Western Locality Shared care Information ~ DMARDs in Rheumatology

This guideline highlights significant prescribing issues. Not all prescribing information and potential adverse effects are listed. Please refer to the BNF and individual product SPC/data sheet for full prescribing data.

Specialist: Please complete letter at the end of this document and send together with the guideline to the GP.

GP: Please indicate whether you wish to share patient's care by completing letter at the end of this document and return to specialist.

GPs are invited to participate. If a GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.

Responsibilities remain with the specialist service until formally accepted by the GP.

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

Introduction and aims of treatment

This guideline covers use of the following DMARDs in adults when initiated for rheumatic diseases, including rheumatoid arthritis, psoriatic arthritis and other autoimmune conditions such as systemic lupus erythematosus (SLE), scleroderma or vasculitis (click on each drug to jump to supporting information)**:**

- Azathioprine
- Ciclosporin (Neoral®)
- Leflunomide
- Methotrexate weekly via oral or subcutaneous (sc) routes
- Mycophenolate mofetil (Cellcept®) – **unlicensed use**
- Sulfasalazine

The use of these medicines for other indications is outside the scope of this guideline.

To jump to monitoring requirements, click here.

To jump to shared care agreement letter, click here.

Specialist responsibilities

Consultants may decide to delegate some of these tasks to members of their team; however the responsibility for ensuring the following are undertaken remains with the consultant:

1. Decision to prescribe DMARD or combination of DMARDs made in conjunction with the patient/carer
2. Update records with list of existing drugs from available resources and ensure there are no drug interactions with current medication.
3. Discuss benefits and side effects of treatment with patient or patient's carers including, where appropriate, for female and male patients, the risks associated with pregnancy and need for reliable method of contraception. (See specific details for **mycophenolate mofetil & leflunomide** below). Ensure patient's understanding of risks and benefits
4. For **mycophenolate mofetil** record patient consent to unlicensed use and, if applicable, understanding of the need for effective contraception
5. For female patients of child-bearing age starting **methotrexate, mycophenolate mofetil, leflunomide** – exclude pregnancy before initiating treatment

6. Refer patient to specialist nurse service where appropriate (e.g. new patient) for advice on taking the drug, its cautions, side effects associated with treatment, monitoring requirements and the timing of re-assessment and by whom
7. Provide patient (and/or carer) with written information on use, side effects, dosage, need for monitoring of medication and a booklet for recording test results. For methotrexate the purple booklet must be used. Ensure that patient understands that they should bring the booklet to each hospital or GP practice appointment and that they are responsible for entering tests results. Discuss options with patient or carer for those who are not able to record results in booklet.
8. For **methotrexate**, refer to MHRA Drug safety update, Sept 2020: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing (see methotrexate "supporting information" section below).
9. To ensure the patient is trained to self-administer subcutaneous methotrexate, if appropriate
10. Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster is not recommended
11. Undertake baseline tests and screening (see below). Consider comorbidities in relation to drug choice, screening, drug dosage and monitoring
12. Initiate treatment, supply 28 days medication.
13. For patients starting methotrexate prescribe folic acid at a minimum dose of 5mg once weekly
14. Send a letter to the GP, asking them whether they are willing to participate in the sharing of care for a particular patient. Include results of any relevant baseline tests, and confirm the frequency of ongoing monitoring. Prescribing and monitoring responsibility remains with the specialist until formally accepted by the GP
15. Advise the GP (in writing) of dose changes, changes in monitoring requirements, results of monitoring, assessment of adverse events or when to stop treatment. Urgent changes to treatment should be communicated by telephone to GP
16. Continue to review the patient at agreed specified intervals, sending a written summary to the GP whenever the patient is reviewed, including the current dose to be prescribed
17. Report adverse events to MHRA via the yellow card scheme where appropriate

General practitioner responsibilities

Ensure a timely reply is sent to specialist in response to request for sharing of care.

