NHS South Yorkshire Integrated Care Board

DMARDs

Shared Care Guideline for the prescribing of Disease modifying antirheumatic drugs (DMARDs) in rheumatology patients

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1.0 Background Information

The use of disease modifying antirheumatic drugs (DMARDs) in treating early and established stages of Inflammatory Arthritis (IA) and in managing Connective Tissue diseases (CTD) is accepted practice. General Practitioners (GPs) are becoming more involved in active management of these conditions with the recognition that patients should be referred early for specialist advice and initiation of disease modifying drugs.

DMARDs are relatively toxic treatments that are initiated in secondary care. Once patients are stabilised on their treatment ongoing prescribing and monitoring can be undertaken in primary care, with review in secondary care when appropriate. Due to the nature of these drugs it is vital that the ongoing prescribing and monitoring is agreed between the specialists in secondary care and the patient's GP.

The National Patient Safety Agency published actions to reduce the risks associated with oral Methotrexate[1] following a number of deaths and cases of serious harm (most commonly due to confusion over the dose and frequency of oral methotrexate). The issues described in the NPSA alert relating to methotrexate shared care guidelines have been incorporated into this guideline[1].

Sodium aurothiomalate was discontinued in June 2019. The drug summary has therefore been removed from this document. Any patients prescribed this medication should be referred back to the rheumatology team for review and change in treatment.

2.0 Procedure for Initiating Shared Care Arrangements

Sharing of care assumes communication between the specialist, GP and patient and/or patient's carers. The intention to share care should be explained to the patient/carer and accepted by them.

In cases where shared care arrangements are not in place, or where problems have arisen with the agreement such that patient care may suffer, the responsibility for the prescribing and management of the patient will revert to the secondary care specialist.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. They are responsible for ensuring blood tests are being performed and the results are recorded in the patients monitoring and dosage record.

Patients should be stabilised in secondary care prior to referral to primary care management

Prescriber Responsibilities:

2.1 Secondary Care Team responsibilities

- Diagnosis and assessment, ensuring there are no interactions with concurrent therapy or disease states.
- Notify the patient's GP that treatment has commenced (See Appendix A)
- GPs will be approached at 6 weeks to take on shared care if they feel able to at that time with a view to taking on shared care at 3 months.
- Baseline monitoring along with monitoring until the patient is stabilised
- Ensure patient is fully informed of potential benefits and side effects of treatment
- Ensure patient's guardian/carer is fully informed of the treatment
- Provide a comprehensive treatment package in addition to medications including appropriate information/monitoring sheet(s)
- Where subcutaneous methotrexate is indicated, ensure patient is competent in self-administration. Only patients who are able to self-administer subcutaneous methotrexate are suitable for shared care. Patients who are unable to self-administer subcutaneous methotrexate must remain under the care of the specialist.
- Patients prescribed Methotrexate Oral Solution (Jylamvo® 2 mg/ml oral solution) should receive adequate training in administration of the dose
- Ensure that shared care arrangements are in place before transfer of treatment
    - That the GP has been contacted with a request they take over prescribing
    - The patient's GP has been notified of the results of the baseline tests.
    - That the patient/carer is clear what is being monitored and by whom
    - That the patient knows what significant adverse effects/events to report urgently and to whom they should report (specialist or GP)
- Any dose changes once the patient is established on treatment will be conveyed in writing to the GP for the GP to prescribe
- Extra monitoring needed for dose changes will be organised by Rheumatology team and conveyed to the patient
- Monitor side effects of medication via routine out-patient visits
- Report adverse events to the MHRA at https://yellowcard.mhra.gov.uk/.
- Monitor patient's response to treatment

Patients will be monitored in secondary care until shared care has been accepted by the patient's GP.

Baseline Tests and routine tests
See information regarding updated British Society for Rheumatology Guidelines[2] (February 2017) and individual drugs in section 4.

Disease monitoring
The frequency of review of the patient will depend on the individual patient. The review period must be specified on the shared care referral request.

2.2 Primary Care Team responsibilities

- When the specialist initiates treatment, **reply to the request for shared care as soon as practicable. The GP should reply to the shared care request within 2 weeks.**
- Ensure that shared care arrangements are in place before transfer of treatment
- That the patient/carer is clear what is being monitored and by whom
- That the patient knows what significant adverse effects/events to report urgently and to whom they should report (specialist or GP)
- Check drug interactions with any new medication started or any new conditions diagnosed. Contact specialist team if possible interactions found and discuss with rheumatologist.
- Confirm the specialists have provided the patient/carer with appropriate information sheet(s) for monitoring and/or to alert other clinical staff to the treatment they are receiving.
- Ensure patient's guardian/carer is fully informed of the treatment
- Monitor treatment as stated in the shared care protocol
- Amend prescription as per requests from secondary care for dose changes in patients on established treatment
- Confirm with specialist which changes should trigger urgent referral back to the specialist
- Seek specialist advice promptly as advised in the shared care protocol or if signs/ symptoms of changes occur consistent with DMARD adverse event
- Refer back to the specialist in special situations where medication may need to be changed or stopped e.g. pregnancy. Advice should also be sought before restarting medication which may have been stopped for a specified period of time.
- Report adverse events to the MHRA https://yellowcard.mhra.gov.uk/.
- Report adverse events to the consultant sharing the care of the patient
- Stop treatment on advice of specialist, or immediately if intolerable side effects occur provided that it is safer to do so than to continue. If in doubt contact the specialist.

2.3 Patient / Carer Responsibilities

- Discuss potential benefits and side effects of treatment with the specialist and GP. Identify whether they have a clear picture of these from the specialist and to raise any outstanding queries
- Check that where possible the specialists have provided a patient-held record or information sheet for monitoring and/or to alert other clinical staff to the treatment they are receiving
- Share any concerns they have in relation to treatment with the medicine
- Report any adverse effects to their specialist or GP whilst taking the medicine
- Report to the specialist or GP if they do not have a clear understanding of their treatment
- Participate in the monitoring of therapy and the assessment of outcomes, to assist health professionals to provide safe, appropriate treatment

3.0 Communication

Specialist to GP
The specialist will inform the GP when they have initiated a DMARD. When the patient is near completing the satisfactory initiation period, the specialist will write to the GP to request they take over prescribing and where possible give an indication as to the expected length of treatment. The Specialist will also send a Shared care request form to support the GP in undertaking shared care. (Appendix A)

GP to specialist
If the GP has concerns over the prescribing the DMARD they will contact the specialist as soon as possible.

Contact Details	Telephone No	Fax No	Email
Consultant Rheumatologist Professor A Adebajo Dr Lorraine Croot Dr Victoria Bejarano	01226 432387 01226 432387 01226 432387		aadebajo@nhs.net L.croot@nhs.net v.bejarano@nhs.net
Medicines Information Gillian Turrell	01226 432857	01226 434431	gilliansmith2@nhs.net medicine.information1@nhs.net
Patient Advice Line Rheumatology Call Flow	01226 434960		N/a
Rheumatology Clinical Nurse Specialist Alan Pollard	01226 434960 or 01226 432421		rheumatology.cnsbhnft@nhs.net CNS email for clinical enquires from GPs and other healthcare professionals only

Out of hours information

On Call member of the Medical Team will be available to support GP where necessary.
Please call the BHNFT reception on 01226 430000 and ask for a bleep or telephone number

4.0 Shared Care Guidelines

General Guidance
The following guidance applies to all DMARDs included in this shared care guideline. For specific advice please refer to the individual drug summaries.

