

DMARDs

Shared care

prescribing

guidelines

Updated October 2024

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

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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.

The choice of DMARD should consider co-morbidity and patient preference.

DMARDs are initiated in secondary care and once the patient is stable, prescribing and monitoring may be transferred to primary care in line with the shared care guideline requirements for each specific drug in this guidance.

The National Patient Safety Agency published actions to reduce the risks associated with oral Methotrexate¹ 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 guideline¹.

Shared Care Guideline –remains open to review in light of any new evidence

Amber = *To be initiated and titrated to a stable dose by a specialist with follow up prescribing and monitoring by primary care under a shared care agreement.*

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 requested on ICE and being performed and the results are acted upon.

Patients should be stabilised in secondary care prior to referral to primary care management.
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Prescriber Responsibilities:

Secondary Care Team responsibilities

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol and communicated to primary care.
- Use a shared decision-making approach; to discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling to enable the patient to reach an informed decision. Obtain and document patient consent. Provide an appropriate patient information leaflet.
- Ensure the patient and/or carer understands the dosage regime and how to administer the medication.
- If prescribing subcutaneous methotrexate, ensure the patient/carers is trained to administer safely or liaise with primary care to arrange safe administration by a healthcare professional. If this is not possible the patient should remain under the care of the prescribing specialist. Ensure the patient has access to a purple sharps bin for disposal.
- Assess for contraindications and cautions and interactions.
- Perform baseline monitoring and any future monitoring until the patient is stabilised and transferred to shared care.
- GP's may be approached at 6 weeks to accept shared care if they are willing and able to do so, with a view to taking on the shared care at 3 months.
- Initiate and optimise treatment. Once treatment is optimised, complete the shared care documentation ([Appendix A](#)) and send to patient's GP practice detailing the diagnosis, current and ongoing dose and when the next monitoring is due. Include contact information and state when the patient will next be reviewed in secondary care.
- Patients prescribed Methotrexate Oral Solution (Jylamvo® 2 mg/ml oral solution) should receive adequate training in administration of the dose.
- Confirm that shared care arrangements are in place before transfer of treatment including 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.
 - The patient/carers is clear what is being monitored and by whom.
 - The patient knows what significant adverse effects/events to report urgently and to whom they should report (specialist or GP).
 - The patient is provided with enough medication to enable transfer from secondary care to primary care. Allowing time for the patient to order from surgery and pharmacy to procure the DMARD for collection by the patient.
- 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 and review the patient annually to ensure treatment is still appropriate.

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

Baseline Tests and routine tests

Baseline assessment should include height, weight, blood pressure and laboratory evaluation. See also information regarding updated British Society for Rheumatology Guidelines² (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.

Primary Care Team responsibilities

- The GP should reply to the shared care request within 14 days of the request being made if they are unable to accept the shared care request.
- If accepted, prescribe ongoing treatment as detailed in the specialists' request, taking into account potential drug interactions and as per each individual drug monograph below and ensure the patient/carer is fully informed about the treatment.
- Confirm that:
 - o The patient/carer is clear what is being monitored and by whom
 - o The patient knows what significant adverse effects/events to report urgently and to whom they should report them to. (Specialist or GP). The patient/carer has been provided with appropriate information sheet (s) for monitoring and/or to alert other clinical staff to the treatment they are receiving.
 - o The prescriber is aware of any changes that should trigger urgent referral back to secondary care specialist team.
- Check drug interactions with any new medication started or any new conditions diagnosed. Contact specialist team if possible interactions found and discuss with rheumatologist.
- Conduct the required monitoring as outlined in the specific drug monographs. and amend prescription as per requests from secondary care for dose changes in patients on established treatment.
- 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/> and discuss with the specialist clinical team as appropriate.
- 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.

3.0 Communication

Patient / Carer Responsibilities

- Take medications as per dosage instructions and avoid abrupt withdrawal.
- Attend regularly for monitoring and review appointments with primary care specialist and ensure contact details are up to date. Be aware that medicines may be stopped if they fail to attend.
- Ensure they discuss potential benefits, side effects and concerns with either specialist or GP and that they have a clear understanding of their treatment.
- 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
- Report any adverse effects to their specialist or GP whilst taking the medicine.
- Report the use of any over the counter (OTC) medications to their primary care prescriber and be aware they should discuss with their pharmacist before purchasing any OTC medicines.
- Always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed.

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 but within 14 days of receipt of the shared care documentation where practically 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

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 should be advised to contact their consultant either when planning a pregnancy or as soon as they become aware they are pregnant or 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

Undertake a post-exposure prophylaxis risk assessment.

Post exposure prophylaxis is recommended for individuals who fulfil all of the following criteria:

- significant exposure to chickenpox (varicella) or shingles (zoster) during the infectious period
- at increased risk of severe chickenpox such as immunosuppressed individuals, neonates and pregnant women
- no antibodies to varicella-zoster virus (VZV) – urgent VZV antibody testing can be performed within 24 hours

Further information can be found at:

<https://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles/guidelines-on-post-exposure-prophylaxis-pep-for-varicella-or-shingles-january-2023>

Immunisations

No live vaccine should be given to any immunosuppressed patient². 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.

The [shingles immunisation programme: information for health practitioners](#) and the green book ([chapter 28a](#)) provide advice and guidance about Varicella Zoster and vaccination eligibility. The Varicella-Zoster vaccine may be administered with methotrexate if the weekly MTX dose is 20mg or less.⁵

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 requirements² 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

Drug monitoring and responsibilities for monitoring are now included in each of the drug monographs.

Azathioprine

Background	Azathioprine is an immunosuppressant and 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.
Contraindications and cautions	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Known hypersensitivity to azathioprine. Hypersensitivity to 6-mercaptopurine should alert the prescriber to probable azathioprine hypersensitivity. • Severe infection. • Patients with active/history of pancreatitis. • Severely impaired hepatic or bone marrow function. • Absent or very low thiopurine methyltransferase (TPMT) activity – risk of life-threatening pancytopenia. <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Live vaccines (e.g. oral polio, oral typhoid, MMR, BCG, yellow fever): should be avoided in patients taking azathioprine at a dose greater than 3 mg/kg/day, Please refer to the Green Book Chapter 6 for current advice regarding the use of live vaccines in patients taking immune modulators. • Patients with low thiopurine methyltransferase (TPMT) activity are at increased risk of myelosuppression. Substantial dose reduction is generally required. • 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 and breast-feeding: See pregnancy and breast-feeding section below. • 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.
Initiation and ongoing dose regimen	<p>Azathioprine starting dose is generally 1-3mg/kg per day and should be adjusted in accordance with clinical response and haematological tolerance.</p> <p>If no improvement occurs within 3 months of treatment, consideration should be given to withdrawing Azathioprine.</p> <p>When a therapeutic response is achieved, consideration should be given to reducing to the minimum effective dose.</p> <p>Azathioprine is given orally in tablet form and should not be crushed or chewed.</p> <p>Azathioprine should be taken with or after food in divided doses if preferred. Analgesics and NSAIDs should be continued until a positive response is achieved.</p> <p>The high strength 75mg and 100mg tablets have been assigned a non-formulary grey classification due to safety concerns. Please note: The 25mg and 50mg strength azathioprine tablets have an amber traffic light classification in line with the respective shared care guideline. Doses should be prescribed using the 25mg and/or 50 mg strength tablets and prescribers are discouraged from prescribing half tablets. The total daily dose should be specified on all scripts.</p>

Pregnancy and Breast feeding	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Pregnancy</u> Women planning to become pregnant should not take azathioprine, unless the benefits are outweighed by the risks. Azathioprine should only be used during pregnancy following a careful assessment of risk versus benefit.</p> <p><u>Breast feeding</u> Women receiving azathioprine should avoid breastfeeding unless the benefits outweigh the potential risks, if a decision is made to breastfeed the breastfed infant should be closely monitored for signs of immunosuppression, leukopenia, thrombocytopenia, hepatotoxicity, pancreatitis and other symptoms of 6-mercaptopurine exposure.</p>
Interactions	<ul style="list-style-type: none"> • Allopurinol: Increased azathioprine toxicity. Reduce dose azathioprine by 75%. • ACE inhibitors: Increased risk of anaemia or leukopenia 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.
Monitoring	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care)</p> <ul style="list-style-type: none"> • Height and weight. • Blood pressure. • Full blood count. <p>Urea and Electrolytes (U&E)s, including calculated GFR/creatinine clearance and ALT or AST and serum albumin.</p> <ul style="list-style-type: none"> • 24-hour Urine creatinine if renal function in doubt. • Consider baseline TPMT (thiopurine methyl transferase). • Consider Hepatitis B and C; HIV, varicella zoster, Epstein Barr virus, cytomegalovirus. • Consider pregnancy test prior to initiation • Consider lung disease screening including tuberculosis. This should be undertaken on a case-by-case basis at the discretion of the clinician. • Confirm cervical screening is up to date. <p>Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g. pneumococcal, shingles, influenza, COVID-19). The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised.</p> <p><u>Routine monitoring</u> (Undertaken in secondary care, every 2 weeks until on a stable dose for 6 weeks and then monthly for up to 3 months, until transfer to shared care has been completed),</p> <ul style="list-style-type: none"> • FBC • U+Es

	<ul style="list-style-type: none"> • CrCl • LFTs and serum • 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. <p>Primary care monitoring (Once the transfer to shared care has been completed, monitoring should be undertaken every 3 months. Consider more frequent testing if higher dosage or if renal or hepatic impairment).</p> <ul style="list-style-type: none"> • FBC • U+Es • CrCl • LFTs and serum albumin • 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. See adverse effects management table for further information. <p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care, until the dose has been stable for 6 weeks, then revert to original schedule. Secondary care to prescribe and monitor during this time.</p>								
Adverse Drug Reactions	<p>Very common and common side effects include:</p> <ul style="list-style-type: none"> • Anorexia. • Psychiatric disorders: Affect lability. • Headache. • Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible. • Gastrointestinal disorders: abdominal pain, nausea. • Skin rash, pruritis. <p>There are many side effects listed as frequency not known. Please see SPC or BNF for full side effect information.</p> <p>Please report adverse reactions to the MHRA via the yellow card scheme: Yellow Card Making medicines and medical devices safer</p> <p>Adverse effects management</p> <table> <tr> <th>Result</th><th>Action for primary care</th></tr> <tr> <td> <ul style="list-style-type: none"> • WCC less than $3.7 \times 10^9/L$ • Lymphocytes less than $0.5 \times 10^9/L$ • Neutrophils less than $1.7 \times 10^9/L$ • Platelets less than $140 \times 10^9/L$ • Unexplained eosinophilia; greater than $0.5 \times 10^9/L$ • Unexplained fall in albumin; less than 30g/L </td><td>Withhold treatment and discuss with specialist</td></tr> <tr> <td>MCV > 105 fL</td><td>Consider interruption of treatment, but contact rheumatology for advice</td></tr> <tr> <td> Liver Function Tests ALT and/or AST > 100u/L And/or a sudden increase (e.g. doubling of baseline) </td><td> Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication. </td></tr> </table>	Result	Action for primary care	<ul style="list-style-type: none"> • WCC less than $3.7 \times 10^9/L$ • Lymphocytes less than $0.5 \times 10^9/L$ • Neutrophils less than $1.7 \times 10^9/L$ • Platelets less than $140 \times 10^9/L$ • Unexplained eosinophilia; greater than $0.5 \times 10^9/L$ • Unexplained fall in albumin; less than 30g/L 	Withhold treatment and discuss with specialist	MCV > 105 fL	Consider interruption of treatment, but contact rheumatology for advice	Liver Function Tests ALT and/or AST > 100u/L And/or a sudden increase (e.g. doubling of baseline)	Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.
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	Signs or symptoms of bone marrow suppression e.g. unexplained bleeding or bruising with or without sore throat, mouth ulcers.	Check FBC immediately and discuss with the specialist team. See haematological monitoring above.
	Acute infection	Check FBC and discuss with specialist team if needed.
	Gastrointestinal disorders Nausea	Review for reversible causes. Advise patient to take with food. If no improvement contact the specialist team.
	Suspected pancreatitis	Withhold and discuss with specialist team
<u>Advice to patients and carers</u>	<p>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</p> <p>The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:</p> <ul style="list-style-type: none"> • Signs or symptoms indicating haematological toxicity, e.g. sore throat, infection, unexplained or abnormal bruising or bleeding. • Signs or symptoms of pancreatitis, e.g. abdominal pain, nausea, or vomiting. • Signs of symptoms of hepatic toxicity, e.g. Jaundice (yellowing of the skin or whites of the eyes). <p>The patient should be advised to:</p> <ul style="list-style-type: none"> • That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended. • Tell anyone who prescribes them a medicine that they are taking azathioprine or mercaptopurine. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe. • Always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant. • All women aged 25-64 years old should be encouraged to participate in national cervical cancer screening programmes. There is no need to attend more frequently than recommended. • Patients have a small increased risk of skin cancers so should be advised to wear high factor sunscreen and to wear a hat and protective clothing when in strong sunshine. Sun beds should be avoided. Patients should be advised to carry out regular self-examination of the skin and report if there are any new lesions and/or changes to skin. . • Patients taking azathioprine at a dose of 3 mg/kg or more. should be advised to avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see: <ul style="list-style-type: none"> ○ the Green Book (Chapter 34). ○ UKSHA guidance: Guidelines on post exposure prophylaxis (PEP) for varicella/shingles April 2022 <p><u>Patient information</u> can be found at:</p> <p>https://www.nhs.uk/medicines/azathioprine/ https://patient.info/medicine/azathioprine-azapress-imuran https://www.medicines.org.uk/emc/search?q=azathioprine https://www.versusarthritis.org/about-arthritis/treatments/drugs/azathioprine/</p>	