If GP has agreed to share care:

1. Continue to prescribe DMARD(s) in accordance with guidelines.
2. For **methotrexate**:
    - continue to prescribe oral folic acid 5mg at least once weekly. The dose to be taken at least 24 hours after methotrexate dose. The regimen will depend on the side effects of methotrexate – more folic acid can help
    - refer to MHRA Drug safety update, Sept 2020: Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing (see methotrexate "supporting information" section below)
3. Undertake ongoing monitoring as specified. Review and act on results or reported side-effects as described in monitoring section below
4. Ensure the results of monitoring are recorded in the patient notes and agree a system for communicating results of monitoring to patient, carer/responsible nurse (where patient not self-administering)
5. Respond to advice from secondary care on dose changes and frequency of monitoring

6. Stop treatment in case of a severe adverse event or as per shared care guideline
7. Report to and seek advice from specialist on any aspect of patient care of concern to GP which may affect treatment. Prompt communication with specialist if there is a change in patient's health status. Report adverse events to specialist and to MHRA via yellow card scheme where appropriate
8. Ensure there are no drug interactions with existing drugs and be alert to the possibility of interactions when initiating drugs. There are significant interactions with methotrexate, ciclosporin, and between azathioprine and allopurinol. (See individual drugs below and product literature)
9. Administer influenza vaccine annually unless otherwise advised by the initiating specialist.
10. Check that the patient has had one dose of pneumococcal vaccine (revaccination is not recommended, except every five years in patients whose antibody levels are likely to have declined more rapidly e.g. asplenia) – see BNF or Green Book
11. **Methotrexate**: Ensure that the GP computer system has an alert flag in accordance with NPSA guidance. Record results of monitoring in GP system
12. **Mycophenolate mofetil**: Ensure that women and men understand the need for effective contraception, the risk of harm to the baby, and the need to immediately consult their physician if there is a possibility of pregnancy (see also "Contraception", below)
13. **Leflunomide**: Prescribe a "wash out" regimen (details provided below) in the event of a serious hepatological, haematological, skin reaction or pregnancy in the patient. In cases of confirmed pregnancy or severe toxicity washout should be started and the specialist team contacted. If in doubt regarding cases of toxicity contact may be made first and washout prescribed on specialist advice.

Monitoring

Baseline assessments and frequency of ongoing monitoring is based on recommendations of the British Society of Rheumatology (2017).

Baseline assessment to be completed by the specialist service provider:

- At baseline:
  - Height & weight
  - Blood pressure
  - Full blood count (FBC)
  - U&Es and eGFR
  - ALT and/or AST, and albumin
  - Chest x-ray
  - Consider patient risk factors for viral infections and screen for occult viral infections (hepatitis B and C and HIV) where appropriate
  - **Azathioprine:** Pre-screening for TPMT deficiency and, if required, recommend an alternative dosing and monitoring strategy. This test is sent to an external laboratory and the result is available in 2-4 weeks.
  - **Ciclosporin:** Baseline blood lipid levels
  - **Leflunomide, methotrexate, mycophenolate mofetil:** Pregnancy test in women of childbearing age. Consider contraception as appropriate

Ongoing monitoring during treatment to be completed by the GP:

Refer to tables overleaf

<table>
<tr><th colspan="4">Standard monitoring schedule, for patients receiving azathioprine; ciclosporin*; leflunomide*; methotrexate*; mycophenolate mofetil; and sulfasalazine*</th></tr>
<tr><th>Test</th><th>Frequency</th><th>Results</th><th>Action</th></tr>
<tr><td>FBC</td><td rowspan="3">Every two weeks until on stable dose for 6 weeks, then every month for 3 months, then at least every 12 weeks*.

Following dose increases, monitor every 2 weeks until on a stable dose for 6 weeks, then as above.