Pregnancy and Breast Feeding
When a patient is prescribed a DMARD there are significant issues regarding pregnancy and family planning posed by the potency and teratogenic potential of these drugs. The decision about when and what drugs should be stopped is a decision that needs to be taken in secondary care. Patients planning a pregnancy should be referred for specialist advice. The decisions potentially affect both male and female patients depending on the drugs being used. The overarching principle is to use the lowest dose to control the disease. Please see the individual drug summaries for specific advice on individual drugs.

Exposure to Varicella Zoster Virus
Immunosuppressed Varicella Zoster Virus (VZV) naïve patients have a significant risk of disseminated infection if they are exposed to or contract infection. Therefore, information is passed to all patients in secondary care on DMARD / steroid therapy as to what to do if they are exposed to or contract chicken pox.

Exposed to VZV and within incubation period
- Previous history of chicken pox
  Only treat if develop active infection; usually aciclovir
- No history of chicken pox
  - Urgent assessment of VZV antibodies
  - If antibody status negative: treatment with pooled immunoglobulin
  - If antibody status positive: only treat with aciclovir if develop infection

Active VZV Infection
- Previous history of infection – treat with aciclovir
- No history of chicken pox
  - Urgent assessment of antibodies
  - Detailed clinical assessment and anti-viral treatment dependent on clinical presentation

Immunisations
No live vaccine should be given to any immunosuppressed patient[2]. All patients on DMARDs should be offered annual flu vaccination and the one-off pneumococcal vaccine unless contraindicated. Oral polio should not be given to patients on DMARDs or household contacts.

Varicella-Zoster vaccine (Zostavax®) may be administered with methotrexate if the weekly MTX dose is 20mg or less.[14]

Special Note on Combination Therapy

Patients on more than one DMARD
If more than one DMARD is being prescribed, then the monitoring requirements are such as to fulfil the monotherapy monitoring requirements[2] of each drug (see individual drug summaries below).

Patients prescribed a DMARD and a Biologic
Where patients are prescribed both a DMARD and a Biologic the prescribing and monitoring of the biologic will be undertaken in secondary care. GPs participating in shared care will still undertake the prescribing and monitoring required for the DMARD.

The subcutaneous biologics **do not** need any extra monitoring. Virtually all biologics are given with Methotrexate and the usual 3 monthly blood testing is all that is necessary.

Where other monitoring is needed for Biologics, then this will be undertaken in Secondary Care. (For example, pre-infusion immunoglobulin levels in patients given rituximab).

As with DMARDs, Clinicians in Primary Care need to be aware of the increased infection risk in patients prescribed Biologics. It is recommended to stop the biological agent in cases of infection, particularly if antibiotics are required.

Monitoring

Updated BSR Guidelines (February 2017)[2] have simplified monitoring recommendations for DMARDs (except penicillamine – not covered in the BSR guidelines). Monitoring common to all DMARDs except biologics:

- Baseline assessment should include height, weight, blood pressure and laboratory evaluation - full blood count (FBC), calculated glomerular filtration rate (GFR), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), albumin.
- Patients should be assessed for co-morbidities because these may influence DMARD choice, including evaluation for respiratory disease and screening for occult viral infection.
- When starting or adding a new DMARD: Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks; then once on stable dose, **monthly** FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months. Thereafter, FBC, creatinine/calculated GFR, ALT and/or AST and albumin at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity.
- Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks then revert to previous schedule above.

Exceptions and additions to the standard monitoring schedule for specific DMARDs are included in the individual drug monographs below.

Shared Care Guideline

Azathioprine

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC[3] or BNF[4] for further prescribing information.

Indication

Azathioprine is a well-established and effective treatment for several conditions including rheumatoid arthritis and is used as a steroid sparing agent in other rheumatological conditions.

Pharmacology

Azathioprine's action follows in vivo conversion to 6-mercaptopurine and within cells it is converted to purine thioanologues. The key enzyme in the inactivation of thiopurines is thiopurine s-methyl transferase (TPMT), which is inherited as an autosomal co-dominant trait with up to 10% of the population having little or no enzyme activity. Such individuals are at increased risk of toxicity from azathioprine.

Dose

Azathioprine is given orally in tablet form. Starting dose is usually 50mg daily increasing by 50mg weekly to a maintenance dose of 150mg daily providing no side effects occur. In some circumstances higher doses are given up to 300mg daily. As a guide, the dose should be within 1–2.5mg/kg daily. Occasionally more may be needed in some patients. When used as a steroid sparing agent it is usually used at lower doses of 50–100mg daily. It should be taken with or after food in divided doses if preferred. Analgesics and NSAIDs should be continued until a positive response is achieved.

Monitoring

<u>Baseline tests</u> (To be undertaken by the Rheumatology specialists)
FBC, U&Es, calculated GFR, LFTs and serum albumin
24-hour Urine creatinine if renal function in doubt
Consider TPMT (thiopurine methyl transferase)
Consider Hepatitis B and C; HIV
Consider pregnancy test

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

<u>Routine tests</u>
FBC, U+Es, calculated GFR, LFTs and serum albumin to be undertaken every 2 weeks until on a stable dose for 6 weeks. Then monthly for 3 months and then 3 monthly once the dose and the blood tests are stable. Consider more frequent testing if higher dosage or if renal or hepatic impairment.

Ask about rash, oral ulceration, sore throat, infections or evidence of bruising or bleeding each time. Also ask patients to report these symptoms immediately if they occur while on azathioprine. If patients present with these symptoms perform an urgent blood test. If any of the following occur, stop azathioprine and contact the hospital specialist:

WCC	$<3.7 \times 10^9$/L
Neutrophils	$<1.7 \times 10^9$/L
Platelets	$< 150 \times 10^9$/L
AST or ALT	>3 times normal range
Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min	
Unexplained reduction in albumin <30g/L	

MCV >100f/l continue medication but contact rheumatology for further advice

Also observe trends in results e.g. gradually decreasing white blood cell count. Contact rheumatology specialist for advice where persistent unexplained eosinophilia (eosinophils >0.5x 10^9/L)

If any increase in dose revert back to initial monitoring advice

Adverse Drug Reactions

Mucocutaneous: Urticaria, erythematous rashes, pruritus, oral ulceration.
Haematological: Neutropenia, thrombocytopenia, macrocytosis.
Gastro-intestinal: Nausea (very common), vomiting, abdominal pain and diarrhoea.
Hepatic: Raised transaminases. In the presence of raised transaminases therapy should not be started or continued unless treatment is for autoimmune liver disease.
Renal: Reduce the dose of azathioprine in renal impairment.
Other: Headaches and dizziness.
Conception: Effects of azathioprine on children fathered by men on azathioprine are not known.

Opportunistic infections may occur. Infections can require early and vigorous treatment. Azathioprine may need to be stopped until the infection is clear.

Contraindications

Known hypersensitivity to azathioprine. Hypersensitivity to 6-mercaptopurine should alert the prescriber to probable azathioprine hypersensitivity.

Cautions

Renal impairment: Toxicity of azathioprine may be enhanced. Use doses at the lower end and monitor haematological response.

Hepatic Impairment: Metabolism of azathioprine may be impaired. Regular monitoring required.

Pregnancy: Women planning to become pregnant should not take azathioprine. Benefits considered to be outweighed by the risks. Azathioprine should only be used during pregnancy following a careful assessment of risk versus benefit.

Breast feeding: Azathioprine is excreted in breast milk. Breastfeeding is inadvisable for mothers on azathioprine.

Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor to minimize the risk of skin cancer and photosensitivity.