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Ciclosporin

Background	<p>Ciclosporin is an immunosuppressive agent effective in the treatment of several conditions including rheumatoid arthritis.</p> <p>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).</p>
Cautions and Contraindications	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Known hypersensitivity to ciclosporin or any excipients. • Malignancy. • Uncontrolled hypertension. • Uncontrolled infection. • Concomitant use with St John's Wort, tacrolimus, or substrates for P-glycoprotein or organic anion transporter proteins e.g bosentan, dabigatran, alsikiren. <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Hepatic impairment- Ciclosporin may impair liver function. Dosage adjustment may be necessary. • Ciclosporin predisposes patients to the development of bacterial, fungal, parasitic and viral infections. • Elderly-monitor renal function closely. • Renal impairment- Concomitant administration of NSAIDs increases the risk of renal impairment. Patients should be closely monitored. • Hypertension- Regular monitoring of blood pressure is required during therapy with ciclosporin. • Hyperlipidaemia; ciclosporin may induce a small reversible increase in blood lipids. • Hyperkalaemia: the risk of hyperkalaemia is increased by ciclosporin treatment. • Hypomagnesaemia: ciclosporin increases magnesium excretion, therefore supplementation may be required. • Hyperuricaemia. • Vaccination may be less effective during treatment with ciclosporin. Live attenuated vaccines should be avoided. • Active herpes simplex infections. Allow infection to clear before starting and withdraw if severe infections occur during treatment. • Staphylococcus aureus skin infections. Not an absolute contraindication if infection is controlled but avoid erythromycin unless no other alternative. • Neurological Behçet's syndrome – monitor neurological status. • Lymphoproliferative disorders; discontinue treatment. • All oral dosage forms of ciclosporin contain a form of ethanol. • Due to the increased risk of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.
Initiation and ongoing dose regimen	<p>Transfer to primary care should not occur until dose titration is complete and the patient is stable on a maintenance dose.</p> <p><u>Dose</u></p> <p>Ciclosporin comes as an oral capsule in 10mg, 25mg, 50mg 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</p>

	<p>bioavailability. It is therefore important that ciclosporin is prescribed by brand so patients receive the same brand each time.</p> <p><i>Conditions requiring dose adjustment:</i></p> <ul style="list-style-type: none"> • In patients with nephrotic syndrome and impaired renal function the initial dose should not exceed 2.5 mg/kg/day. • Deteriorating renal function. • Elderly patients: dose selection should be cautious, and start at the low end of the dose.
Pregnancy and breast feeding	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Pregnancy</u> Ciclosporin crosses placenta and use in pregnancy is associated with premature birth and low birth weight. Patients should be advised not to become pregnant during treatment or for three months following cessation of treatment.</p> <p>Information for patients: https://www.medicinesinpregnancy.org/Medicine—pregnancy/Ciclosporin/</p> <p><u>Breast feeding</u> Ciclosporin is transferred into breast milk. Mothers receiving ciclosporin should not breast-feed because of the potential of ciclosporin to cause serious adverse drug reactions in breast-fed infants. A discussion with the patient and consultant is pertinent to help the patient make the decision to abstain from ciclosporin or abstain from breast-feeding, taking into account the benefit of breast-feeding for the newborn and the importance of the medicinal product to the mother.</p>
Interactions	<p>The following drugs increase ciclosporin serum levels:</p> <ul style="list-style-type: none"> • Macrolide antibiotics: erythromycin can increase ciclosporin exposure 4- to 7-fold and may result in nephrotoxicity. Clarithromycin and azithromycin also increases ciclosporin levels. • Grapefruit and grapefruit juice: predicted to increase ciclosporin exposure. • Danazol, diltiazem (at doses of 90 mg/day): may increase ciclosporin blood concentrations by up to 50%. • Digoxin, edoxaban: dose adjustment recommended; levels increased by ciclosporin. • Inhibitors of CYP3A4, P-glycoprotein, or OATP: may increase plasma levels of ciclosporin. Frequent assessment of renal function and careful monitoring for ciclosporin-related side effects may be required; seek specialist advice, e.g. nifedipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, cholic acid and derivatives, protease inhibitors, imatinib, nefazodone. • Doxycycline, tigecycline: may increase ciclosporin concentrations. Monitoring may be required. • Colchicine: levels of ciclosporin and colchicine may be increased. Close clinical observation for toxicity is recommended. • Potassium-sparing medicines, including potassium-sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), and potassium-containing medicines: may lead to significant increases in serum potassium. • Azole antimycotics (e.g. ketoconazole, fluconazole, itraconazole and voriconazole), verapamil, telaprevir: increase exposure to ciclosporin by at least 2-fold. • Aprepitant, netupitant: predicted to increase ciclosporin levels. Use caution.

	<ul style="list-style-type: none"> • Anti-cancer medicines: levels of either medicine may be altered, or risk of immunosuppression increased. • Amiodarone and dronedarone: increases ciclosporin levels. This interaction can occur for a long time after withdrawal of amiodarone, due to its very long half-life (about 50 days). Amiodarone increases serum creatinine. <p>The following drugs decrease ciclosporin serum levels:</p> <ul style="list-style-type: none"> • Inducers of CYP3A4, P-glycoprotein, or OATP: may reduce plasma levels of ciclosporin, e.g., barbiturates, carbamazepine, oxcarbazepine, phenytoin and fosphenytoin, primidone; nafcillin, intravenous sulfadimidine, probucol, orlistat, ticlopidine, sulfapyrazone, terbinafine, apalutamide, enzalutamide, lumacaftor, pitolisant. • Rifampicin: induces ciclosporin metabolism; ciclosporin doses may need to be increased 3- to 5-fold. • Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, intravenous sulfadimidine, probucol, orlistat, hypericum perforatum (St. John's wort), ticlopidine, sulfapyrazone, terbinafine, bosentan. <p>Other interactions:</p> <ul style="list-style-type: none"> • Statins, etoposide, repaglinide, ambrisentan: plasma levels may be increased by ciclosporin; close clinical observation for toxicity is recommended. Doses of statins should be reduced, and temporarily withheld or discontinued if patients develop signs and symptoms of myopathy or have risk factors for severe renal injury secondary to rhabdomyolysis. Avoid simvastatin and rosuvastatin. • Nephrotoxic drugs, e.g. aminoglycosides (including gentamicin, tobramycin), colistimethate, amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); fibric acid derivatives (e.g. bezafibrate, fenofibrate); non-steroidal anti-inflammatory drugs (NSAIDs, including diclofenac, naproxen, sulindac); melphalan, histamine H2-receptor antagonists (e.g. cimetidine, ranitidine); methotrexate: may have synergistic effects; close monitoring of renal function is recommended. . • Ticagrelor: exposure increased by ciclosporin. Use with caution or avoid. • Lercanidipine: exposure increased by ciclosporin, avoid or use with caution and separate doses by at least 3 hours. . • Nifedipine: increased risk of gingival hyperplasia. . • Caspofungin: exposure increased by ciclosporin. Liver monitoring recommended. . • Anti-cancer medicines: levels of either medicine may be altered, or risk of immunosuppression increased. • Rifaximin: levels markedly increased by ciclosporin. Caution advised. . • Octreotide, pasireotide, lanreotide: decreases oral absorption of ciclosporin; increase in the ciclosporin dose or a switch to intravenous administration could be necessary. . • Tacrolimus: risk of pharmacokinetic interaction and nephrotoxicity. Avoid. • Everolimus and sirolimus: ciclosporin increases levels of both drugs, and may increase serum creatinine. . • Baricitinib, filgotinib, tofacitinib: Increased risk of immunosuppression • Ritonavir: close monitoring advised, ciclosporin dose adjustment may be needed. .
Monitoring	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care)</p> <ul style="list-style-type: none"> • FBC. • U&Es. • LFTs. • Creatinine/ calculated GFR, serum albumin and serum folate. • Weight. • HbA1c.