Patient factors where continued monthly monitoring is recommended (unless otherwise specified):
• Previous toxicity or deranged FBC or LFTs while on DMARDs
• Chronic kidney disease (CKD 3)
• Pre-existing liver disease

Additional urgent monitoring tests should be carried out within 24 hours for any patient with acute kidney injury (AKI).</td><td>WCC < 3.5 x 10^9/L
Neutrophils < 1.6 x 10^9/L
Eosinophils >0.5 x 10^9/L
Platelets < 140 x 10^9/L
MCV > 108fl
(If blood samples are not being analysed by Derriford Hospital lab, confirm MCV threshold for action with specialist.)</td><td rowspan="3">If results meet specified criteria, stop treatment and refer to specialist.
If isolated MCV rise, check for other causes (B12, folate, thyroid function and alcohol consumption). If results are normal, refer to specialist.
If concerned about sequential drops in FBC indices (possibly still within normal range), consider an early re-test/seek specialist advice.
If deterioration in renal function, dose adjustment may be necessary; if toxicity suspected or dosing advice required refer to specialist team.</td></tr>
<tr><td>Creatinine/eGFR</td><td>Creatinine increase >30% over 12 months and/or eGFR <60ml/min/1.73m^2</td></tr>
<tr><td>ALT and/or AST and albumin</td><td>ALT and/or AST >100 U/L
Albumin unexplained reduction to <30g/L</td></tr>
<tr><td>Warning signs and symptoms</td><td>Patients must be aware of and report warning symptoms. Patients reporting these between appointments should prompt an urgent review within 24 hours. Signpost patient to alternative provider if this is not possible e.g. weekend/bank holiday

Sulfasalazine: ask about rash or oral ulceration at each visit.

Methotrexate, leflunomide: ask about new or increasing breathlessness & dry cough at each visit</td><td colspan="2">For patients experiencing mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, rash, unexplained illness or infection:

Additional urgent monitoring tests (as above) should be carried out within 24 hours. Signpost patient to alternative provider if this is not possible e.g. weekend/bank holiday

For patients receiving methotrexate, or leflunomide, who have new or increasing breathlessness & dry cough:

Arrange chest x-ray (consider infection and to exclude pneumonitis) and refer to specialist team.</td></tr>
<tr><td colspan="4">* See overleaf for exceptions and additions to standard laboratory monitoring schedule</td></tr>
</table>

*** Exceptions to standard laboratory monitoring schedule:**

- **Ciclosporin or a combination of leflunomide + methotrexate:** All the above but extend **monthly** monitoring for at least 12 months before considering reduced frequency on an individual patient basis (specialist to advise), plus additional monitoring requirements, see below
- **Leflunomide:** All the above plus additional monitoring requirements, see below
- **Sulfasalazine:** All the above standard monitoring for 12 months then no routine monitoring for stable patients

Other factors that may increase risk of toxicity include moderate renal impairment, extremes of body weight, polypharmacy (especially other haematotoxic/ hepatotoxic/ nephrotoxic drugs), comorbidities, age > 80 years. Where more frequent ongoing monitoring is required due to a combination of patient factors this will be advised by the specialist prescriber.

Additional monitoring requirements, for patients receiving ciclosporin; and leflunomide

Test	Frequency	Results	Action
Ciclosporin (in addition to the above standard monitoring schedule)			
Blood pressure	At each monitoring visit (as above) to promptly identify and minimise cardiovascular risks	Raised BP	Treat hypertension as per local formulary guidance A rise in BP does not indicate withdrawal of ciclosporin unless resistant to treatment – refer to specialist team.
Glucose		Raised glucose	Consider alongside patient and cardiovascular risk factors using appropriate screening tools. Treat as appropriate and discuss with specialist if continued concern.
Leflunomide (in addition to the above standard monitoring schedule)			
Blood pressure	At each monitoring visit (as above)	Raised BP	Treat hypertension as per local formulary guidance A rise in BP does not indicate withdrawal of leflunomide unless resistant to treatment – refer to specialist team.
Weight		Significant fall in weight	Weight loss (usually insignificant) is a common side-effect and monitoring is recommended in product SPC. If concerned discuss with specialist.

Infections

Contact microbiology if a patient not known to be immune to chickenpox comes into contact with **shingles or chickenpox**, for advice on whether varicella-zoster immune globulin (VZIG) or other treatment is indicated.

Mycophenolate mofetil, azathioprine, ciclosporin: In patients suffering from chickenpox or active skin lesions from shingles, withhold. Patients with chickenpox: contact microbiologist for consideration of admission to hospital for IV antivirals. Patients with shingles: if any vesicles are still present (regardless of the time of onset), treat with aciclovir (800mg five times a day for 7 days).