Drug Interactions

Allopurinol: Increased azathioprine toxicity. Reduce dose azathioprine by 75%.
ACE inhibitors: Increased risk of anaemia or leucopenia with captopril or enalapril.
Antibacterials: Increased risk of haematological toxicity with co-trimoxazole or trimethoprim.
Anticoagulants: Azathioprine possibly reduces anticoagulant effect of warfarin and acecoumarol
Febuxostat: manufacturer advises avoidance of azathioprine
Antivirals: azathioprine myelosuppressive effects enhanced by ribavirin – avoid
Clozapine – increased risk agranulocytosis
Sulfasalazine, mesalazine, olsalazine – inhibit TPMT enzyme. Increased risk myelosuppression

Live vaccines should be avoided

Shared Care Guideline

Ciclosporin

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC[5] or BNF[4] for further prescribing information.

Indication

Ciclosporin is an immunosuppressive agent effective in the treatment of several conditions including rheumatoid arthritis.

Pharmacology

Ciclosporin effect and toxicity is dose dependent. It is metabolised by cytochrome p450 isoenzyme CYP 3A4. Drugs may alter ciclosporin levels by inducing or inhibiting this enzyme. Ciclosporin is also transported back into the gut lumen by the intestinal P. glycoprotein which is also inhibitable or inducible by other drugs (see drug SPC).

Dose

Ciclosporin comes as an oral capsule in 10, 25, 50 and 100mg strengths. Usual starting dose is 1 – 2 mg/kg daily in two divided doses for the first 6 weeks. The dose is then increased by 25mg every 2 weeks until effective therapy is reached or toxicity occurs. Maximum dose 4mg/kg. Toxicity is indicated by an increase in creatinine or serum potassium. Different brands have different bioavailability. It is therefore important that ciclosporin is prescribed by brand so patients receive the same brand each time.

Monitoring

Baseline tests (To be undertaken by the Rheumatology specialists)
FBC, U&Es, calculated GFR, LFTs and serum albumin, BP, 24hr Urine Creatinine clearance if renal function in doubt, urate, lipids
Consider Hepatitis B and C; HIV
Consider pregnancy test

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
FBC, LFTs, U&Es, calculated GFR, serum albumin, urinalysis and BP to be monitored every 2 weeks until on a stable dose for 6 weeks. Then monthly for 3 months (can be extended for a longer period depending on individual patient response), then every 3 months. Urate & lipids to be monitored every 2-3 months (Optional)
Blood pressure to be monitored at each blood test
Pay particular attention to serum creatinine and potassium levels

More frequent checks are necessary when the ciclosporin dose is increased, or concomitant treatment with a NSAID is initiated or its dose increased.

If patients present with symptoms of potentially severe adverse effects **stop Ciclosporin** and perform an urgent blood test:

If any of the following occur at any time contact the hospital specialist:

WCC	$<3.7 \times 10^9$/L
Neutrophils	$<1.7 \times 10^9$/L
Platelets	$< 150 \times 10^9$/L
AST or ALT	> 3 times normal range
Potassium	>5.5mmol/l

Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min
Unexplained reduction in albumin < 30g/L

Hypertension (BP >160/95 or risen by > 20mmHg)

MCV >100f/l continue medication but contact rheumatology for further advice

Also observe trends in results e.g. gradually decreasing white blood cell count. Contact rheumatology specialist for advice where persistent unexplained eosinophilia (eosinophils >0.5x 10^9/L)

If any increase in dose revert back to initial monitoring advice.

Adverse Drug Reactions

Please refer to SPC for full list
Mucocutaneous: Urticaria, erythematous rashes, pruritus, oral ulceration and gum hyperplasia.
Haematological: Leucopenia, anaemia, thrombocytopenia.
Cardiovascular: Hypertension, oedema, hyperlipidaemia.
Gastro-intestinal: Diarrhoea, (if not severe and tolerable may resolve in time), nausea, dyspepsia.
Hepatic impairment: Dosage adjustment may be necessary. If transaminases rise >3 times normal range stop drug .
Renal: Renal impairment and nephropathy are significant and common problems. Hyperkalaemia
Other: Headaches, tremor, fatigue, convulsions, myalgia, hyperglycaemia, hypomagnesaemia.

Contraindications

Contraindicated in abnormal renal function, uncontrolled hypertension, uncontrolled infections and malignancy**. Contraindicated in pregnancy**. Ciclosporin crosses placenta and use in pregnancy is associated with premature birth and low birth weight. Patients should be advised not to become pregnant for three months following cessation of treatment.

Cautions

Ciclosporin predisposes patients to the development of bacterial, fungal, parasitic and viral infections.
Renal impairment: Concomitant administration of NSAIDs increases the risk of renal impairment. Patients should be closely monitored.
Hepatic Impairment: Ciclosporin may impair liver function. Dosage adjustment may be necessary.
Regular monitoring of blood pressure is required during therapy with ciclosporin
Potential risk of skin malignancy: patients on ciclosporin should be warned to avoid excess ultraviolet light exposure.

Drug Interactions

Many drugs interact with Ciclosporin. Please refer to the Summary of Product Characteristics for a full list.

The following drugs increase ciclosporin serum levels:
Antibiotics – Erythromycin, clarythromycin, fluoroquinolones.
Antifungals – Ketoconazole, itraconazole, fluconazole, terbinafine
Calcium channel blockers- Diltiazem, verapamil, nicardipine, amlodipine
Other- Colchicine, digoxin, oral contraceptives, allopurinol.amiodarone, H2 blockers, orlistat, grapefruit juice.

The following drugs decrease ciclosporin serum levels:
Anti-epileptics – Phenytoin*, carbamazapine*, primidone
Antibiotics – Rifampicin*, sulphonamides, trimethoprim.
(* These agents may double the rate of ciclosporin elimination)

Nephrotoxic drugs: Care should be taken when prescribing ciclosporin with other drugs that exhibit nephrotoxic synergy e.g. aminoglycosides, NSAIDs methotrexate, ciprofloxacin, trimethoprim.

Ciclosporin may reduce the clearance of digoxin, colchicine, prednisolone, statins and etoposide. Increased risk muscle toxicity with statins and colchicine.

Caution is required with concomitant use of potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists or potassium containing drugs - risk of significant increases in serum potassium.

Hydroxychloroquine

***Please note:** Hydroxychloroquine was reclassified as Amber G in November 2015. Hydroxychloroquine still requires initiation by a specialist, but ongoing prescribing and monitoring can be undertaken in primary care with no formal sign up of shared care.*

***This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC[6] or BNF[4] for further prescribing information**.*

Indication

Hydroxychloroquine is an antimalarial drug licensed for the treatment of active rheumatoid arthritis but is also used in the management of connective tissue disease.

Dose

The minimum effective dose should be employed. Usually started at a dose of 200mg bd for the first 3 months then reduced to 200mg daily as a maintenance dose if effective. The maintenance dose may be increased to 400mg daily by the specialist, if the response lessens. Aim for 3-5mg/kg/day. The dose should not exceed 6.5mg/kg/day (calculated from lean body weight NOT actual body weight) and will be either 200mg or 400mg per day. Treatment should be discontinued if there is no improvement by 6 months.

Monitoring

Baseline tests (To be undertaken by the Rheumatology specialists)
FBC, U&Es, LFTs,

Patients are expected to arrange their own routine baseline and annual optician reviews. There is no longer a requirement for the patient to have an ophthalmology baseline assessment.

All patients will have an ophthalmological examination after 5 years of treatment with hydroxychloroquine and annually thereafter. The specialist team will refer patients to the ophthalmology clinic for this.

For patients with additional risk factors for retinopathy e.g. high dose of hydroxychloroquine (greater than 5mg/kg/day), Systemic Lupus Erythematosus, concomitant tamoxifen therapy or impaired renal function (eGFR <60ml/min/1.73m^2), monitoring will be started after 1 year, the specialist team will refer patients to the ophthalmology clinic.