	<ul style="list-style-type: none"> • Height and Blood pressure. • Assess for co-morbidities. • Serum lipids and uric acid. • Serum magnesium. • Consider pregnancy test if appropriate in women of child-bearing age. • Screening for HIV, hepatitis B and C. • Screening for lung disease (including tuberculosis) should be considered on a case-by-case basis. <p><i>The rheumatology specialist will assess and monitor the patient's response to treatment until the patient has been stabilised on a dose for 4 weeks or more.</i></p> <p><u>Routine monitoring</u> (Undertaken in secondary care, every 2 weeks until on a stable dose for 6 weeks and then monthly for up to 3 months or until transfer to shared care has been completed),</p> <ul style="list-style-type: none"> • FBC. • U+Es. • BP. <p>Calculated GFR, LFTs and serum albumin frequent monitoring is appropriate in patients with higher risk of toxicity. Monitoring of ciclosporin levels would normally be undertaken by the specialist.</p> <p><u>Primary care monitoring</u> (Once the transfer to shared care has been completed, monitoring should be undertaken every 3 months).</p> <ul style="list-style-type: none"> • FBC. • U and E. • BP. • HbA1c. • ALT and AST, albumin and bilirubin- frequency as dictated by secondary care. • Serum lipids, uric acid and magnesium- every 6 months. • Shingles vaccine (age 70-79), influenza vaccine, other vaccination as per national schedule. <p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care, until the dose has been stable for 6 weeks, then revert to original schedule. Secondary care to prescribe and monitor during this time</p>
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Adverse Drug Reactions	<p>Very common and common side effects include:</p> <ul style="list-style-type: none"> • Leukopenia, • Metabolism and nutritional disorders – Hyperlipidaemia, Hyperglycaemia, anorexia, hyperuricaemia, • Nervous system disorders – Tremor, headache, convulsions, paraesthesia, • Hypertension, • Gastrointestinal disorders – Nausea, vomiting, abdominal discomfort/pain, • Abnormal hepatic function, • Skin and soft tissue disorders – Hirsutism, Acne, hypertrichosis, • Musculoskeletal – Myalgia, muscle cramps, • Renal dysfunction, • Pyrexia, fatigue at administration site. <p>Please see SPC or BNF for full side effect information.</p> <p>Please report adverse reactions to the MHRA via the yellow card scheme: www.mhra.gov.uk/yellowcard</p> <p>If patients present with symptoms of potential adverse effects perform an urgent blood test.</p> <table border="1"> <thead> <tr> <th colspan="2">Adverse effects management</th></tr> <tr> <th>Result</th><th>Action for primary care</th></tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> • WCC less than 3.5 x10⁹/L • Lymphocytes less than 0.5 x10⁹/L • Neutrophils less than 1.6 x10⁹/L • Platelets less than 140 x10⁹/L • Unexplained eosinophilia; greater than 0.5x10⁹/L • Unexplained fall in albumin; less than 30g/L </td><td>Withhold treatment and discuss with specialist</td></tr> <tr> <td>MCV>105 fL</td><td>Consider interruption of treatment, but contact rheumatology for advice</td></tr> <tr> <td> Liver Function Tests ALT and/or AST>100u/L And/or a sudden increase (e.g. doubling of baseline) Jaundice </td><td> Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication. </td></tr> <tr> <td> Renal function Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min </td><td>Withhold and discuss with specialist</td></tr> <tr> <td>Signs or symptoms of bone marrow suppression e.g. unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers</td><td> Check FBC immediately and withhold treatment whilst awaiting results. Discuss with specialist teams </td></tr> <tr> <td>Acute infection</td><td>During serious infections (e.g. requiring intravenous antibiotics or hospitalisation) temporarily withhold ciclosporin until the patient has recovered. Consider</td></tr> </tbody> </table>	Adverse effects management		Result	Action for primary care	<ul style="list-style-type: none"> • WCC less than 3.5 x10⁹/L • Lymphocytes less than 0.5 x10⁹/L • Neutrophils less than 1.6 x10⁹/L • Platelets less than 140 x10⁹/L • Unexplained eosinophilia; greater than 0.5x10⁹/L • Unexplained fall in albumin; less than 30g/L 	Withhold treatment and discuss with specialist	MCV>105 fL	Consider interruption of treatment, but contact rheumatology for advice	Liver Function Tests ALT and/or AST>100u/L And/or a sudden increase (e.g. doubling of baseline) Jaundice	Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.	Renal function Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min	Withhold and discuss with specialist	Signs or symptoms of bone marrow suppression e.g. unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers	Check FBC immediately and withhold treatment whilst awaiting results. Discuss with specialist teams	Acute infection	During serious infections (e.g. requiring intravenous antibiotics or hospitalisation) temporarily withhold ciclosporin until the patient has recovered. Consider
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		additional investigations (e.g. FBC), if clinically appropriate.
	Hyperkalaemia	Review other medicines affecting potassium levels e.g. ACE inhibitors, diuretics. Discuss with specialist.
	Elevated uric acid	If intended to treat as gout, discuss with specialist team due to the potential for interaction of urate-lowering medicines with ciclosporin.
	Hyperlipidaemia	Discuss with specialist. Reduction in ciclosporin may be required.
	Gum hypertrophy	Discuss with specialist
Advice to patients and carers	<p>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</p> <p>The patient should be advised to report any of the following signs and symptoms to their GP without delay:</p> <ul style="list-style-type: none"> • Symptoms of chickenpox or contact with a person with chickenpox or shingles. • Sore throat, high temperature, skin rash, swollen glands, or any other signs or symptoms of infection. • Signs or symptoms of liver problems, such as yellow skin or eyes (jaundice), itching all over, nausea or vomiting. • Unexplained bleeding or bruising, black stools, or blood in the vomit or stools. • Seizures, confusion, disorientation, visual disturbance • Gum swelling or growth (gingival hyperplasia) • Suspected or confirmed pregnancy. <p>Advise the patient:</p> <ul style="list-style-type: none"> • More frequent drinks of water are necessary when the ciclosporin dose is increased, or concomitant treatment with a NSAID is initiated or the NSAID dose is increased. • To always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes pregnant or wishes to become pregnant. • Tell anyone who prescribes them a medicine that they are taking ciclosporin. • Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe. • That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended. • To avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is 	

	<p>exposed, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see:</p> <ul style="list-style-type: none">○ the Green Book (Chapter 34).○ UKHSA Guidance: Guidelines on post exposure prophylaxis (PEP) for varicella/shingles. <ul style="list-style-type: none">• Patients have a small increased risk of skin cancers so should be advised to wear high factor sunscreen and to wear a hat and protective clothing when in strong sunshine. Sun beds should be avoided. Patients should be advised to carry out regular self-examination of the skin and report if there are any new lesions and/or changes to skin.• All oral dosage forms of ciclosporin contain a form of ethanol, a 500mg dose is the equivalent of up to approximately 15 ml beer or 6 ml wine.• To maintain good oral hygiene, to reduce the risk of gum swelling. <p>Patient information can be found at: https://patient.info/medicine (Search for brand of ciclosporin prescribed) https://www.versusarthritis.org/about-arthritis/treatments/drugs/disease-modifying-anti-rheumatic-drugs-dmards/</p>
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Hydroxychloroquine

Background	<p>Hydroxychloroquine is an antimalarial drug licensed for the treatment of active rheumatoid arthritis but is also used in the management of connective tissue disease.</p> <p>Hydroxychloroquine is licensed for the treatment of active rheumatoid arthritis.</p>
Cautions and Contraindications	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Hypersensitivity to hydroxychloroquine or 4-aminoquinoline compounds • Pre-existing maculopathy of the eye. <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Concurrent use of medicines which may cause adverse ocular or skin reactions. • Diabetes mellitus, and those taking anti-diabetic drugs (including SGLT-2 inhibitors) for any indication (hydroxychloroquine treatment may lower blood glucose. Hypoglycaemia may be severe with loss of consciousness). • Glucose-6-phosphate dehydrogenase deficiency. • Increased risk of retinopathy with high doses (>5 mg/kg/day), long-term treatment (>5 years), • eGFR <60 mL/min/1.73m² or concurrent tamoxifen use. • Myasthenia gravis or psoriasis (may exacerbate). • Porphyria cutanea tarda, and other acute porphyrias. • Renal or hepatic disease and concurrent use of drugs known to affect these organs. • Sensitivity to quinine. • Severe gastrointestinal, neurological (especially for those with a history of epilepsy – may lower the seizure threshold), or blood disorders. • Significant cardiac arrhythmias due to the risk of QT interval prolongation.
Initiation and ongoing dose regimen	<p><u>Initiation dose:</u> The minimum effective dose should be employed. 200mg to 400mg daily. Usually started at a dose of 200mg daily to 200mg twice daily for the first 3 months then reduced to 200mg daily as a maintenance dose if effective.</p> <p><u>Maintenance dose:</u> Maintenance should be 200mg daily but may be increased to 400mg if response lessens. Dose should not exceed 5mg/kg/day (based on lean body weight, not actual body weight) due to the risk of toxicity.</p> <p>Treatment should be discontinued if no improvement in 6 months.</p>
Pregnancy and breast feeding	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Pregnancy</u> Hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. If treatment with hydroxychloroquine is necessary during pregnancy, the lowest effective dose should be used.</p> <p>In case of prolonged treatment during pregnancy, hydroxychloroquine safety profile in particular ophthalmological side effects should be taken into account for child monitoring.</p> <p><u>Breast feeding</u> Hydroxychloroquine is excreted in breast milk (less than 2% of the maternal dose after bodyweight correction).</p>

	There are very limited data on the safety in the breastfed infant during hydroxychloroquine long- term treatment; the prescriber should assess the potential risks and benefits of use during breastfeeding, according to indication and duration of treatment.
Interactions	<ul style="list-style-type: none"> • Drugs that can prolong the QT interval: for example, amiodarone, moxifloxacin, quinine, citalopram. Avoid concomitant use; possible increased risk of QT prolongation/ventricular arrhythmias. • Cimetidine: possible increase in plasma concentration of hydroxychloroquine. • Antidiabetic drugs and/or insulin: hypoglycaemic effect may be enhanced, may need dose adjustment of antidiabetic medication (reduction in insulin dose). • Tamoxifen: increased risk of retinal toxicity, necessitates annual ophthalmic monitoring. • Drugs affecting the convulsive threshold: Hydroxychloroquine can lower convulsive threshold. Co-administration of hydroxychloroquine with e.g. mefloquine may increase the risk of convulsions. • Neostigmine and pyridostigmine: effects may be antagonised by hydroxychloroquine. • Ciclosporin: possible increase in plasma concentration of ciclosporin (combination used by some specialists). • Digoxin: possible increase in plasma concentration of digoxin. Monitor serum digoxin levels closely. Penicillamine: possible increased risk of haematological toxicity. • Antiepileptics: activity of antiepileptic drugs may be impaired with hydroxychloroquine. Additionally, hydroxychloroquine may lower the seizure threshold. • Antacids and calcium carbonate-containing supplements: may reduce absorption of hydroxychloroquine; separate administration by at least four hours. Other calcium salts do not appear to interact. • Intra-dermal rabies vaccine: possible reduced antibody response. • Topiramate – increased risk of toxicity when co-administered with valproate, monitor for signs and symptoms of encephalopathy or hyperammonaemia.
Monitoring	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care)</p> <ul style="list-style-type: none"> • Full blood count (FBC) • Urea and electrolytes (U&E), including calculated GFR/creatinine clearance, serum albumin. • Height and weight. • Blood pressure. • ECG if concerns exist regarding the QT interval within the first year of treatment with hydroxychloroquine all patients will have an ophthalmological examination. The specialist team will refer patients to the ophthalmology clinic for this. The examination will include testing visual acuity, careful ophthalmoscopy, fundoscopy, central visual field testing with a red target, and colour vision. Baseline retinal screening using optical coherence tomography (OCT) will also be performed within 1 year of starting therapy and then annually if hydroxychloroquine is continued for >5 years or where doses of ≥400mg/day are used. <p><u>Patients are expected to have annual optician reviews in years 1-4. (Patient to organise themselves). At 5 years the specialist will refer again to ophthalmology clinic for yearly follow up including OCT.</u></p> <p>The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised.</p> <p><u>Routine monitoring</u> (Undertaken in secondary care).</p> <ul style="list-style-type: none"> • No routine ongoing laboratory testing is required. • The specialist will retain the responsibility for monitoring the patient's ongoing response to treatment and advise if a dose change or treatment

