	Annual drug cost
7.5mg/0.15ml	£12.87	£669.24
10mg/0.2ml	£13.26	£689.52
12.5mg/0.25ml	£14.35	£746.2
15mg/0.3ml	£14.41	£749.32
17.5mg/0.35ml	£15.25	£793
20mg/0.4ml	£15.56	£809.12
22.5mg/0.45ml	£16.11	£837.72
25mg/0.5ml	£16.13	£838.76
27.5mg/0.55ml SPECIALIST ONLY	£16.50	£858
30mg/0.6ml SPECIALIST ONLY	£16.56	£861.12

Cost - Zlatal© (25mg/ml) (Drug Tariff June 2020)

Strength	Cost per Syringe	Annual drug cost
7.5mg/0.3ml	£13.37	£695.24
10mg/0.4ml	£13.77	£716.04
12.5mg/0.5ml	£14.85	£772.20
15mg/0.6ml	£14.92	£775.84
17.5mg/0.7ml	£15.75	£819
20mg/0.8ml	£16.06	£835.12
22.5mg/0.9ml	£16.61	£863.72
25mg/1ml	£16.64	£865.28

Cytotoxic Bins – Prescribe a 1L bin (allowable on an FP10) Sharpsafe© sharpsguard© - cytotoxic bin purple lid

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.
Wiltshire	Contact Council for waste disposal http://www.wiltshire.gov.uk/hazardous-clinical-waste	0300 456 0102

References

- BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Ledingham J et al. *Rheumatology*, Volume 56, Issue 6, 1 June 2017, Pages 865–868: https://doi.org/10.1093/rheumatology/kew479 or https://academic.oup.com/rheumatology/article/56/6/865/3053478
- RCN guidance on the administration of subcutaneous methotrexate for inflammatory arthritis: https://www.rcn.org.uk/professional-development/publications/pub-005564
- Patient held booklet: https://www.nras.org.uk/publications/methotrexate-information-leaflet-and-blood-monitoring-and-record-booklet
- Methotrexate treatment books available from http://www.nhsforms.co.uk/ SEE BNF for details
- British National Formulary March 2020 Metoject - https://bnf.nice.org.uk/medicinal-forms/methotrexate.html
- Summary of Product Characteristics Metoject: https://www.medicines.org.uk/emc/product/5443
- Summary of Product Characteristics Zlatal: https://www.medicines.org.uk/emc/product/7270/smpc