The ophthalmological examination for all patients should include both spectral domain optical coherence tomography (SD- OCT) and fundus autofluorescence (FAF), widefield if available. Visual field testing should be undertaken for patients with abnormalities on SD-OCT or FAF consistent with hydroxychloroquine retinopathy.

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
Renal function annually if over 70yrs old; pre-existing renal impairment or known hypertension/diabetes

At review ask about visual impairment not corrected by glasses. If visual abnormality detected stop hydroxychloroquine and refer first to an optometrist.

Adverse Drug Reactions

Ocular effects: *Retinopathy* with changes in pigmentation and visual field defects. *Corneal changes* including oedema and opacities have been reported. Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible may also occur.
Dermatologic effects: pruritus, pigmentary changes in skin and mucous membranes, bleaching of hair and alopecia. Erythema multiforme, Stevens-Johnson syndrome and photosensitivity have been reported. May precipitate attacks of psoriasis.
Gastrointestinal effects: Nausea, diarrhoea, anorexia, abdominal pain and, rarely, vomiting may occur.
Cardiomyopathy which may result in cardiac failure and in some cases death
CNS effects: Dizziness, vertigo, tinnitus, hearing loss, headache
Hematologic effects: Anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells and thrombocytopenia have been reported.
Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups
Psychiatric reactions: A range of psychiatric reactions, including rare cases of suicidal behaviour have been associated with hydroxychloroquine, noted to be typically within the first month of treatment. Events have been reported in patients with no previous history of psychiatric disorders. (MHRA Feb 2022).
Information about these reactions have been added to the Summary of Product Characteristics and Patient Information Leaflets.
Patients should be advised to contact a doctor immediately if they experience new or worsening mental health problems (such as irrational thoughts, anxiety, hallucinations, and feeling confused or feeling depressed, including thoughts of self-harm or suicide). Family members or caregivers may also be advised to be vigilant for these reactions and the need to seek medical advice if they occur**.**

Contraindications

Known hypersensitivity to 4-aminoquinoline compounds.
Pre-existing maculopathy of the eye.

Cautions

Hydroxychloroquine crosses the placenta. and is excreted in small amounts in breast milk**.** It is generally considered safe in pregnancy and breastfeeding.

Use hydroxychloroquine with caution in patients with renal or hepatic impairment.
Use with caution in patients with severe gastrointestinal, neurological or blood disorders.
Although the risk of bone marrow depression is low, periodic blood counts are advisable.

Hydroxychloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms.

Drug Interactions

Hydroxychloroquine can increase the risk of cardiovascular events and cardiovascular mortality when given with macrolide antibiotics (azithromycin, erythromycin, clarithromycin). MHRA February 2022 The benefits and risks should be carefully considered before prescribing systemic azithromycin or other systemic macrolide antibiotics (erythromycin or clarithromycin) to patients being treated with hydroxychloroquine. The specialist team advise that patients withhold hydroxychloroquine whilst taking **ALL** antibiotics.

Hydroxychloroquine sulphate may increase plasma digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.

Hydroxychloroquine may increase the plasma concentration of ciclosporin (potential for increased ciclosporin toxicity).

There is an increased risk of ventricular arrythmias when hydroxychloroquine is given with the following drugs: amiodarone, moxifloxacin, droperidol.

As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a 4 hour interval be observed between Plaquenil and antacid dosing.

Hydroxychloroquine may enhance the effects of a hypoglycaemic treatment; a decrease in doses of insulin or antidiabetic drugs may be required.

Shared Care Guideline

Leflunomide

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC[7] or BNF[4] for further prescribing information.

Indication

Leflunomide is an effective treatment for inflammatory arthritis. It has a comparable efficacy and toxicity profile to methotrexate.

Pharmacology

Leflunomide's active metabolite A771726is 99% protein bound and excreted equally in urine and faeces. It has a long half-life of approximately 2 weeks.

Dose

Leflunomide is usually considered for patients with active rheumatoid arthritis or psoriatic arthritis where methotrexate and sulphasalazine have been ineffective. It is available in tablet form of either 10mg or 20mg. The 100mg loading dose is not recommended as this increases the risk of adverse effects. The recommended daily dose is 10mg or 20mg once daily. Patients of uncertain alcohol intake or who take other hepatotoxic drugs warrant extra vigilance (see cautions below).

Monitoring

Baseline tests (To be undertaken by the Rheumatology specialists)
FBC, U&Es, calculated GFR, LFTs and serum albumin, Blood pressure on 2 occasions 2 weeks apart and body weight.
Consider Hepatitis B and C; HIV
Consider pregnancy test, chest x-ray and PFTs.

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
FBC U&Es, calculated GFR, LFTs and serum albumin, weight and BP – monitor every two weeks until on a stable dose for 6 weeks, then monthly for 3 months. Monitor every three months once a stable dose is reached. More frequent monitoring in patients at higher risk of toxicity, or if clinically indicated

If patients present with symptoms of potential adverse effects (see below) stop leflunomide and perform an urgent blood test:

If any of the following occur, **stop leflunomide** and contact the hospital specialist:

WCC	$<3.7 \times 10^9$/L
Neutrophils	$<1.7 \times 10^9$/L
Platelets	$< 150 \times 10^9$/L
AST or ALT	2-3 times upper normal limit – discuss with specialist team. If > 3 x normal–stop medication, consider washout and seek specialist advice

Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min
Unexplained reduction in albumin < 30g/L

MCV >100f/l continue medication but contact rheumatology for further advice

Also observe trends in results e.g. gradually decreasing white blood cell count. Contact rheumatology specialist for advice where persistent unexplained eosinophilia (eosinophils >0.5x 10^9/L)

Blood pressure	If >140/90 treat in line with NICE guidance. If BP remains uncontrolled, stop leflunomide and consider washout (seek specialist advice)
Weight	If >10% weight loss with no other cause identified, stop and consider washout (seek specialist advice)
Other	Stop leflunomide seek specialist advice if: ulcerative stomatitis; skin/mucosal reactions (stop and consider washout - risk of Stevens-Johnson syndrome); pruritis/rash; peripheral neuropathy; abnormal LFTs; breathlessness or infection (stop, perform chest x-ray and PFTs); abdominal pain nausea, diarrhoea.

Adverse Drug Reactions

Mucocutaneous: Urticaria, erythematous rashes, pruritus, worsening of psoriasis, oral ulceration, and alopecia.
Haematological: Neutropenia, thrombocytopenia, macrocytosis and rarely anaemia.
Gastro-intestinal: Diarrhoea, (if not severe and tolerable may resolve in time), nausea, vomiting, abdominal pain, occasionally weight loss.
Hepatic: Elevation of liver parameters. If transaminases rise >3 times normal range stop drug. Re-challenge on reduced 10mg dose.
Respiratory: Interstitial lung disease which may be fatal (rare).
Renal: Renal failure. Reduce the dose in renal impairment.
Other: Headaches, depression and irritability, peripheral neuropathy, severe pneumonitis (rare hypersensitivity reaction), and enteritis.
Infection: Opportunistic infections may occur. Infections can require early and vigorous treatment and may require leflunomide to be stopped until the infection is clear.

Contraindications

Hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients.

- Patients with impairment of liver function or moderate to severe renal insufficiency.
- Patients with severe immunodeficiency states, e.g. AIDS.
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
- Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.
- **Conception/pregnancy**. Pregnant women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and thereafter as long as the plasma levels of the active metabolite are above 0.02 mg/l. Pregnancy must be excluded before start of treatment with leflunomide.

  Manufacturers recommend 2 years should elapse from cessation of therapy before elective pregnancy. In practice if Leflunomide is washed out and two serum levels 14 days apart both read <0.02mg/l then the risk of foetal toxicity is very low. Refer to drug SPC.