During a **serious** infection STOP methotrexate, leflunomide, sulfasalazine, azathioprine, mycophenolate mofetil and ciclosporin. During minor infections (e.g. uncomplicated UTI treated with a short antibiotic course) treatment can be continued.

Do not stop treatment prior to surgery unless significant high-risk of infection where an individual patient plan should be made.

Vaccines

Live vaccines are contraindicated for patients on azathioprine, mycophenolate mofetil, ciclosporin, leflunomide, methotrexate. These vaccines include measles, mumps and rubella; BCG; Varicella-Zoster; poliomyelitis – oral Sabin vaccine; yellow fever; typhoid – oral.

Flu and pneumococcal vaccines should be given (see GP responsibilities above).

Patient/carer responsibilities

1. Understand the importance of monitoring treatment and attend specialist appointments and/ or GP appointments to ensure timely monitoring can be completed (in accordance with the prescribing guideline)
2. Understand that treatment will be stopped if they do not attend for monitoring and treatment reviews
3. Ensure that the results of monitoring are recorded in their record booklet
4. Ensure they have a clear understanding of the treatment, expected benefits and potential side effects
5. Take (or support administration of) medication as directed by the prescriber
    - For **methotrexate** this must be ONCE A WEEK on the SAME DAY EACH WEEK
6. MUST report any of the following to their GP and/or specialist: mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, unexplained rash and any unexplained illness/infection.
7. **Methotrexate, leflunomide**: MUST report new or increasing breathlessness and dry cough
8. Report any adverse effects to the GP and/or specialist regarding their treatment
9. Use a reliable method of contraception during treatment and also for the minimum period following discontinuation of mycophenolate mofetil, methotrexate, and leflunomide (see supporting information below). Discuss plans to conceive with specialist
10. Advise the GP immediately if pregnancy is suspected
11. Store their medicines safely and securely and dispose of any unused medication appropriately
12. Promptly seek medical advice if they think they have taken too much medication

Advice and support

Rheumatology

E-mail advice (for GPs only to seek advice on established rheumatology patients): Plymouth.rheumatology@nhs.net

This email is monitored daily Monday to Friday. A response should be received within 48 working hours from a Rheumatologist

For urgent queries please contact the rheumatology registrar, research fellow or on-call rheumatologist via Derriford switchboard (9am-5pm Monday to Friday)

Derriford Medicines Information: 01752 439976

Medicines Optimisation Teams

- NEW Devon CCG, Western Locality 01752 398800
- Kernow CCG 01726 627953

Date ratified: November 2018
(Shared care agreement letter contact details updated 9th July 2020)
(AZA MHRA DSU added June 2025)

References

BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology*, Volume 56, Issue 6, 1 June 2017, 865–868. https://doi.org/10.1093/rheumatology/kew479

BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology*, Volume 55, Issue 9, 1 September 2016, 1693–1697. https://doi.org/10.1093/rheumatology/kev404
Mycophenolate – updated advice on contraception can be found at: https://www.gov.uk/drug-safety-update/mycophenolate-mofetil-mycophenolic-acid-updated-contraception-advice-for-male-patients

Current BNF can be accessed at: https://bnf.nice.org.uk/

Individual product SPCs for full prescribing data can be accessed at: www.medicines.org.uk

Information on vaccines for patients with underlying diseases can be accessed at: https://www.gov.uk/government/publications/immunisation-of-individuals-with-underlying-medical-conditions-the-green-book-chapter-7

Improving compliance with oral methotrexate guidelines. Patient safety alert, NPSA, 1 June 2006 https://www.sps.nhs.uk/wp-content/uploads/2018/02/2006-NRLS-0279-Oral-methotrexate-PSA-2006-06-01-v1.pdf

MHRA Drug Safety Update, September 2020: Methotrexate once-weekly for autoimmune diseases: https://www.gov.uk/government/publications/drug-safety-update-monthly-newsletter

Supporting Information

Individual drug information is provided below for each drug below. **This is intended to highlight significant prescribing issues and not to provide full prescribing information for each drug.**

Please refer to individual product SPCs for full prescribing data; these can be accessed at www.medicines.org.uk and current BNF.