	<p>cessation is appropriate. This would usually be in annual review with the specialist.</p> <p>Primary care monitoring</p> <ul style="list-style-type: none"> • Annual renal function for all patients (particularly important for those with renal impairment, diabetes, hypertension or aged over 70yrs). • <u>Ensure the patient organises a standard eye test in years 1,2 ,3 and 4.</u> • Reminder to specialist when the patient is approaching 5 years of treatment (or 1yr in patients with increased risk factors e.g concomitant tamoxifen usage; impaired renal function <60ml/min) to organise ophthalmology clinic appointment. • Patients aged 70-79 years could be eligible for the shingles vaccine (herpes zoster). See The Green book for more information. • Annual influenza vaccine. • COVID-19 vaccine 												
Adverse Drug Reactions	<p>Very common and common side effects include:</p> <ul style="list-style-type: none"> • Anorexia. • Psychiatric disorders: Affect lability. • Headache. • Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible. • Gastrointestinal disorders: abdominal pain, nausea. • Skin rash, pruritis. <p>There are many side effects listed as frequency not known. Please see SPC or BNF for full side effect information.</p> <p>Please report adverse reactions to the MHRA via the yellow card scheme: www.mhra.gov.uk/yellowcard</p> <table border="1"> <thead> <tr> <th colspan="2">Adverse effects management</th></tr> <tr> <th>Result</th><th>Action for primary care</th></tr> </thead> <tbody> <tr> <td>Retinopathy monitoring: possible or definite retinal toxicity</td><td> <p>Possible retinopathy: Consider whether withholding is in the best interests of the patient. Discuss with specialist. (See Royal college of ophthalmologists guidelines on managing possible retinopathy. https://www.rcophth.ac.uk/resources-listing/2609/).</p> <p>Definite retinopathy: primary care to ensure WITHOLD treatment and urgent discussion with specialist.</p> </td></tr> <tr> <td>Vision disturbances including blurred vision, changes in visual acuity or abnormal colour vision</td><td>Discuss with specialist team and refer to ophthalmology</td></tr> <tr> <td>Signs or symptoms of bone marrow suppression e.g. unexplained bleeding or bruising with or without sore throat, mouth ulcers.</td><td>Check FBC immediately and discuss with the specialist team. See haematological monitoring above.</td></tr> <tr> <td> <p>Infections</p> <p>Infection requiring antibiotics</p> <p>Recurrent or opportunistic infections</p> </td><td> <p>Temporarily withhold mycophenolate until the patient has recovered.</p> <p>Review for reversible causes. Withhold and discuss with specialist team.</p> </td></tr> </tbody> </table>	Adverse effects management		Result	Action for primary care	Retinopathy monitoring: possible or definite retinal toxicity	<p>Possible retinopathy: Consider whether withholding is in the best interests of the patient. Discuss with specialist. (See Royal college of ophthalmologists guidelines on managing possible retinopathy. https://www.rcophth.ac.uk/resources-listing/2609/).</p> <p>Definite retinopathy: primary care to ensure WITHOLD treatment and urgent discussion with specialist.</p>	Vision disturbances including blurred vision, changes in visual acuity or abnormal colour vision	Discuss with specialist team and refer to ophthalmology	Signs or symptoms of bone marrow suppression e.g. unexplained bleeding or bruising with or without sore throat, mouth ulcers.	Check FBC immediately and discuss with the specialist team. See haematological monitoring above.	<p>Infections</p> <p>Infection requiring antibiotics</p> <p>Recurrent or opportunistic infections</p>	<p>Temporarily withhold mycophenolate until the patient has recovered.</p> <p>Review for reversible causes. Withhold and discuss with specialist team.</p>
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	Exposure to chickenpox or shingles	Contact specialist team for advice. See the Green Book (chapter 34) for detailed advice on risk assessment and post exposure prophylaxis
	Gastrointestinal disorders Very common adverse effects include nausea and vomiting, abdominal cramps, diarrhoea and dyspepsia. GI ulceration, bleeding and perforation.	Review for reversible causes. Advise patient to take with food. If no improvement contact specialist team. Review for reversible causes. Withhold and discuss urgently with specialist team.
	Suspected pancreatitis	Withhold and discuss with specialist team
	Skin disorders Skin hypertrophy, acne, alopecia Rash	Review for reversible causes. Discuss with specialist team if symptoms become troublesome. Review for possible causes. If cause of rash thought to be hydroxychloroquine or immune-mediated, withhold and discuss with specialist team.
	Other <ul style="list-style-type: none"> Neurological symptoms, psychiatric disorders (inc rare cases of suicidal behaviour), sudden onset or worsening shortness of breath, cough or dyspnoea 	Review for reversible causes. Events have been noted in patients with no previous history of psychiatric disorders. (See SPC and BNF and PIL's).Withhold and discuss with specialist team.
	Suspicion of malignancy	Discuss with specialist team. Refer for diagnosis and treatment of malignancy.
	<p>Advice to patients and carers</p> <p><u>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</u></p> <p>The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:</p> <ul style="list-style-type: none"> Vision disturbances including blurred vision, changes in visual acuity or abnormal colour-vision. Signs or symptoms of bone marrow suppression, such as a sore throat, oral ulceration, abnormal bleeding or bruising, or other signs of infection. Rash. Muscle weakness. Symptoms of hypoglycaemia, including dizziness, weakness, or hunger. Actual or planned pregnancy or breastfeeding. <p>The patient should be advised:</p> <ul style="list-style-type: none"> Avoid over-the-counter and prescribed antacids for four hours before and after doses of hydroxychloroquine. A number of patients who take hydroxychloroquine may experience some loss of their peripheral and central vision. Patients who drive must inform the DVLA if their eyesight is affected. For further information see: https://www.gov.uk/driving-eyesight-rules That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended. Tell anyone who prescribes them a medicine that they are taking hydroxychloroquine. 	

	<ul style="list-style-type: none">• Always ask a pharmacist before purchasing any medicines over the counter, including herbal.• Book a standard eye test years 1- 4 with an optician. There may be a charge for this appointment.• 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.• To always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant. <p>Patient information can be found at: General information: https://patient.info/medicine/hydroxychloroquine-tablets-quinoric https://www.medicines.org.uk/emc/search?q=hydroxychloroquine Rheumatology: https://versusarthritis.org/about-arthritis/treatments/drugs/hydroxychloroquine/</p>
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Leflunomide

Background	Leflunomide is an effective treatment for inflammatory arthritis. It has a comparable efficacy and toxicity profile to methotrexate. Leflunomide's active metabolite A771726 is 99% protein bound and excreted equally in urine and faeces. It has a long half-life of approximately 2 weeks.
Cautions and Contraindications	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Hypersensitivity to leflunomide or any of the ingredients (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiform). • Patients with impairment of liver function or moderate to severe renal insufficiency. • Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome. • Patients with severe immunodeficiency states, e.g. AIDS. • Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. • Severe hypoproteinaemia. • Serious infection. • Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis. • Pregnancy and breastfeeding, or patients who are not using effective contraception during treatment. People of child-bearing potential should use effective contraception for up to 2 years after stopping treatment. Avoid where possible in people of child-bearing potential. <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Anaemia: avoid if significant and due to causes other than rheumatoid or psoriatic arthritis. • Localised or systemic infection which may be more severe. • History of HIV, tuberculosis, hepatitis B or C. • Impaired bone-marrow function, leucopenia, or thrombocytopenia: avoid if significant and due to causes other than rheumatoid or psoriatic arthritis. • Use of concurrent haematotoxic or hepatotoxic DMARDs e.g. methotrexate. <p>There is a theoretical risk of male-mediated foetal toxicity so effective contraception should be used throughout treatment. Those patients wishing to father a child should discuss with the specialist who may want to follow the washout procedure before attempting conception. Patients of uncertain alcohol intake or who take other hepatotoxic drugs warrant extra vigilance.</p>
Initiation and ongoing dose regimen	<p>Dose (Leflunomide is usually considered for patients with active rheumatoid arthritis or psoriatic arthritis where methotrexate and sulfasalazine have been ineffective)</p> <p>Women of childbearing age must undergo a pregnancy test prior to starting leflunomide.</p> <p><u>Initial stabilisation dose</u> Initial dose of 10-20mg daily. The loading period will be prescribed by the specialist and 100mg loading dose is not recommended as this increases the risk of adverse effects.</p> <p><u>Maintenance dose (following initial stabilisation).</u> Due to the very long half-life, doses of 10mg and 20mg may be given on alternate days.</p>
Pregnancy and breast feeding	The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.

	<p>Pregnancy Leflunomide is contra-indicated in pregnancy. Women of childbearing potential must use effective contraception during and up to 2 years after treatment or up to 11 days after treatment if a washout is performed. (See SPC section 4.6 for further information)</p> <p><u>The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the consultant immediately for pregnancy testing, and if positive, the consultant and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of the active metabolite, by instituting the drug elimination procedure described below, at the first delay of menses may decrease the risk to the foetus from leflunomide.</u></p> <p>Breast feeding Leflunomide or its metabolites pass to breast milk. Breast feeding women should not take leflunomide. The patient should contact the rheumatology specialist if they are considering conceiving or in cases of pregnancy.</p> <p>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</p>
Interactions	<ul style="list-style-type: none"> • Anticoagulants: The anticoagulant effect of vitamin K anticoagulants (e.g. warfarin) may be increased by leflunomide. Close INR monitoring and follow-up is recommended. • Live vaccines (e.g. oral polio, oral typhoid, MMR, BCG) should generally be avoided. There is evidence that doses at or below 20mg leflunomide, as either monotherapy or in combination with 20mg prednisolone per day or less, can safely receive live shingles vaccinations. Clinician discretion is advised. • JAK kinase inhibitors, e.g. baricitinib, filgotinib: due to the increased risk of immunosuppression. • Colestyramine and activated charcoal: Co-administration leads to a rapid and significant decrease in plasma levels of leflunomide metabolites by interrupting enterohepatic recirculation. Leflunomide may increase the risk of exposure to these products: Repaglinide, paclitaxel, pioglitazone, cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, zidovudine, venetoclax. • Rosuvastatin levels may be increased by leflunomide. A maximum rosuvastatin dose of 10mg is recommended. Caution is recommended with other statins and dose reduction may be required. • 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, phenprocoumon and tolbutamide <p>Please check SPC section 4.5 for full interactions list.</p>
Monitoring	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care) Pregnancy should be excluded prior to commencing treatment.</p> <ul style="list-style-type: none"> • FBC. • U&Es. • LFTs. • Creatinine/ calculated GFR, serum albumin and serum folate. • Weight and weight. • Blood pressure. • Assess for co-morbidities. • Screening for viral infections e.g. HIV, hepatitis B and C, varicella zoster.

	<ul style="list-style-type: none"> Screening for lung disease (including tuberculosis) should be considered on a case-by-case basis. <p><i>The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised.</i></p> <p>Routine monitoring (Undertaken in secondary care, every 2 weeks until on a stable dose for 6 weeks and then monthly for 3 months until transfer to shared care has been completed),</p> <ul style="list-style-type: none"> FBC. U and E, including creatinine and CrCL. LFT's. Calculated GFR. AST and/or ALT, and albumin. <p><u>Following a dose change repeat every 2 weeks until the dose has been stable for 6 weeks.</u></p> <p>Primary care monitoring (Once the transfer to shared care has been completed, monitoring should be undertaken every 3 months).</p> <ul style="list-style-type: none"> FBC. U and E, including creatinine and CrCL. LFT's. Calculated GFR. AST and/or ALT, and albumin <p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care, until the dose has been stable for 6 weeks, then revert to original schedule. Secondary care to prescribe and monitor during this time.</p>						
<p>Adverse Drug Reactions</p>	<p>Very common and common side effects include:</p> <ul style="list-style-type: none"> Blood and lymph disorders: leukopenia. Immune system disorders: mild allergic reactions. Metabolism and nutritional disorders: CPK increased. Nervous system disorders: paraesthesia, headache, dizziness, peripheral neuropathy. Gastrointestinal disorders: diarrhoea, nausea, vomiting, oral mucosal disorders (e.g., aphthous stomatitis, mouth ulceration), abdominal pain, colitis including microscopic colitis such as lymphocytic colitis, collagenous colitis. Hepatobiliary disorders: elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin). Skin and subcutaneous tissue disorders: increased hair loss, eczema, rash (including maculopapular rash), pruritus, dry skin. General disorders: anorexia, weight loss (usually insignificant), asthenia. <p>Please see SPC or BNF for full side effect information, including rare side effects. Please report adverse reactions to the MHRA via the yellow card scheme: www.mhra.gov.uk/yellowcard</p> <table border="1" data-bbox="448 1727 1477 2047"> <thead> <tr> <th colspan="2">Adverse effects management</th></tr> <tr> <th>Result</th><th>Action for primary care</th></tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> WCC less than 3.7 x 10⁹/L Lymphocytes less than 0.5 x10⁹/L Neutrophils less than 1.6 x10⁹/L Platelets less than 120 x10⁹/L </td><td>Withhold treatment and discuss with specialist.</td></tr> </tbody> </table>	Adverse effects management		Result	Action for primary care	<ul style="list-style-type: none"> WCC less than 3.7 x 10⁹/L Lymphocytes less than 0.5 x10⁹/L Neutrophils less than 1.6 x10⁹/L Platelets less than 120 x10⁹/L 	Withhold treatment and discuss with specialist.
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	<ul style="list-style-type: none"> Unexplained eosinophilia; greater than $0.5 \times 10^9/L$ Unexplained fall in albumin; less than 30g/L 	
	Liver function tests AST or ALT elevated 2-3 times> than normal AST or ALT elevated >3 times normal	Withhold treatment and discuss with specialist team. Withhold treatment, consider washout and/or contact specialist team for advice.
	Renal function Creatinine increase of greater than 30% from baseline in the last 12 months or GFR reduces to less than 60mL/min	Withhold treatment and discuss with specialist team.
	Mean cell volume >105 fL	Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently Consider interruption in treatment. But contact rheumatology for advice.
	Blood pressure	Treat hypertension in line with NICE guidance. If BP remains uncontrolled, withhold leflunomide and discuss with specialist team
	Weight	If >10% weight loss with no cause identified, withhold leflunomide and discuss with specialist team.
	Signs or symptoms of bone marrow suppression, e.g. unexplained bleeding or bruising with or without sore throat, mouth ulcers	Check FBC immediately and discuss with the specialist team. See haematological monitoring above.
	Acute infection	During serious infections temporarily withhold leflunomide until the patient has recovered. Consider if additional investigations (e.g. FBC) and washout procedure required – discuss with specialist team
	Gastrointestinal disorders Nausea Diarrhoea	Review for reversible causes. Advise patient to take with food. If no improvement, discuss with specialist teams. Diarrhoea is common and usually settles. If persistent or severe, withhold and discuss with specialist team
	Ulcerative stomatitis, haematemesis, black or bloody stools, or suspected pancreatitis.	Withhold and discuss with specialist team. Washout, under specialist advice, may be required if severe
	Symptoms of interstitial lung disease persistent cough, dyspnoea, fever	If leflunomide-induced lung disease is suspected, discuss with specialist team urgently. Consider washout procedure if there is any delay in contacting specialist team.
	Other symptoms <ul style="list-style-type: none"> Skin rash 	