  Male patients should also be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should be advised. If Leflunomide is washed out and two serum levels 14 days apart both read <0.02mg/l,(and after a waiting period of at least 3 months) the risk of foetal toxicity is very low. Refer to drug SPC

- Breast-feeding women

Cautions/Drug Interactions

See drug SPC for full list of drug interactions

Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) should be used with caution following assessment of risks and benefits.

Caution is advised when leflunomide is given together with drugs metabolised by CYP2C9 such as rifampicin, phenytoin, warfarin, phenprocoumon and tolbutamide.

Colestyramine or activated powdered charcoal should be avoided unless used in the washout process as they cause rapid and significant decreases in plasma A771726

Due to the risk of hepatotoxicity, consumption of alcohol should be avoided during therapy with leflunomide.

Live vaccines should be avoided

Shared Care Guideline

Methotrexate (oral or sub-cutaneous)

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPCs[8,9,10,11] or BNF[4] for further prescribing information.

Indication

Methotrexate is used in the treatment of adults with severe, active, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy.

Pharmacology

Methotrexate inhibits the enzyme dihydrofolate reductase. Its main effect is the inhibition of DNA synthesis, but it also acts directly on both RNA and protein synthesis. It is a folic acid antagonist and is classified as an antimetabolite cytotoxic agent.

The MHRA has noted that Methotrexate is a **weekly** dose and attention should be paid to the **strength** of Methotrexate tablets prescribed and the **frequency** of dosing.

The National Patient Safety Agency has published actions to reduce the risks associated with oral Methotrexate. The advice relating to shared care guidelines has been included in this guidance.[1]

Dose

Methotrexate is administered **ONCE weekly** and the prescription should specify the day of the week the dose should be administered/taken.

Methotrexate Tablets

Methotrexate tablets should be swallowed whole (not crushed or chewed) and should be taken with or after food. The usual dose for moderate to severe active rheumatoid arthritis is:

- Initially 10mg to 20mg once weekly. However, the starting dose may vary depending on the severity of the condition and patient characteristics such as age, renal function and other comorbid conditions.
- Dose increased by 2.5mg-5mg at 4 weekly intervals according to clinical response

The maximum oral dose is 30mg once a week in divided doses (15mg twice a day). *The recommendation is that when a tablet formulation is indicated only 2.5mg tablets should be prescribed and dispensed for patients receiving oral Methotrexate.*

Methotrexate Oral Solution (Jylamvo® 2 mg/ml oral solution)

- This formulation should be reserved for patients unable to take methotrexate tablets.
- It is the responsibility of the specialist team to determine which patients are suitable for self-administration of Jylamvo. An assessment should be made as to whether the patient is able to understand and accurately measure the correct dose.
- Appropriate patient training should be given before prescribing is handed over to primary care.
- Each 1 ml of the solution contains 2 mg methotrexate. A 10ml oral syringe is provided with the solution and includes major graduations at every 1ml and minor graduations at every 0.25 ml.
- Educational materials for healthcare professionals is available at: https://www.medicines.org.uk/emc/rmm/1064/Document

See Appendix C for advice on safe use of Methotrexate Oral Solution

Sub-cutaneous methotrexate

The usual dose of subcutaneous methotrexate is 7.5mg weekly. This can be increased by 2.5mg weekly to a maximum weekly dose of 30mg.

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Subcutaneous methotrexate is available as pre-loaded pens. Metoject® and Nordimet® are the preferred brands. Choice of device should be made in consultation with the patient. Brand prescribing is advised to ensure that the patient receives the device that they have been trained on.

Guidance for administering Metoject® pre-loaded pen can be found at:
https://vimeo.com/136832870

Guidance for administering Nordimet® can be found at:
http://nordimet.co.uk/hcp/support-materials/

Metoject® subcutaneous injection contains 50mg/ml methotrexate and is available in the following strength pens:
Metoject PEN 7.5 mg; 10mg; 12.5mg; 15mg; 17.5mg; 20mg; 22.5mg; 25mg; 27.5mg and 30mg solution for injection in pre-filled pen

SPC for Metoject® can be found at the following link:
http://www.medicines.org.uk/emc/medicine/28982

Nordimet® subcutaneous injection contains 25mg/ml methotrexate and is available in the following strength pens:
Nordimet® 7.5 mg; 10mg; 12.5mg; 15mg; 17.5mg; 20mg; 22.5mg and 25mg solution for injection in pre-filled pen

SPC for Nordimet® can be found at the following link:
http://www.medicines.org.uk/emc/medicine/33073

Only those patients who are able to self-administer subcutaneous methotrexate are suitable for shared care. Those patients who are unable to self-administer subcutaneous methotrexate should remain under the care of the specialist team.

See **Appendix B** for safe use and disposal of subcutaneous methotrexate injections.

Methotrexate is a folic acid antagonist. Folic acid 5mg tablet supplement should be taken between one and six days a week, according to the patient and their experience of side effects. Folic acid should NOT be taken on the same day as Methotrexate.

Monitoring

Baseline tests (To be undertaken by the Rheumatology specialists)
FBC (incl. differential WCC and platelets), U&E, LFT, calculated GFR and serum albumin, urinalysis; chest x-ray and PFT and where there is clinical concern consider baseline chest HRCT.
Consider pregnancy test.

NPSA MTX monitoring books and patient information should be supplied to all patients

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
FBC, U&Es, LFTs calculated GFR and serum albumin, to be monitored every two weeks until dose stabilised, then monthly for 3 months, then 3 monthly thereafter unless the dose changes. More frequent monitoring may be required if psoriatic

arthritis, diabetes, obesity, uncertain alcohol intake or concomitant medication which may reduce the renal excretion of methotrexate.

If patients present with symptoms of potential adverse effects (see below) stop methotrexate and perform an urgent blood test:

If any of the following occur at any time stop medication and contact the hospital specialist:

WCC <3.7 x 10^9/L
Neutrophils <1.7 x 10^9/L
Platelets < 150 x 10^9/L
AST or ALT > 3 times normal range
Unexplained reduction in albumin < 30g/L

MCV >100f/l continue medication but contact rheumatology for further advice

Also observe trends in results e.g. gradually decreasing white blood cell count. Contact rheumatology specialist for advice where persistent unexplained eosinophilia (eosinophils>0.5x 10^9/L)

In doses used to treat patients in rheumatology MTX does not cause renal impairment or deterioration of usual levels. However, it can accumulate in renal impairment.
-If there is a significant change from usual eGFR levels, please address any possible cause.
-MTX dose can be halved temporarily if eGFR drops to 30-50. It should be withheld if eGFR drops below 30.
Please contact the Rheumatology team to highlight this deterioration for further advice on medium-term MTX dose.

Adverse Drug Reactions

Skin: Stevens-Johnson Syndrome, erythematous rashes, pruritus, urticaria, photosensitivity, minor hair thinning
Haematopoietic**:** anaemia, thrombocytopenia, and neutropenia
Gastrointestinal: Nausea, anorexia, oral ulcers, abdominal pain, diarrhoea
Central Nervous System: Headaches, drowsiness, ataxia and blurred vision
Other rare: Hepatotoxicity, Pulmonary toxicity (acute pneumonitis or chronic pulmonary fibrosis).

The patient should be advised to report any of the following signs or symptoms without delay: Cough, fever, breathlessness, sore throat, bruising, mouth ulcers, jaundice, infections, rash, shingles or chickenpox.

- New or increasing dyspnoea/cough – Withold and discuss with specialist team urgently
- Rash or oral ulceration, nausea, vomiting or diarrhoea – Withold until discussed with member of specialist team
- Abnormal bruising or severe sore throat, fever – Immediate FBC and withhold until result available.