Dosage and administration

The normal dose range is 50mg to 200mg daily. The target dose will be clearly specified in the clinic letter.

Use doses at the lower end of the range for patients with hepatic or renal impairment and monitor more closely.

Contraindications and precautions

Refer to product SPC for azathioprine.

Patients with deficiency in the enzyme thiopurine methyltransferase (TPMT) have a higher risk of bone marrow toxicity.

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

Increased risk of developing non-Hodgkin's lymphomas and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas and uterine cervical cancer in situ.

Patients receiving azathioprine must **not** receive immunization with live vaccines.

Pregnancy and lactation (BSR guidelines September 2016)

Recent BSR guidelines state azathioprine is compatible throughout pregnancy at a dose not exceeding 2mg/kg/day. However since all drugs can potentially affect the unborn child female patients of child-bearing age should be advised that when planning pregnancy they should discuss medication with the rheumatology team at least six months prior to conception. There is no evidence that paternal exposure to azathioprine results in adverse outcomes.

Azathioprine may pass into the breast milk in low concentrations, but levels of active metabolites are undetectable in infants. There are theoretical concerns of adverse effects in infants which have not been confirmed in small studies, but long term follow up is lacking.

Important safety information

MHRA Drug Safety Update (May 2025): Thiopurines and intrahepatic cholestasis of pregnancy (ICP)

- Cholestasis of pregnancy has rarely been reported in association with azathioprine therapy
- This risk is believed to also apply to the other thiopurine drugs, mercaptopurine and tioguanine
- It may occur earlier in pregnancy than non drug-induced cholestasis of pregnancy, and it may not respond to ursodeoxycholic acid
- Withdrawal or dose reduction of the thiopurine drug may improve liver function tests
- Remain vigilant to signs and symptoms of ICP in pregnant patients taking thiopurines (intense itching without a rash, nausea, and loss of appetite) and discuss any concerns with clinicians managing the patient's immunosuppressant therapy and a hepatologist, as necessary
- If cholestasis of pregnancy occurs, a case-by-case assessment is required to determine the appropriate course of action. Consider the risks and benefits of remaining on the product against the risks and benefits of stopping.
- In patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM)

Adverse effects

Common and uncommon: (see SPC for further information)

- Nausea – can be relieved by administering tablets after meals
- Bone marrow depression, leucopenia, thrombocytopenia and anaemia
- Hypersensitivity reactions
- Cholestasis, abnormal liver function tests, pancreatitis
- Increased susceptibility to infections

Drug interactions

This list is not exhaustive, for additional information, and further interactions, consult the BNF and product SPCs for azathioprine.

- ACE inhibitors – increased risk of anaemia and/or leucopenia especially in renal impairment
- Allopurinol – increased haematological toxicity of azathioprine, reduce dose of azathioprine to one quarter of usual dose
- Anticoagulants – possible reduction in anticoagulant effect of coumarins including warfarin, monitor INR closely
- Febuxostat – concomitant use not recommended as may result in increased levels of azathioprine increasing toxicity
- Sulfasalazine inhibits TPMT enzyme. Risk of bone marrow suppression and leucopenia with concurrent use of azathioprine

Dosage and administration

The usual starting dose in secondary care is 1.5 - 2.5mg/kg per day for six weeks, increasing usually to 3.5mg/kg per day according to response and tolerability. The dose should not exceed 4mg/kg per day. The dose will be made clear in clinic correspondence.

Doses are given orally in two divided doses using 10mg, 25mg, 50mg and/or 100mg capsules.

The brand must be specified due to differences in bioavailability. The oral brand in Plymouth is Neoral®

Contraindications and precautions

Refer to product SPC for Neoral®.

Patients should be warned of a theoretical but unquantifiable risk of lymphomas and other malignancies, notably skin cancers. Patients should be warned to avoid excess unprotected sun exposure and should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Regular monitoring of blood pressure is required during Neoral® therapy. If hypertension develops, appropriate antihypertensive treatment must be instituted. Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin.

Patients receiving ciclosporin must **not** receive immunization with live vaccines.