		<ul style="list-style-type: none"> Contact specialist team and consider washout if severe. 	
Advice to patients and carers	<p>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</p> <p>The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:</p> <ul style="list-style-type: none"> Symptoms of chickenpox or contact with a person with chickenpox or shingles. Persistent cough, shortness of breath, or any other problems with breathing. Sore throat, high temperature, skin rash, swollen glands, or any other signs or symptoms of infection Signs or symptoms of liver problems, such as yellow skin or eyes (jaundice), itching all over, nausea or vomiting. Unexplained bleeding or bruising, black stools, or blood in the vomit or stools. Suspected or confirmed pregnancy. Any tingling, numbness or weakness in extremities that may indicate peripheral neuropathy. <p>The patient should be advised:</p> <ul style="list-style-type: none"> Moderate their alcohol intake to no more than 4 units per week while taking leflunomide. Taking alcohol and leflunomide together increases the risk of liver injury. Tell anyone who prescribes them a medicine that they are taking leflunomide. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies and ask if they are safe. To always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant. The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant. <p>Remind patient to take half an hour before food or on an empty stomach.</p> <p><u>Patient information</u> can be found at: Leflunomide in rheumatoid arthritis: Leflunomide in rheumatoid arthritis (RA) NRAS Versus arthritis patient information. https://www.versusarthritis.org/about-arthritis/treatments/drugs/leflunomide/</p>		

Methotrexate

Background	<p>Methotrexate is used in the treatment of adults with severe, active, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy.</p> <p>Methotrexate inhibits the enzyme dihydrofolate reductase. Its main effect is the inhibition of RNA and protein synthesis. It is a folic acid antagonist and is classified as an antimetabolite cytotoxic agent.</p> <p>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.</p> <p>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</p>
Cautions and Contraindications	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Severe hepatic impairment. • Hypersensitivity to methotrexate or any of the excipients. • Severe renal impairment – CrCL less than 30ML/min. • Known active peptic ulceration. • Ascites or pleural effusion: drain prior to treatment to reduce the risk of methotrexate accumulation. • Severe infections (acute or chronic) or immunodeficiency syndromes. • Vaccination with live vaccines during treatment with methotrexate at immunosuppressive doses. • Concomitant use of medicines with anti-folate properties, e.g. trimethoprim, co-trimoxazole. • Liver disease including fibrosis, cirrhosis, recent or active hepatitis. • Pre-existing blood dyscrasias such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia. • 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. <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Renal impairment (if severe-see above): dose reduction required. • Alcohol dependence. • Hepatic impairment, particularly if due to alcohol use. • Respiratory disease. • Elderly patients (a lower dose should be considered). • Concomitant use with hepatotoxic or haematotoxic medicines. • History of chronic or recurrent infection (e.g. frequent infective COPD exacerbations, or recurrent urinary tract infection). • Conditions which increase the risk of dehydration (e.g. vomiting) may increase the risk of toxicity. Consider interrupting treatment until symptoms cease. • Women of childbearing age. Methotrexate is teratogenic. Advice use of contraception for at least 6 months after taking methotrexate.
Initiation and ongoing dose regimen	<p>Transfer of monitoring and prescribing to primary care is normally after the patient has been on a stable dose for a minimum of 6 weeks.</p> <p><u>Dose</u> <u>Oral tablets</u></p> <ul style="list-style-type: none"> • 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 oral dose for moderate to severe rheumatoid arthritis should not exceed a total weekly dose of 25mg.

	<ul style="list-style-type: none"> The prescriber should specify the day of intake on the prescription. <p><u>Oral solution</u> (reserved for patients unable to swallow methotrexate tablets)</p> <ul style="list-style-type: none"> 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 from healthcare professionals are available at: https://www.medicines.org.uk/emc/rmm/1064/Document 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. The oral dose for moderate to severe rheumatoid arthritis should not exceed a total weekly dose of 25mg. 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: <p><u>Sub-cutaneous methotrexate</u></p> <p>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.</p> <p>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. <u>Brand prescribing</u> is advised to ensure that the patient receives the device that they have been trained on.</p> <p>Patients will require prescribing a sharps bin (Sharpsguard 5L PURPLE bin) for safe disposal of subcutaneous injections. As methotrexate is cytotoxic a purple sharps bin should be prescribed. Please add directions to dosage to say, 'Please dispose of injection device in a cytotoxic drugs-PURPLE sharps bin'. The patient should be counselled by the initiating prescriber on safe disposal of injection devices. Barnsley council offer advice/services with regards to the disposal of clinical waste from patients' homes. Further information and contact details can be found on the Barnsley Metropolitan Borough Council website at Clinical waste (barnsley.gov.uk). Local discussion regarding the disposal of sharps bins are ongoing and additional information will be provided in due course.</p>
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	<p>Guidance for administering Metoject® pre-loaded pen can be found at: https://metojectathome.ie/wp-content/uploads/2021/01/Metoject-Patient-Information-Leaflet.pdf.</p> <p>See the instructions for use section.</p> <p>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</p> <p>SPC for Metoject® can be found at the following link: http://www.medicines.org.uk/emc/medicine/28982</p> <p>Guidance for administering Nordimet® can be found at: https://nordimet.co.uk/patient-support/support-for-adults/</p> <p>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</p> <p>SPC for Nordimet® can be found at the following link: http://www.medicines.org.uk/emc/medicine/33073</p> <p>Only those patients who can 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.</p>
Pregnancy and breast feeding	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Pregnancy</u> Effective contraception should be used by women and continued for at least 3 months after stopping treatment with methotrexate.</p> <p><u>Breast feeding</u> Contra-indicated in breast feeding.</p>
Interactions	<ul style="list-style-type: none"> Co-administration of medicinal products which cause folate deficiency (e.g. trimethoprim and co-trimoxazole) can lead to increased methotrexate toxicity and is contraindicated. Particular caution should therefore also be exercised in the presence of existing folic acid deficiency. 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. Leflunomide: increased risk of bone marrow and liver toxicity; increased monitoring and vigilance required. Ciclosporin: increased risk of nephrotoxicity and methotrexate toxicity. Drugs with hepatotoxic, haematotoxic or nephrotoxic effects: Increased frequency of monitoring may be recommended. Azathioprine and mercaptopurine: not advised due to increased risk of toxicity. Sulfasalazine: may increase risk of bone marrow and liver toxicity. However, this combination is used in clinical practice without incident. Be aware of trends in monitoring parameters. .

	<ul style="list-style-type: none"> • Live vaccines (e.g. oral polio, oral typhoid, MMR, BCG, Zostavax®) are advised in line with the national schedule for all patients, unless the patient is taking a dose of methotrexate or other immunosuppressive drug that exceeds those specified in the Green Book. Doses below this level are not considered sufficiently immunosuppressive and these patients can receive live vaccines. Clinician discretion is advised. Please refer to the Green Book Chapter 6 for current advice. • Avoid concomitant use of cytotoxics, clozapine, and olanzapine: increased risk of agranulocytosis. • Retinoids: increased risk of hepatotoxicity and may increase plasma levels of methotrexate. • Levetiracetam: may increase plasma levels of methotrexate. • Phenytoin: possible increased methotrexate toxicity, and decreased phenytoin effect. • NSAIDs, COX-2 inhibitors, aspirin: may reduce excretion of methotrexate, increasing risk of toxicity. These drugs are frequently used with methotrexate without incident, and aspirin at antiplatelet doses is unlikely to interact to a significant degree. Be aware of trends in monitoring parameters. • Theophylline and other methylxanthines: may reduce methotrexate efficacy. • Methotrexate may reduce theophylline clearance. • Anticonvulsants: may reduce methotrexate levels. • Colestyramine: may increase elimination of methotrexate. • Alcohol: consumption of alcohol increases the risk of hepatotoxicity. Patients should moderate their alcohol intake to no more than 14 units per week. • Azopropazone: excretion of methotrexate reduced. • Digoxin: absorption decreased by methotrexate. • PPI's. <p>Further information may be found in section 4.5 of the SPC</p>
<p>Monitoring</p>	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care)</p> <ul style="list-style-type: none"> • FBC, U&Es, LFTs, Creatinine/ calculated GFR, serum albumin and serum folate • Weight • Height and Blood pressure • Assess for co-morbidities. • Screening for HIV, hepatitis B and C. • Screening for lung disease (including tuberculosis) should be considered on a case-by-case basis. • Consider screening for pregnancy in women of childbearing age. <p>NPSA Methotrexate monitoring books and patient information should be supplied to all patients.</p> <p>The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised.</p> <p>Routine monitoring (Undertaken in secondary care, every 2 weeks until on a stable dose for 6 weeks and then monthly for up to 3 months until transfer to shared care has been completed),</p> <ul style="list-style-type: none"> • FBC. • U+Es (including CrCL). • ALT and/or AST and albumin. • CRP &/or ESR. <p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care until the dose has been stable for 6 weeks, then revert to 3 monthly.</p> <p>More frequent monitoring may be considered in patients with psoriatic arthritis, diabetes, obesity, uncertain alcohol intake or concomitant medication which may reduce the renal excretion of methotrexate.</p>