Contraindications

Severe renal or hepatic impairment.
Pre-existing blood dyscrasias such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
Liver disease including fibrosis, cirrhosis, recent or active hepatitis
Active infectious disease such as tuberculosis, HIV, and overt or laboratory evidence of immunodeficiency syndrome(s).
Ulcers of the oral cavity and known active gastrointestinal ulcer disease

Pregnancy or breast-feeding. Effective contraception should be used by women and continued for at least 3 months after stopping treatment with methotrexate. Contra-indicated in breast feeding.
Patients with a known allergic hypersensitivity to Methotrexate
Concomitant use with drugs with anti-folate properties.

Cautions

Methotrexate should be used with extreme caution in:

- Elderly patients (a lower dose should be considered)
- Patients with ulcerative disorders of the GI tract
- Patients with psychiatric disorders
- Caution - underlying chest disease/smoker
- Where history of excessive alcohol intake
- Patients exposed to chickenpox. If patients are exposed to chicken pox and are not immunised by prior infection or vaccination, they may need passive immunisation with varicella-zoster immunoglobulin if the contact risk is appreciable. Discuss immediately with secondary care.

Drug Interactions

Aspirin / NSAIDs: increased Methotrexate toxicity, sometimes life-threatening cases have been reported with concurrent administration, the risk is lowest for those on low dose Methotrexate, with normal renal function. If an NSAID is introduced FBC should be checked one week later.
Co-trimoxazole and trimethoprim must be avoided. Other antibiotics may increase serum concentration of methotrexate. If a patient who is taking methotrexate requires antibiotics, stop Methotrexate until antibiotics are finished and infection is healed. Methotrexate can be restarted at the usual dose afterwards. A simple viral infection does not require discontinuation of Methotrexate.
Antimalarials: pyrimethamine
Clozapine
Ciclosporin
Corticosteroids: increased risk of haematological toxicity
Antiepileptics: phenytoin
Leflunomide
PPIs : possible increased risk of Methotrexate toxicity

Avoid live vaccines (Varicella-Zoster vaccine safe if weekly MTX dose 20mg or less)

Shared Care Guideline

Penicillamine

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC[12] or BNF[4] for further prescribing information

Indication

Penicillamine is licensed for the treatment of severe active rheumatoid arthritis.

Pharmacology

Penicillamine is a thiol-group containing chelating agent. It is strongly plasma-protein bound.

Dose

Treatment is usually started at 125mg daily taken at least half an hour before food/milk or last thing at night. If no problems occur the dosage may be increased to:

- 250mg tablet daily for 1 week
- 375mg daily for 1 week
- Then two 250mg tablets daily

500mg daily in divided doses for 3 months is recommended. Further increases may be necessary if limited clinical response, with a usual maximum of 750mg daily (rarely more). Doses should be taken on an empty stomach at least half an hour before food or last thing at night.

Pyridoxine daily may be required for patients on long term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin.

If remission is established and has been sustained for six months, gradual reduction by 125 to 250mg amounts every 12 weeks may be attempted.

Monitoring

Baseline tests (To be undertaken by the Rheumatology specialists)
FBC, platelets, renal function and urinalysis (for proteinuria and blood)

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
During the first two months of therapy full blood counts and urinalysis should be carried out every 2 weeks and also in the week after any increase in dose; then monthly for 4 months; then 3 monthly thereafter.

Stop and contact hospital specialist if:

WCC	<3.7 $10^{9/}$L
Neutrophils	<1.7 $10^{9/}$L
Platelets	<150 $10^{9/}$L
Proteinuria/Blood	>1+

Rash - Antihistamines/steroid cover or temporary reduction in dose can control urticarial rash.

Unusual bruising/mouth ulceration/loss of taste. If proteinuria and negative MSU, suggest PCI and GFR (or 24 hour urine for CrCl and protein)

Adverse Drug Reactions

Nausea, anorexia, fever and rash may occur early in therapy, especially when full doses are given from the start. Urticarial reactions have also been reported.

Reversible loss of taste may occur and rarely, mouth ulceration/stomatitis has occurred.

Thrombocytopenia occurs commonly and leucopenia less often. Deaths from agranulocytosis and aplastic anaemia have occurred.

Proteinuria occurs in up to 30% of patients and is partially dose-related

Haematuria may occur rarely

Contraindications

Hypersensitivity to penicillamine or any of the ingredients.
Agranulocytosis, aplastic anaemia or severe thrombocytopenia due to penicillamine.
Lupus erythematosus.
Moderate or severe renal impairment

Cautions

Caution in patients with renal insufficiency; reduction in dose may be needed as will longer intervals between dose increases. Careful monitoring is necessary in the elderly; increased toxicity has been observed in this patient population regardless of renal function.

Penicillamine should be used with caution in patients who have had adverse reactions to gold. Concomitant or previous treatment with gold may increase the risk of side effects with penicillamine treatment.

Haematuria is rare, but if it occurs in the absence of renal stones or other known cause, treatment should be stopped immediately.

Pregnancy and breastfeeding: The safety of penicillamine for use during pregnancy has not been established. There is also lack of safety data on use in breast feeding patients. Contact the rheumatology specialist if patient considering conceiving or in cases of pregnancy.

Drug Interactions

Oral absorption of penicillamine may be reduced by concomitant administration of iron, antacids or zinc. They should not be taken within 2 hours of taking penicillamine

Oral absorption of digoxin may be reduced by concomitant administration of penicillamine. Digoxin should not be taken within 2 hours of taking penicillamine

Concomitant use of NSAIDs and other nephrotoxic drugs may increase the risk of renal damage.

Avoid concomitant use of gold, clozapine (may potentiate the blood dyscrasias).

Shared Care Guideline

Sulfasalazine

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC[13] or BNF[4] for further prescribing information.

Indication

Sulfasalazine is a well-established and effective treatment for several different conditions, including inflammatory arthritis and inflammatory bowel disease.

Dose

Sulfasalazine is available as an oral preparation in tablet or syrup form. The dose should be titrated gradually to reduce the risk of GI side effects. Treatment usually starts with a dose of 500mg daily increasing weekly by 500mg increments until a maintenance dose of 2 to 3 grams daily is achieved. Maximum dose 40mg/kg/day. Enteric coated preparations should be used as they are better tolerated.

Monitoring

Baseline tests (To be undertaken by the Rheumatology specialists)
FBC, U&Es, LFTs, Creatinine/ calculated GFR, serum albumin and serum folate

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
FBC, U+Es, calculated GFR, LFTs and serum albumin to be undertaken every 2 weeks until on a stable dose for 6 weeks, then monthly for 3 months and then 3 monthly once the dose and the blood tests are stable.

Routine monitoring can cease if stable after 12months of therapy with sulfasalazine alone.

If patients present with symptoms of potential adverse effects (see below) perform an urgent blood test. If any of the following occur, **stop sulfasalazine** and contact the hospital specialist:

WCC	$<3.7 \times 10^9$/L
Neutrophils	$<1.7 \times 10^9$/L
Platelets	$< 150 \times 10^9$/L
AST or ALT	> 3 times normal range

Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min
Unexplained reduction in albumin < 30g/L
Proteinuria/Blood >1+

MCV >100f/l continue medication but contact rheumatology for further advice

Also observe trends in results e.g. gradually decreasing white blood cell count. Contact rheumatology specialist for advice where persistent unexplained eosinophilia (eosinophils>0.5×10^9/L)

The patient should be counselled to report any sore throat, fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness during treatment.