Pregnancy and lactation (BSR guidelines September 2016)

BSR guidelines state ciclosporin is compatible throughout pregnancy at the lowest effective dose with monitoring of maternal blood pressure, renal function, blood glucose and drug levels. However since all drugs can potentially affect the unborn child female patients of child-bearing age should be advised that when planning pregnancy they should discuss medication with the rheumatology team at least six months prior to conception. There is no evidence that paternal exposure to ciclosporin results in adverse outcomes.

Ciclosporin may pass into the breast milk in low concentrations, but levels are usually undetectable in infants. Women taking ciclosporin should not be discouraged from breastfeeding.

Adverse effects

Some patients feel a burning sensation in their hands and feet during the first weeks of therapy. This may disappear with continued therapy, if not discuss this with the rheumatology team.

The most important side effects, which need monitoring, are impairment of renal function and hypertension.

Common and uncommon: (see SPC for further information)

- **Common:** Hypercholesterolaemia, hyperkalaemia, hypomagnesaemia, hyperuricaemia, renal dysfunction, gout, gastrointestinal disturbances, gingival hyperplasia, hepatic dysfunction, hypertrichosis, muscle disorders, tremor, paraesthesia, headache, predisposition to infection
- **Uncommon:** Haemolytic anaemia, thrombocytopenia, haemolytic uraemic syndrome, menstrual disorders, gynaecomastia, diabetes, pancreatitis, allergic rash, muscle weakness, myopathy, oedema, weight increase, signs of encephalopathy or demyelination (e.g. convulsion, confusion etc.), motor polyneuropathy

Drug interactions

There are multiple drug interactions with ciclosporin. This list is not exhaustive, for additional information, and further interactions, consult the BNF and product SPC for a comprehensive list.

Particular care should be taken with prescribing in combination with compounds known to have nephrotoxic effects.

- Food: Grapefruit or Grapefruit juice may increase ciclospoin levels (not to be ingested for 1 hour prior to dose of ciclosporin or avoid grapefruit consumption
- Drugs that **reduce** ciclosporin blood levels include: St. John's Wort (Hypericum perforatum), carbamazepine, phenytoin

- Drugs that **increase** ciclosporin blood levels include: Macrolide antibiotics, amiodarone, diltiazem, verapamil, ‘conazole’ antifungals, danazol
- Use with nephrotoxic drugs increases the risk of nephrotoxicity – use with caution and monitor renal function e.g. Non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics, quinolones, trimethoprim, fibrates
- Use with caution and monitor with drugs that also increase potassium levels: ACE inhibitors, A2RBs
- An increased risk of myopathy occurs with **statins**. Avoid simvastatin and other statin doses need to be adjusted – see individual product literature
- Drugs where levels are increased by ciclosporin:
    - Tacrolimus, ticagrelor, tofacitinib, aliskeren, dabigatran – avoid concomitant use
    - Colchicine – avoid or use lower colchicine dose
    - Digoxin – monitor levels and adjust dose

Leflunomide

Leflunomide has a long duration of action because it has an active metabolite with a very long half-life.

Leflunomide can rarely cause very serious hepatotoxicty, haemotoxicity, allergic reactions and dermatological reactions, which can occur even after leflunomide has been stopped. The potential toxicity and long duration of effect require caution when changing to or adding another potentially hepatotoxic or haemotoxic agent.

Should such toxicities occur, or when switching to another DMARD after treatment with leflunomide, a washout procedure should be performed (see below).

Dosage and administration

Leflunomide therapy may be started with a loading dose of 100mg once daily for 3 days; however the consultants at UHPNT rarely use this loading dose.

N.B. there is potential for confusion between 10mg and 100mg tablets primary care doctors will never be asked to prescribe the 100mg tablets.

The recommended maintenance dose for rheumatoid arthritis is leflunomide 10mg to 20mg once daily. Patients may be started on leflunomide 10mg or 20mg depending on the severity (activity) of the disease.

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

Contraindications and precautions

Refer to product SPC for leflunomide.

Contraindications: severe immunodeficiency states (e.g. AIDS), severe hyoprotinaemia, hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption.

Do not start therapy if significantly impaired bone marrow function, severe renal impairment, or liver impairment.