	<p>If patients present with symptoms of potential adverse effects stop methotrexate and perform an urgent blood test:</p> <p>Primary care monitoring (Once the transfer to shared care has been completed, monitoring should be undertaken every 3 months).</p> <ul style="list-style-type: none"> • FBC. • U+Es (including CrCL). • ALT and/or AST and albumin. • CRP &/or ESR. <p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care, until the dose has been stable for 6 weeks, then revert to original schedule. Secondary care to prescribe and monitor during this time.</p>												
Adverse Drug Reactions	<p>Very common and common side effects include:</p> <ul style="list-style-type: none"> • Infections (Respiratory or cutaneous bacterial). • Leukopenia. • Nervous system disorders: headache, dizziness, fatigue. • Gastrointestinal disorders: stomatitis, anorexia, nausea, vomiting, diarrhoea. • Hepatobiliary disorders: elevated transaminase concentrations (ASAT, ALAT). • Skin and subcutaneous tissue disorders: erythematous rash, alopecia. <p>There are numerous side effects where the frequency is stated as not known. Please see SPC or BNF for full side effect information.</p> <p>Please report adverse reactions to the MHRA via the yellow card scheme: www.mhra.gov.uk/yellowcard</p> <table border="1"> <thead> <tr> <th colspan="2">Adverse effects management</th></tr> <tr> <th>Result</th><th>Action for primary care</th></tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> • WCC less than 3.5 x10⁹/L • Lymphocytes less than 0.5 x10⁹/L • Neutrophils less than 1.6 x10⁹/L • Platelets less than 140 x10⁹/L • Unexplained eosinophilia; greater than 0.5x10⁹/L </td><td>Withhold treatment and discuss with specialist</td></tr> <tr> <td>MCV>100 fL</td><td>Continue treatment, but contact rheumatology for advice</td></tr> <tr> <td> Liver Function Tests ALT and/or AST>100u/L And/or a sudden increase (e.g. doubling of baseline) Jaundice </td><td> Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication. </td></tr> <tr> <td> Renal function Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min GFR 30-50 GFR < 30 ml/min </td><td> Discuss with specialist team. Methotrexate dose may be halved temporarily. Discuss with specialist team. Withhold and discuss with specialist team. </td></tr> </tbody> </table>	Adverse effects management		Result	Action for primary care	<ul style="list-style-type: none"> • WCC less than 3.5 x10⁹/L • Lymphocytes less than 0.5 x10⁹/L • Neutrophils less than 1.6 x10⁹/L • Platelets less than 140 x10⁹/L • Unexplained eosinophilia; greater than 0.5x10⁹/L 	Withhold treatment and discuss with specialist	MCV>100 fL	Continue treatment, but contact rheumatology for advice	Liver Function Tests ALT and/or AST>100u/L And/or a sudden increase (e.g. doubling of baseline) Jaundice	Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.	Renal function Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min GFR 30-50 GFR < 30 ml/min	Discuss with specialist team. Methotrexate dose may be halved temporarily. Discuss with specialist team. Withhold and discuss with specialist team.
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	Signs or symptoms of bone marrow suppression e.g unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers	Check FBC immediately and withhold treatment whilst awaiting results. Discuss with specialist teams
	Acute infection Infections requiring antibiotics	Temporarily withhold methotrexate until the patient has recovered. Consider additional investigations (e.g. FBC), if clinically appropriate.
	Gastrointestinal disorders Nausea, vomiting, diarrhoea, unintentional weight loss	Review for reversible causes. Enquire which day of the week the patient takes methotrexate and which day they take folic acid and review dosing schedule.
	Symptoms of interstitial lung disease e.g persistent cough, dyspnoea, fever	If methotrexate induced lung disease is suspected, withhold treatment and discuss with specialist team urgently.
	Other symptoms <ul style="list-style-type: none"> • Skin rash • Diffuse alopecia • Breathlessness/cough • Peripheral neuropath 	Consider withholding treatment and discussing with specialist.
Advice to patients and carers	<p>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</p> <p>The patient should be advised to report any of the following signs or symptoms without delay:</p> <ul style="list-style-type: none"> • Symptoms of chickenpox or contact with a person that has chickenpox or shingles. • New or increasing symptoms of Cough, fever, breathlessness • Sore throat, mouth ulcers rash or any other signs of infection. • Signs or symptoms of liver problems, such as jaundice (yellow skin), itching all over, nausea or vomiting. • Swelling of the hands, feet or ankles • Unexplained bruising, black stools, or blood in the vomit or stools. <p>The patient or carer should be advised:</p> <ul style="list-style-type: none"> • What shared care means for their treatment, what to expect, and their responsibilities under shared care. • Methotrexate is taken once weekly on the same day each week. • Methotrexate should be swallowed whole (not crushed or chewed) and taken with or after food. • If a patient thinks they have taken too much methotrexate they should immediately seek advice from their prescriber, or NHS 111. • Patients will only ever be prescribed methotrexate 2.5 mg tablets. • Which day or days they should take their folic acid, with emphasis that methotrexate and folic acid should not be taken on the same day. . • Moderate their alcohol intake to no more than 14 units per week while taking methotrexate. More information can be found at https://www.nhs.uk/live-well/alcohol-support/calculating-alcohol-units/. Taking alcohol and methotrexate together increases the risk of liver injury. . • Tell anyone who prescribes them a medicine that they are taking methotrexate. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe. . • Skin may be more sensitive to exposure to UV light while taking methotrexate. If this occurs use appropriate self-care: e.g. sun avoidance, protective clothing, 	

	<p>avoiding tanning (including tanning beds) and to purchase and use a broad spectrum sunscreen (at least SPF30). ·</p> <ul style="list-style-type: none"> • To always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant. • Not to drive or operate heavy machinery if methotrexate affects their ability to do so safely, e.g. due to fatigue or dizziness. · • That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended. • Carers should wear single-use gloves to handle the methotrexate tablets. Anyone handling the tablets should wash their hands afterwards. • For patients taking 20mg/week or more: to avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see: the Green Book (Chapter 34) or the UKSHA guidance: Guidelines on post-exposure prophylaxis (PEP) for varicella/shingles April 2022 / <p>Patient information can be found at: https://www.nhs.uk/medicines/methotrexate/ https://patient.info/medicine/methotrexate-maxtrex-metoject-2 (note covers tablets and injections) https://www.versusarthritis.org/about-arthritis/treatments/drugs/methotrexate/</p>
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Mycophenolate

Background	<p>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.</p> <p>Mycophenolate is an immunosuppressant drug which has been shown to be of benefit in patients with rheumatoid arthritis, systemic Lupus Erythematosus and other connective tissue diseases.</p>
Cautions and Contraindications	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Hypersensitivity to mycophenolate mofetil or any excipients. • Pregnancy or breastfeeding. <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Localised or systemic infection. • Very frail or elderly patients. • Patients with suspected lymphoproliferative disorder. • Patients with unexplained anaemia, leukopenia or thrombocytopenia. • Active gastrointestinal disease. • Live vaccines (e.g. oral polio, oral typhoid, MMR, BCG, yellow fever): should usually be avoided in patients taking mycophenolate. Live shingles vaccine should be avoided in patients taking mycophenolate 1g/day or more, or lower doses together with prednisolone 7.5 mg/day or more. Please refer to the Green Book Chapter 6 (cautions and contraindications), together with chapters for the specific vaccine under consideration, for current advice. A non-live vaccine can still be used. Contact the specialist if further guidance is required. • Dose reduction or discontinuation should be considered for patients in cases of clinically significant COVID-19. • As there is a potential increased risk of malignancy, any pre-malignant disease should be adequately treated before starting therapy and patients should be up to date with relevant national cancer screening programmes. • Due to the increased risk of skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. • Avoid if previous hepatitis B or C infection, or recurrent shingles. • Marked renal failure (eGFR below 25 mL/min). • Paternal exposure. Limited evidence does not indicate an increased risk of malformations or miscarriages in pregnancies where the father is taking mycophenolate. However, mycophenolate is genotoxic and the risk cannot be fully excluded. It is therefore recommended that male patients or their female partners use reliable contraception during treatment, and for at least 90 days after stopping mycophenolate. See MHRA Drug Safety Update: Mycophenolate mofetil, mycophenolic acid, updated contraception advice for male patients (Feb 2018) • Patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate. <p>In addition, the MHRA have also issued the following Drug Safety Updates for mycophenolate:</p> <p>Mycophenolate mofetil: pure red cell aplasia (Dec 2014)</p> <p>Mycophenolate mofetil (CellCept) and mycophenolic acid: risk of hypogammaglobulinaemia and risk of bronchiectasis (Jan 2015)</p>
Initiation and ongoing dose regimen	<p>Dose to be determined by the specialist based on indications and severity. 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</p>

	<p>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).</p> <p>Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 gram, but unnecessary switching should be avoided, due to pharmacokinetic differences. Switches should only be performed by, or with the advice of, the specialist team. Mycophenolic acid should usually be reserved for patients who do not tolerate mycophenolate mofetil.</p> <p>Renal impairment: If GFR <25ml/min commence on 250mg twice daily and gradually titrate, not exceeding 1g twice a day.</p>
Pregnancy and breast feeding	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Pregnancy</u> Mycophenolate mofetil should not be used during pregnancy A pregnancy test should be performed prior to initiation of mycophenolate.</p> <p><u>Breast feeding</u> Breastfeeding is contraindicated in women taking mycophenolate, since it is excreted into breast milk.</p>
Interactions	<ul style="list-style-type: none"> • 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. • Further immunosuppression e.g. azathioprine, ciclosporin, sirolimus: increased risk of bone marrow suppression. • Cholestyramine: reduced absorption of mycophenolate. • Ciclosporin: reduced mycophenolate exposure. • Ganciclovir: mycophenolate possibly increases the plasma concentration of ganciclovir. • Telmisartan: may reduce mycophenolate exposure. • Isavuconazole: possible increased risk of mycophenolate adverse effects due to increase exposure to mycophenolate or its metabolite. • Live vaccines: Increased risk of generalised infection. Consult the green book for the most up to date advice. • 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.
Monitoring	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care)</p> <ul style="list-style-type: none"> • Full blood count (FBC) • Urea and electrolytes (U&E), including calculated GFR/creatinine clearance, serum albumin • Height and weight

	<ul style="list-style-type: none"> • Blood pressure • Screening for viral infections including HIV, Hepatitis B and C, varicella zoster, Epstein Barr virus, cytomegalovirus. • Woman of childbearing age should have a negative pregnancy test Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended. A second test should be done 8-10 days after the first one and immediately before starting mycophenolate mofetil, unless exceptional circumstances exist whereby a delay in the initiation of treatment would cause harm to the patient and the prescriber is satisfied that a single test is adequate to rule out pregnancy. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). See MHRA Drug Safety Update for more detail. • Screening for lung disease, including tuberculosis, should be undertaken at clinician discretion on a case-by-case basis. . • Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (eg pneumococcal, shingles, influenza, COVID 19) <p>The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised</p> <p><u>Initial monitoring</u> (Undertaken by secondary care)</p> <ul style="list-style-type: none"> • FBC • U&E • AST and/or ALT, and albumin <p><u>Routine monitoring</u> (Undertaken in secondary care, every 2 weeks until on a stable dose for 6 weeks and then monthly for up to 3 months until transfer to shared care has been completed),</p> <ul style="list-style-type: none"> • FBC • U&E • AST and/or ALT, and albumin <p>The specialist will retain the responsibility for monitoring the patient's ongoing response to treatment and advise if a dose change or treatment cessation is appropriate. This would usually be in annual review with the specialist.</p> <p><u>Primary care monitoring. (undertaken every 3 months).</u></p> <ul style="list-style-type: none"> • FBC • U&E • AST and/or ALT, and albumin <p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care, until the dose has been stable for 6 weeks, then revert to original schedule. Secondary care to prescribe and monitor during this time.</p>
<p>Adverse Drug Reactions</p>	<p>Very common and common side effects include:</p> <ul style="list-style-type: none"> • Fever • <u>Psychiatric and CNS</u>: agitation, confusional state, depression, anxiety, insomnia, convulsions, tremor, somnolence, paraesthesia. • <u>Cardiac</u>: tachycardia • Vascular disorders: hypotension, hypertension, vasodilation. • <u>Blood and lymph disorders: Haematological</u>: 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. • <u>Gastro-intestinal</u>: 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, pulmonary fibrosis
- 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, hematuria raised blood creatinine.
- Nervous system disorder: dizziness, headache, pyrexia, chills, oedema, malaise, asthenia, pain.
- Metabolism and nutrition disorders: Acidosis, , hypercholesterolemia, hyperglycaemia, hyperkalaemia, hyperlipidaemia, hypocalcaemia. hypokalaemia, hypomagnesemia, hypophosphotaemia, gout.

Please see [SPC](#) or BNF for full side effect information.

Please report adverse reactions to the MHRA via the yellow card scheme:
www.mhra.gov.uk/yellowcard

As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance.