Adverse Drug Reactions

Mucocutaneous: Urticaria, erythematous rashes, pruritus, oral ulceration, skin pain, and alopecia.
Haematological: Neutropenia, thrombocytopenia, macrocytosis and rarely aplastic anaemia, folic acid deficiency.
Gastro-intestinal: Nausea, vomiting, taste disturbance, abdominal pain and diarrhoea.
Hepatic: Isolated minor rises in transaminases may occur. Withdrawal results in resolution and drug re-challenge can lead to recurrence. Persistent or rising levels of transaminases may indicate either hepatic necrosis or granulomatous hepatitis both of which have been reported with Sulfasalazine.
Renal: Proteinuria, crystalluria. Reduce the dose in renal impairment.
Pulmonary: Cough**,** Pneumonitis (extremely rare).
Conception: Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of the drug appears to reverse these effects within 2 to 3 months.
Drug induced lupus: In patients with photosensitivity drug induced lupus is a risk. (Note NSAIDs are known photosensitisers).
Other: Headaches, depression and irritability, severe pneumonitis (rare hypersensitivity reaction), and enteritis. Patients should be advised not to become pregnant or attempt to father a child for three months following cessation of treatment.
Infection: Opportunistic infections may occur. Infections can require early and vigorous treatment and may require sulfasalazine to be stopped until the infection is clear.
Psychiatric reactions: patients are advised to contact a doctor immediately if they experience new or worsening mental health problems (such as irrational thoughts, anxiety, hallucinations, and feeling confused or feeling depressed, including thoughts of self-harm or suicide). Family members or caregivers are also advised to be vigilant for these reactions and the need to seek medical advice if they occur.

Contraindications

Known sulphonamide allergy (absolute contraindication) or salicylate hypersensitivity
Patients with porphyria
Men whose partners are planning a pregnancy.
Patients with known photosensitivity and/or raised ANA.

Cautions

Sulfasalazine should not be given to patients with impaired hepatic function, impaired renal function or with blood dyscrasias, unless the potential benefit outweighs the risk.

Use with caution in patients with severe allergy or bronchial asthma.

Sulfasalazine may cause haemolytic anaemia, therefore use with caution in patients with G-6-PD deficiency.

Ensure adequate fluid intake during treatment to minimise the risk of crystalluria and kidney stone formation.

Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of the drug appears to reverse these effects within 2 to 3 months.

The specialist team advise that patients on sulfasalazine should stop medication if they have an infection that requires treatment with antibiotics or antiviral medication, or if they feel too unwell to work or confined to bed or house.

Pregnancy and breast feeding - where deemed appropriate continue in pregnancy, but combine with folic acid 5mg daily. Sulfasalazine and sulfapyridine are found in low levels in breast milk. Sulfasalazine is thought to be safe in breastfeeding a full term healthy infant.

Drug Interactions

Possibly interact with cardiac glycosides – reduce digoxin absorption
Azathioprine/mercaptopurine – bone marrow suppression, leucopenia
Sulphonamides and hypoglycaemic agents – increased risk hypoglycaemia

Shared Care Guideline

Mycophenolate Mofetil

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC[15] or BNF[4] for further prescribing information.

Indication
Mycophenolate is an immunosuppressant drug which has been shown to be of benefit in patients with Systemic Lupus Erythematosus and other connective tissue diseases.

Pharmacology
Mycophenolate is a reversible inhibitor of inosine monophosphate dehydrogenase. It inhibits purine synthesis, with potent cytostatic effects on both T- and B-lymphocytes. Following absorption mycophenolate is metabolised to its active metabolite MPA.

Dose[15]
In connective tissue disease starting dose 500mg at night week 1, 500mg twice daily week 2, 500mg morning and 1g night week 3 and then 1g twice a day. If there is gastric intolerance consider giving as 500mg four times a day. If indicated the dose may be increased to 1.5g twice a day (max 40mg/kg/day).

Renal impairment: If GFR <25ml/min commence on 250mg twice daily and gradually titrate, not exceeding 1g twice a day.

Monitoring
Baseline tests (To be undertaken by the Rheumatology specialists)

FBC, U&E, LFT, calculated GFR/creatinine clearance, serum albumin. Lipids and BP

Hepatitis B and C Varicella immune status (avoid if re-current herpes/shingles)

Consider Pregnancy Test

The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised

Routine tests
FBC,U+Es, LFTs calculated GFR/creatinine clearance, serum albumin to be undertaken at week one; then every two weeks until on a stable dose for 6 weeks; then monthly for three months. Then if stable, FBC, U+Es, LFTs calculated GFR/creatinine clearance, serum albumin should be monitored every three months. Also consider monitoring lipids.

Advise patients to report immediately any signs or symptoms of bone marrow suppression. Ask about rash, oral ulceration, sore throat, infections or evidence of bruising or bleeding at every review. If patients present with these symptoms perform an urgent blood test.
If any of the following occur, stop mycophenolate and contact the rheumatology specialists:

WCC < 3.7 x 10^9/L
Neutrophils <1.7 x 10^9/L
Platelets < 150 x 10^9/L
AST or ALT >3 times the upper limit of the normal range
Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min
Unexplained reduction in albumin < 30g/L

MCV >100f/l continue medication but contact rheumatology for further advice

Also observe trends in results e.g. gradually decreasing white blood cell count. Contact rheumatology specialist for advice where persistent unexplained eosinophilia (eosinophils >0.5x 10^9/L)

Adverse Drug Reactions

Psychiatric and CNS: agitation, confusional state, depression, anxiety, insomnia, convulsions, tremor, somnolence, paraesthesia.
Cardiac: tachycardia, hypotension, hypertension, vasodilation.
Haematological: Leucopenia, thrombocytopenia, anaemia, pancytopenia, leucocytosis.
Opportunistic infections may occur (bacterial, fungal, viral and protozoal), Infections can require early and vigorous treatment. Mycophenolate may need to be stopped until the infection is clear.
Gastro-intestinal: vomiting, diarrhoea, nausea, GI haemorrhage, peritonitis, ileus colitis, GI ulceration, gastritis, constipation, dyspepsia, flatulence, sepsis, gastrointestinal candidiasis.
Respiratory: pleural effusion, cough, dyspnoea, interstitial lung disease
Skin: skin cancer, benign neoplasm of skin, skin hypertrophy, acne, rash, alopecia.
Hepatic: derangement of LFT's, jaundice, hepatitis, hyperbilirubinaemia
Renal: urinary tract infections, renal impairment.
Other: electrolyte disturbance, anorexia, dizziness, headache, pyrexia, chills, oedema, malaise, asthenia, pain.

Pregnancy: women taking mycophenolate should not become pregnant as there is insufficient data on teratogenicity. Exclude pregnancy before starting treatment. Use highly effective contraception during therapy and for 6 weeks after stopping. Contact rheumatologist if patient considering conceiving or in case of pregnancy.

Breast feeding: breastfeeding is contraindicated in women taking mycophenolate, since it is excreted into breast milk.

Contraindications

Patients with a hypersensitivity to mycophenolate mofetil or mycophenolic acid

Cautions

Renal impairment

Use mycophenolate with extreme caution in patients with active serious GI disease.

Neoplasms: increased risk of developing lymphomas and other malignancies, particularly of the skin. Exposure to sunlight and UV light should be limited; patients should wear protective clothing and use a sunscreen with a high protection factor to minimise the risk of skin cancer and photosensitivity.

Drug Interactions

Aciclovir: Mycophenolate has been shown to increase plasma concentrations of Aciclovir when administered concurrently. Of clinical significant in patients with moderate to severe renal impairment.

Antacids and proton pump inhibitors (PPIs): Decreased mycophenolic acid (MPA) exposure when co-administered with antacids, such as magnesium and aluminium hydroxides, and PPIs, including lansoprazole and pantoprazole.

Cholestyramine: reduced absorption of mycophenolate.