Adverse effects management	
Result	Action for primary care
<ul style="list-style-type: none"> - White blood cells less than $3.5 \times 10^9/L$ - Lymphocytes less than $0.5 \times 10^9/L$ - Neutrophils less than $1.6 \times 10^9/L$ - Platelets less than $140 \times 10^9/L$ - Eosinophilia greater than $0.5 \times 10^9/L$ 	Withhold and discuss with specialist team urgently.
MCV > 105 fL	Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently. Consider interruption in treatment.
Liver Function Tests ALT or AST > 3 x upper limit of normal (ULN), or any sudden increases (e.g. double of baseline), OR Unexplained fall in serum albumin < 30g/L	Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.
Renal function Creatinine rise > 30% over 12 months, or calculated GFR reduces to < 60ml/min	Withhold and discuss with specialist team
Signs or symptoms of bone marrow suppression e.g. unexplained bleeding or bruising with or without sore throat, mouth ulcers.	Check FBC immediately and discuss with the specialist team. See haematological monitoring above.
Infections Infection requiring antibiotics Recurrent or opportunistic infections	Temporarily withhold mycophenolate until the patient has recovered.

	Exposure to chickenpox or shingles	Review for reversible causes. Withhold and discuss with specialist team. Contact specialist team for advice. See the Green Book (chapter 34) for detailed advice on risk assessment and post exposure prophylaxis
	Gastrointestinal disorders Very common adverse effects include nausea and vomiting, abdominal cramps, diarrhoea and dyspepsia.	Review for reversible causes. Advise patient to take with food. If no improvement contact specialist team.
	GI ulceration, bleeding and perforation	Review for reversible causes. Withhold and discuss urgently with specialist team.
	Suspected pancreatitis	Withhold and discuss with specialist team
	Skin disorders Skin hypertrophy, acne, alopecia Rash	Review for reversible causes. Discuss with specialist team if symptoms become troublesome. Review for possible causes. If cause of rash thought to be mycophenolate or immune-mediated, withhold and discuss with specialist team.
	Other Neurological symptoms, psychiatric disorders, sudden onset or worsening shortness of breath, cough or dyspnoea	Review for reversible causes. Withhold and discuss with specialist team.
	Suspicion of malignancy	Discuss with specialist team. Refer for diagnosis and treatment of malignancy.
Advice to patients and carers	<p>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</p> <p>The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay:</p> <ul style="list-style-type: none"> • Rash • Abdominal pain or jaundice (skin or whites of the eyes appear yellow) • Signs and symptoms suggestive of bone marrow suppression e.g. sore throat, oral ulceration, abnormal bruising or bleeding, or signs of infection. • Exposure to chickenpox or shingles or if the patient develops chicken pox or shingles. • Pregnancy or planning to become pregnant. <p>The patient should be advised:</p> <ul style="list-style-type: none"> • During a serious infection (requiring antibiotics) mycophenolate mofetil should be temporarily discontinued until the patient has recovered from the infection. • If exposed to chickenpox or shingles patient must alert their primary care prescriber or specialist team and seek advice. • That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended. 	

	<ul style="list-style-type: none"> • Tell anyone who prescribes them a medicine that they are taking mycophenolate. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe. Patients have a small increased risk of skin cancers so should be advised to wear high factor sunscreen and to wear a hat and protective clothing when in strong sunshine. Sun beds should be avoided. Patients should be advised to carry out regular self-examination of the skin and report if there are any new lesions and/or changes to skin. • Mycophenolate mofetil may cause somnolence, confusion, dizziness, tremor or hypotension, and therefore patients are advised to use caution when driving or using machines. • To always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant. • Not to donate blood during treatment or for 6 weeks after stopping, and not to donate semen during treatment or for 90 days after stopping. • To avoid contact with people with chicken pox or shingles and report any such contact urgently to their primary care prescriber. If the patient is exposed, contact the specialist for advice. For detailed advice on risk assessment and post exposure prophylaxis following exposure to chicken pox and shingles, see: <ul style="list-style-type: none"> - the Green Book (Chapter 34). - UKHSA guidance: Guidelines on post exposure prophylaxis (PEP) for varicella/shingles. <p>Patient information can be found at: General information: https://patient.info/medicine/mycophenolate-mofetil-cellcept-myfenax Rheumatology: https://www.versusarthritis.org/about-arthritis/treatments/drugs/mycophenolate/</p>
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Penicillamine

Background	<p>Penicillamine is licensed for the treatment of severe active rheumatoid arthritis.</p> <p>Penicillamine is a thiol-group containing chelating agent. It is strongly plasma-protein bound.</p>
Cautions and Contraindications	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Hypersensitivity to penicillamine or any of the ingredients. • Agranulocytosis, aplastic anaemia or severe thrombocytopenia due to penicillamine. • Lupus erythematosus. • Moderate or severe renal impairment <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Care should be taken in patients with renal insufficiency (see dose information). • Low platelets (count below 120,000 per mm³) or WBC <2,500 per mm³ (see ADR section). • Elderly population. Careful monitoring needed as toxicity 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. • Antihistamines, steroid cover, or temporary reduction of dose will control urticarial reactions. • Reversible loss of taste may occur. Mineral supplements to overcome this are not recommended. • Haematuria is rare, but if it occurs in the absence of renal stones or other known cause, treatment should be stopped immediately. • A late rash, described as acquired epidermolysis bullosa and penicillamine dermopathy, may occur after several months or years of therapy. This may necessitate a reduction in dosage. • Breast enlargement has been reported as a rare complication of penicillamine therapy in both women and men (see section 4.8). Danazol has been used successfully to treat breast enlargement which does not regress on drug discontinuation. • The use of DMARDs, including penicillamine, has been linked to the development of septic arthritis in patients with rheumatoid arthritis, although rheumatoid arthritis is a stronger predictor for the development of septic arthritis than the use of a DMARD. • Deterioration of the neurological symptoms of Wilson's disease (dystonia, rigidity, tremor, dysarthria) have been reported following introduction of penicillamine in patients treated for this condition. This may be a consequence of mobilisation and redistribution of copper from the liver to the brain. • Pyridoxine daily may be given to patients on long term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement of this vitamin. • These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Initiation and ongoing dose regimen	<p><u>Dose</u></p> <p>Treatment is usually started at 125mg daily.</p> <ul style="list-style-type: none"> • Dose may be increased by 125mg every four to twelve weeks until remission occurs This dose increase would be undertaken by secondary care. • The minimum maintenance dose to achieve suppression of symptoms should be used and treatment should be discontinued if no improvement occurs within 12 months. • Improvement may not occur for some months.

	<ul style="list-style-type: none"> The usual maintenance dose is 500 mg to 750 mg daily. However, up to 1500 mg daily may be required. Reduction in maintenance dosage by 125 mg to 250 mg every 12 weeks may be attempted after a period of 6 months continuous remission. This would only occur after discussion with secondary care colleagues. Patients with renal impairment should be initiated at a low dose with increment intervals a minimum of 12 weeks. Fortnightly monitoring for toxicity is mandatory.
Pregnancy and breast feeding	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Pregnancy</u> The safety of penicillamine for use during pregnancy has not been established.</p> <p><u>Breast feeding</u> Due to the lack of data on the use in breast-feeding patients and the possibility that penicillamine may be transmitted to newborns through breast milk, penicillamine should only be used in breast-feeding patients when it is considered absolutely essential by the physician.</p> <p>Contact the rheumatology specialist if patient considering conceiving or in cases of pregnancy.</p>
Interactions	<ul style="list-style-type: none"> If concomitant oral iron, digoxin or antacid therapy is indicated, this should not be given within two hours of taking penicillamine. Concomitant use of NSAIDs and other nephrotoxic drugs may increase the risk of renal damage. Concomitant use of gold: concomitant use is not recommended. Concomitant use of clozapine: penicillamine may potentiate the blood dyscrasias seen with clozapine. Concomitant use of zinc: oral absorption of penicillamine may be reduced by concomitant administration of zinc; absorption of zinc may also be reduced by penicillamine. Pyridoxine daily may be given to patients on long term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin.
Monitoring	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care)</p> <ul style="list-style-type: none"> FBC. U&Es. LFTs. Creatinine/ calculated GFR, serum albumin and serum folate. Weight. Height and Blood pressure. Assess for co-morbidities. Screening for viral infections e.g. HIV, hepatitis B and C, varicella zoster. Screening for lung disease (including tuberculosis) should be considered on a case-by-case basis. <p>The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised.</p> <p><u>Routine monitoring</u> (Undertaken in secondary care every 2 weeks for 8 weeks, then monthly for 4 months or until transfer to shared care has been completed).</p>

	<ul style="list-style-type: none"> • During the first eight weeks of therapy full blood count, renal function and urinalysis should be carried out every 2 weeks, then monthly for 4 months, then every 3 months. • Full blood counts, renal function, urinalysis and protein should be performed after any increase in dose; then monthly for 12 months; then 3 monthly thereafter. <p>Ask patient about any sore throat, cough, haemoptysis, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers or rashes at each encounter with the patient.</p> <p><u>Transfer to primary care after the patient is stable and preferably after 4 monthly blood test.</u></p> <p><u>Primary care monitoring (Undertaken every 3 monthly).</u></p> <ul style="list-style-type: none"> • FBC • U and E's • LFT's • Creatinine/ calculated GFR, serum albumin and serum folate <p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care, until the dose has been stable for 6 weeks, then revert to original schedule. Secondary care to prescribe and monitor during this time.</p>
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Adverse Drug Reactions	<p>Very common and common side effects include:</p> <ul style="list-style-type: none"> • Thrombocytopenia • Proteinuria <p>Many potential side effects may occur, the incidence of which are unknown. Please see SPC or BNF for full side effect information.</p> <p>Please report adverse reactions to the MHRA via the yellow card scheme: www.mhra.gov.uk/yellowcard</p> <table border="1"> <thead> <tr> <th colspan="2">Adverse effects management</th></tr> <tr> <th>Result</th><th>Action for primary care</th></tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> • WCC less than $2.5 \times 10^9/L$ • Lymphocytes less than $0.5 \times 10^9/L$ • Neutrophils less than $1.6 \times 10^9/L$ • Platelets less than $120 \times 10^9/L$ • Unexplained eosinophilia; greater than $0.5 \times 10^9/L$ • Unexplained fall in albumin; less than 30g/L </td><td>Withhold treatment and discuss with specialist</td></tr> <tr> <td>Hb fall >1g in 4 weeks or below 10g</td><td>Check for increased disease activity Ask about NSAID use and symptoms of GI blood loss or dyspepsia and stop NSAIDS if implicated. Check MCV and iron studies Consider endoscopy</td></tr> <tr> <td>Proteinuria >1+</td><td>MSU, if negative withhold and check protein creatinine index (PCI) or 24 hour urinary protein. Stop if proteinuria > 0.5g/24 hours & contact Rheumatology department.</td></tr> <tr> <td>Gastrointestinal disorders Nausea, vomiting, diarrhoea, unintentional weight loss</td><td>Review for reversible causes. Advise patient to take with food and at night. If no improvement, discuss with specialist teams.</td></tr> <tr> <td>Bleeding disorders Bruising, bleeding</td><td>Check FBC and clotting screen. Contact secondary care for advice if needed.</td></tr> <tr> <td>Other symptoms Skin rash Altered taste Mouth ulceration</td><td> <ul style="list-style-type: none"> • Stop if severe or consider antihistamine purchased over the counter. • Continue treatment as may settle down. • Check WBC. Check for candida and treat accordingly. If severe contact specialist team for advice. </td></tr> </tbody> </table>	Adverse effects management		Result	Action for primary care	<ul style="list-style-type: none"> • WCC less than $2.5 \times 10^9/L$ • Lymphocytes less than $0.5 \times 10^9/L$ • Neutrophils less than $1.6 \times 10^9/L$ • Platelets less than $120 \times 10^9/L$ • Unexplained eosinophilia; greater than $0.5 \times 10^9/L$ • Unexplained fall in albumin; less than 30g/L 	Withhold treatment and discuss with specialist	Hb fall >1g in 4 weeks or below 10g	Check for increased disease activity Ask about NSAID use and symptoms of GI blood loss or dyspepsia and stop NSAIDS if implicated. Check MCV and iron studies Consider endoscopy	Proteinuria >1+	MSU, if negative withhold and check protein creatinine index (PCI) or 24 hour urinary protein. Stop if proteinuria > 0.5g/24 hours & contact Rheumatology department.	Gastrointestinal disorders Nausea, vomiting, diarrhoea, unintentional weight loss	Review for reversible causes. Advise patient to take with food and at night. If no improvement, discuss with specialist teams.	Bleeding disorders Bruising, bleeding	Check FBC and clotting screen. Contact secondary care for advice if needed.	Other symptoms Skin rash Altered taste Mouth ulceration	<ul style="list-style-type: none"> • Stop if severe or consider antihistamine purchased over the counter. • Continue treatment as may settle down. • Check WBC. Check for candida and treat accordingly. If severe contact specialist team for advice.
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Advice to patients and carers	<p>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</p> <p>Remind patient to take half an hour before food or on an empty stomach.</p>																

Shared Care Guideline –remains open to review in light of any new evidence

Amber = To be initiated and titrated to a stable dose by a specialist with follow up prescribing and monitoring by primary care under a shared care agreement.

	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Patient information</u> can be found at: https://patient.info/medicine/penicillamine-2 https://www.medicines.org.uk/emc/search?q=hydroxychloroquine</p>
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Sulfasalazine

Background	<p>Sulfasalazine is a disease modifying antirheumatic drug (DMARD) used to treat several rheumatological conditions.</p> <p>This shared care protocol does not cover the treatment of people less than 18 years old.</p>
Cautions and Contraindications	<p><u>Contraindications</u></p> <ul style="list-style-type: none"> • Known sulphonamide allergy (absolute contraindication) or salicylate hypersensitivity • Patients with porphyria <p><u>Cautions</u></p> <ul style="list-style-type: none"> • Hepatic or renal impairment. . • Pre-existing blood dyscrasias. • Severe allergy or bronchial asthma. . • Glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of haemolytic anaemia. . • Folic acid deficiency. . • Adequate fluid intake should be maintained during treatment to avoid crystalluria and kidney stone formation. • Slow acetylator status increases the risk of sulfapyridine-related adverse drug reactions (ADRs) which can present as a drug-induced lupus-like syndrome. • Sulfasalazine should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. • Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of drug appears to reverse these effects within 2 to 3 months. Avoid use in men whose partners are planning a pregnancy. • Patients with known photosensitivity and/or raised ANA. • Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include urea, ammonia, LDH, α-HBDH and glucose. It is possible that alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), or thyroxine may also show interference when sulfasalazine treatment is given at high doses. Consult with the testing laboratory regarding the methodology used. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings.
Initiation and ongoing dose regimen	<ul style="list-style-type: none"> • Transfer of monitoring and prescribing to primary care is normally after the patient has been treated for 3 months, the dose has been optimised and with satisfactory investigation results for at least 4 weeks. • The duration of treatment & frequency of review will be determined by the specialist based on clinical response and tolerability. • All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician. • Termination of treatment will be the responsibility of the specialist. <p><u>Dose</u></p> <p>500mg daily, increasing by 500mg each week (dose titrated slowly to reduce the risk of GI side effects) until 2-3g per day in divided doses is reached according to response.</p>

	Enteric coated tablets are preferred as better tolerability. Only enteric coated tablets are licensed for use in rheumatoid arthritis.
Pregnancy and breast feeding	<p>The specialist should ensure patients are informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The patient should be advised to always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p><u>Pregnancy</u> No evidence of teratogenicity. Where deemed appropriate by specialist to continue in pregnancy, combine with folic acid 5mg daily.</p> <p><u>Breast feeding</u> Sulfasalazine is found in low levels in breast milk. Sulfasalazine is thought to be safe in breastfeeding a healthy, full-term infant.</p>
Interactions	<ul style="list-style-type: none"> • Digoxin: Reduced absorption may be seen when used concomitantly with sulfasalazine. • Sulfonamides are chemically similar to some oral hypoglycaemic agents and may cause hypoglycaemia. Patients receiving sulfasalazine and hypoglycaemic drugs should closely monitor blood glucose. • Azathioprine and 6-mercaptopurine: Possible risk of bone marrow suppression and leukopenia. • Folate absorption and metabolism may be reduced by sulfasalazine. • Darolutamide and voxilaprevir may increase exposure to sulfasalazine, manufacturer advises avoid. • Coadministration of oral sulfasalazine and methotrexate may potentiate an increase in gastrointestinal adverse events, especially nausea.
Monitoring	<p><u>Baseline monitoring:</u> (To be undertaken in secondary care)</p> <ul style="list-style-type: none"> • FBC. • U&Es. • LFTs, Creatinine/ calculated GFR, serum albumin and serum folate. • Weight. • Height and Blood pressure. • Assess for co-morbidities.. • Screening for HIV, hepatitis B and C. • Screening for lung disease (including tuberculosis) should be considered on a case-by-case basis. <p>The rheumatology specialist will assess and monitor the patient's response to treatment until the patient is stabilised.</p> <p><u>Routine monitoring</u> (Undertaken in secondary care, every 2 weeks until on a stable dose for 6 weeks and then monthly for up to 3 months until transfer to shared care has been completed),</p> <ul style="list-style-type: none"> • FBC. • U+Es. • Calculated GFR, LFTs and serum albumin <p><u>Primary care monitoring</u> (Once the transfer to shared care has been completed, monitoring should be undertaken every 3 months).</p> <ul style="list-style-type: none"> • FBC. • U+Es. • Calculated GFR, LFTs and serum albumin • <p><i>Routine monitoring can cease if stable after 12months of therapy with sulfasalazine alone.</i></p>

	<p>If there is a dose change the above tests should be repeated every 2 weeks by secondary care, until the dose has been stable for 6 weeks, then revert to original schedule. Secondary care to prescribe and monitor during this time.</p>												
Adverse Drug Reactions	<p>Very common and common side effects include:</p> <ul style="list-style-type: none">• Leukopenia.• Loss of appetite.• Insomnia.• Dizziness.• Headache.• Taste disorders.• Tinnitus.• Cough.• Gastric distress.• Nausea.• Pruritis.• Purpura.• Arthralgia.• Fever. <p>Please see <u>SPC</u> or BNF for full side effect information.</p> <p>Opportunistic infections may occur. Infections can require early and vigorous treatment and may require sulfasalazine to be stopped until the infection is clear. If in doubt, please contact secondary for advice.</p> <p>Please report adverse reactions to the MHRA via the yellow card scheme: www.mhra.gov.uk/yellowcard</p> <p>If patients present with symptoms of potential adverse effects perform an urgent blood test. If any of the following occur, contact the hospital specialist</p> <table><tr><th colspan="2">Adverse effects management</th></tr><tr><th>Result</th><th>Action for primary care</th></tr><tr><td><ul style="list-style-type: none">• WCC less than 3.5 x10⁹/L• Lymphocytes less than 0.5 x10⁹/L• Neutrophils less than 1.6 x10⁹/L• Platelets less than 140 x10⁹/L• Unexplained eosinophilia; greater than 0.5x10⁹/L• Unexplained fall in albumin; less than 30g/L</td><td>Withhold treatment and discuss with specialist</td></tr><tr><td>MCV>105 fL</td><td>Consider interruption of treatment, but contact rheumatology for advice</td></tr><tr><td>Liver Function Tests ALT and/or AST>100u/L And/or a sudden increase (e.g. doubling of baseline) Jaundice</td><td>Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.</td></tr><tr><td>Renal function Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min</td><td>Use clinical judgement and repeat in one week. If still> 30% increase from baseline, withhold treatment and discuss with specialist team.</td></tr></table>	Adverse effects management		Result	Action for primary care	<ul style="list-style-type: none">• WCC less than 3.5 x10⁹/L• Lymphocytes less than 0.5 x10⁹/L• Neutrophils less than 1.6 x10⁹/L• Platelets less than 140 x10⁹/L• Unexplained eosinophilia; greater than 0.5x10⁹/L• Unexplained fall in albumin; less than 30g/L	Withhold treatment and discuss with specialist	MCV>105 fL	Consider interruption of treatment, but contact rheumatology for advice	Liver Function Tests ALT and/or AST>100u/L And/or a sudden increase (e.g. doubling of baseline) Jaundice	Withhold and discuss with specialist team. Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication.	Renal function Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min	Use clinical judgement and repeat in one week. If still> 30% increase from baseline, withhold treatment and discuss with specialist team.
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	Signs or symptoms of bone marrow suppression e.g unexplained bleeding or bruising with or without sore throat, purpura, mouth ulcers	Check FBC immediately and withhold treatment whilst awaiting results. Discuss with specialist teams
	Acute infection	During serious infections (e.g. requiring intravenous antibiotics or hospitalisation) temporarily withhold sulfasalazine until the patient has recovered. Consider additional investigations (e.g. FBC), if clinically appropriate.
	Gastrointestinal disorders Nausea, vomiting, diarrhoea, unintentional weight loss	Review for reversible causes. Advise patient to take with food. If no improvement, discuss with specialist teams.
	Other symptoms <ul style="list-style-type: none"> • Skin rash • Diffuse alopecia • Breathlessness/cough • Peripheral neuropathy 	Consider withholding treatment and discussing with specialist. For widespread rash, discontinue and discuss with specialist urgently.
Advice to patients and carers	<p>The specialist will counsel the patient regarding the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets.</p> <p>Remind patient that enteric coated tablets should be swallowed whole and not crushed.</p> <p>The patient should be advised to report any of the following signs and symptoms to their GP without delay:</p> <ul style="list-style-type: none"> • Sore throat, mouth ulcers, fever, malaise, swollen lymph nodes, or unexplained bleeding or bruising. • Progressive skin rash with blisters or oral ulcerations – see below • Nausea, vomiting, diarrhoea, jaundice, dark urine and unintentional weight loss • Hair loss • Breathlessness, infection or cough • Symptoms of peripheral neuropathy e.g. pins and needles, numbness or burning pain in extremities <p>Advise the patient:</p> <ul style="list-style-type: none"> • Life-threatening skin reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfasalazine. The highest risk for occurrence is within the first weeks of treatment. Patients should be advised to report a progressive skin rash often with blisters or mucosal lesions, or any other sign of hypersensitivity. • During a serious infection, sulfasalazine should be temporarily discontinued until the patient has recovered from the infection. • Tell anyone who prescribes them a medicine that they are taking sulfasalazine. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe. • That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended. • Sulfasalazine may cause a harmless yellow-orange discolouration of body fluids and skin. Certain types of extended wear soft-contact lenses may be permanently stained. • To maintain adequate fluid intake during treatment to reduce the risk of crystalluria and kidney stones. • Sulfasalazine oral suspension contains 4.7 mg of alcohol (ethanol) in each 5ml, equivalent to less than 1ml of beer or wine. The small amount of alcohol in this medicine will not have any noticeable effects. • To always use contraception and to contact the specialist team should they become pregnant or planning to become pregnant or breastfeed. The specialist 	

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	<p>should resume prescribing responsibilities if a woman becomes or wishes to become pregnant.</p> <p>Patient information can be found at: https://www.nhs.uk/medicines/sulfasalazine/https://patient.info/medicine/sulfasalazine-salazopyrin-sulazine https://www.versusarthritis.org/about-arthritis/treatments/drugs/sulfasalazine/</p>
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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:

Previous monitoring undertaken by secondary care:

Parameter	Date of test	Result
e.g. Blood Pressure	22/04/2024	130/70

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 _____

I have commenced the patient on:

Drug: - _____

Dose _____

GP signature: _____ Date: _____

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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:

[DMARDs shared care prescribing](#)

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