Ganciclovir: mycophenolate possibly increases the plasma concentration of ganciclovir.

Rifampicin: decrease in active metabolite MPA exposure of 18% to 70%. May require monitoring and mycophenolate dose adjustment.

Sevelamer: plasma concentration of mycophenolate possibly reduced by sevelamer. Administer mycophenolate at least one hour before or three hours after sevelamer to minimise the impact on absorption of mycophenolate.

Norfloxacin and metronidazole: bioavailability of mycophenolate possibly reduced by norfloxacin and metronidazole particularly if administered together

Ciprofloxacin and co-amoxiclav: plasma concentration of mycophenolate possibly reduced by ciprofloxacin and co-amoxiclav.

Substances known to undergo renal tubular secretion may compete with mycophenolate, and raise plasma concentrations of either mycophenolate or the other substance undergoing tubular secretion.

Live vaccines: live vaccines should not be given due to impaired immune response. Antibody response to other vaccines may be reduced.

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Appendix A - Shared Care request form

Specialist to complete when requesting GP to enter a shared care arrangement.GP to return signed copy of form (**Fax back to 01226 435411**). Both parties should retain a signed copy of the form in the patient's record.

From (**Specialist**): _____ **To** (**GP**): _____

Patient details

Name: _____ ID Number: _____

Address:_____ DOB: _____

Diagnosed condition: _____

Drug Name and formulation	Dose	Date initiated

Subcutaneous Methotrexate brand patient initiated on:

☐ **Metoject®** ☐ **Nordimet®**

Monitoring: The following monitoring should be undertaken by the GP:

Parameter	Date next test due	Frequency

Communication:

Consultant
Telephone number: 01226 432387

Specialist Nurse
Telephone number: 01226 434960

Confirmation of acceptance/rejection of shared care

Specialist (Doctor/Nurse) name: _____

Specialist (Doctor/Nurse) signature: _____ Date: _____

I, Dr ……., can confirm I :

☐ accept the request to participate in shared care for the patient named above.

☐ reject the request to participate in shared care for the patient named above. The reason for this being ……..

GP signature: _____ Date: _____

To save resources you have been sent appendix A of the shared care document. The full document (**DMARDs** Shared Care Guideline for the prescribing of Disease modifying antirheumatic drugs (DMARDs) in rheumatology patients*)* can be accessed on the Barnsley BEST website at the following link: http://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/

Or via the Barnsley Area Formulary www.barnsleyformulary.nhs.uk

Appendix B
Recommendations for the storage, administration and disposal of subcutaneous methotrexate in the community

Statement of Purpose
Following training, most patients in the community will self-administer their methotrexate injections. These recommendations aim to provide information on safe handling of methotrexate

Storage
The patient should be advised regarding the safe and appropriate storage of the injections in accordance with manufacturer's guidance. The methotrexate injections must be stored below 25 degrees Celsius, out of the reach of children and pets and protected from light. There must be a cytotoxic waste bin at the site where injection will take place.

Administration
Methotrexate should not be administered by pregnant or breast feeding women. As methotrexate can cause blood dyscrasias and pulmonary toxicity, prior to administration the patient should consider if they have experienced breathlessness, a dry or productive cough, fever, mouth ulcers, nausea or any overt signs of infection. The injection should not be given and medical advice sought if any of these have occurred.

The Metoject® pre-filled pen or Nordimet® pre-filled pen instructions for administration should be followed.

Spillage
The risk of spillage is low due to the use of pre-filled pens and the small volumes used however:

- A cytotoxic (purple topped) waste bin should be available for disposal of any waste. If there is any surface leak out from the injection site, a little pressure should be applied to the area which should then be wiped using cotton wool or tissue and these should be disposed of in the purple topped box.
- If methotrexate comes in contact with the skin the area should be washed liberally with soap and cold water for several minutes
- If methotrexate enters the eyes, they should be irrigated thoroughly with large amounts of tap water for several minutes and medical advice sought if any side effects are experienced.

Disposal of cytotoxic waste
It is the prescriber's responsibility to ensure systems are in place to ensure safe disposal of any cytotoxic waste.

- All methotrexate pens, syringes, needles and gloves must be disposed of in a purple sharps container. For home use, these are prescribed on an FP10 as: Sharpsguard® (Daniels) 1 litre and 5 litre containers or Sharpsafe® (Frontier) 1 litre and 1.8 litre containers. The 1.8 litre Sharpsafe® bin or 1 litre and 5 litre Sharpsguard® bins are better able to accommodate the syringes/pens and needles. NB. Not all practice computer systems list the colour of the container and so prescribers may need to manually add the word 'purple' to the prescription to ensure a cytotoxic one is supplied.
- The sharps container should be kept closed until three quarters full when it should then be locked and disposed of in the correct way. Patients are able to keep their sharps bins for up to 3 months prior to disposal.
- Full sharps bins should be taken to the GP practice or to BHNFT (Rheumatology clinic when patients are attending for review) for disposal. Information regarding sharps bin disposal should be provided to the patient as part of the training process.

Note: There has been a change to how patients dispose of Sharps Bins. The 'drop boxes' for patients to dispose of sharps bins have been removed from LIFT buildings. This means that patients are no longer able to dispose of sharps bins at LIFT buildings. Practices should accept full sharps bins from their own patients and dispose of them in the same way they dispose of GP waste. SY ICB is looking at ways to support practices with this.

For current information please see the DMARD guideline holding page:
DMARDS - rheumatology / sharps bin Shared care guideline (barnsleyccg.nhs.uk)

Shared Care Protocol –remains open to review in light of any new evidence
***Amber**= To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care.*
***Please note:** Empty sharps bins must be prescribed by the GP on an FP10.*

References

- Metoject® summary of product characteristics (SPC) http://www.medicines.org.uk/emc/medicine/28982
- Nordimet® summary of product characteristics (SPC) http://www.medicines.org.uk/emc/medicine/33073

Appendix C

Safe Use of Methotrexate Oral Solution 2mg/ml (Jylamvo®)

- This formulation should be reserved for patients unable to take methotrexate tablets. An assessment should be made as to whether the patient is able to measure and understand the correct dose. Appropriate patient training should be given before prescribing is handed over to primary care.
- Each 1 ml of the solution contains 2 mg methotrexate. The 10ml oral syringe provided with the solution should be used to measure the dose to ensure accurate withdrawal of the required volume.
- The patient's ability to accurately measure the required dose should be discussed with every prescription.
- Patients should be reminded that the dose is **weekly**
- When prescribing Jylamvo® the dose should be expressed in mg (with the ml equivalence in brackets).
- After swallowing the dose the patient should drink some water to ensure that there is no methotrexate residue left in the mouth.
- Anyone handling methotrexate should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling methotrexate.
- Contact with the skin or mucous membrane must be avoided. If methotrexate comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.
- Spillages must be wiped immediately.
- The oral syringe should be washed immediately after use with fresh warm, soapy water and rinsed well in accordance with the manufacturer's instructions. All parts of the syringe should be completely dry before using it for the next dose.
- The oral solution should be stored below 25°C with the bottle kept tightly closed. The shelf life after first opening is 3 months
- Any unused medicinal product or waste material should be disposed of via purple cytotoxic/cytostatic pharmaceutical waste container: http://barnsleybest.nhs.sitekit.net/commissioning/Infection%20control/Infection%20Prevention%20and%20Control%20NHS%20Barnsley%20CCG.pdf
- To ensure the medicine is used correctly and reduce risk of medication errors all healthcare professionals who prescribe or dispense Jylamvo should famliarise themselves with the Guide for Healthcare professionals available at: https://www.medicines.org.uk/emc/rmm/1064/Document