Due to the potential additive hepatic effects it is recommended that alcohol consumption should be minimal (1-2 units per week) during treatment with leflunomide.

Patients receiving leflunomide must **not** receive immunization with live vaccines.

Pregnancy and lactation (BSR guidelines September 2016)

Based on limited evidence that leflunomide may cause serious birth defects leflunomide is not recommended in women planning pregnancy. There is no human evidence of increased congenital abnormalities if colestyramine washout is given.

Women of childbearing potential must use effective contraception during and for up to 2 years after treatment or until washout is completed and levels undetectable (see below).

Women considering pregnancy should discuss risks with their physician and undergo cholestyramine washout before switching to an alternative medication compatible with pregnancy.

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 physician immediately for pregnancy testing, and if positive, leflunomide should be stopped and washout given.

Breastfeeding is not recommended.

Washout procedure

To be used in the cases of toxicity, pregnancy or where washout is desired prior to starting an alternative DMARD.

After stopping treatment with leflunomide:

- Prescribe cholestyramine 8g to be taken 3 times daily for a period of 11 days
- Alternatively 50g of activated powdered charcoal may be prescribed to be taken 4 times daily for a period of 11 days

For plasma concentrations below 0.02 mg/L no teratogenic risk is to be expected. Following either of the washout procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/l and fertilisation is required.

Both cholestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that reliable contraception with oral contraceptives may not be guaranteed during the washout procedure with cholestyramine or activated powdered charcoal. Use of alternative contraceptive methods is recommended.

Adverse effects

Very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported in patients treated with leflunomide. As soon as skin and/or mucosal reactions are observed which raise the suspicion of such severe reactions, leflunomide and any other possibly associated medication must be discontinued, and the washout procedure (above) initiated immediately. A complete washout is essential in such cases. Re-exposure to leflunomide is contra-indicated.

Common and uncommon: (see SPC for further information):

- Leucopenia (leucocytes >2 G/l), anaemia, mild thrombocytopenia (platelets <100 G/l)
- Mild allergic reactions
- CPK increased
- Hypokalaemia, hyperlipidemia, hypophosphataemia
- Anxiety
- Paraesthesia, headache, dizziness, peripheral neuropathy
- Mild increase in blood pressure
- Diarrhoea, nausea, vomiting, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), abdominal pain
- Taste disturbances
- Elevation of liver parameters (transaminases [especially ALT], less often gamma-GT, alkaline phosphatase, bilirubin)
- Increased hair loss, eczema, rash (including maculopapular rashand urticaria), pruritus, dry skin
- Tenosynovitis
- Anorexia, weight loss (usually insignificant), asthenia

Drug interactions

Interactions with leflunomide are generally due to increased risk of myelosuppression or hepatoxicity when used with other agents which also increase these risks. See BNF or SPC.

- Leflunomide enhances the effects of warfarin and other coumarin anticoagulants – monitor closely.

MHRA Drug Safety Update (September 2020): Methotrexate once-weekly for autoimmune diseases: new measures to reduce risk of fatal overdose due to inadvertent daily instead of weekly dosing

Advice for prescribers:

- before prescribing methotrexate, make sure that the patient is able to understand and comply with once-weekly dosing
- consider the patient's overall polypharmacy burden when deciding which formulation to prescribe, especially for a patient with a high pill burden
- decide with the patient which day of the week they will take their methotrexate and note this day down in full on the prescription
- inform the patient and their caregivers of the potentially fatal risk of accidental overdose if methotrexate is taken more frequently than once a week; specifically, that it should not be taken daily
- advise patients of the need to promptly seek medical advice if they think they have taken too much
- Refer to the MHRA Drug Safety Update for more information

Patient Safety Agency has highlighted the risks when prescribing methotrexate including failings from poor monitoring of therapy which have led to fatalities. This guideline incorporates their recommendations.

Why do health professionals make mistakes?

A once weekly dosage is very unusual. Only a tiny proportion of medicines administered in the UK are taken at this frequency. Whilst drug packaging has reminders of the correct dose, in practice these are not sufficiently eye-catching to prevent mistakes. Also, the packaging for the 10mg strength tablet looks very similar to the 2.5mg strength tablet.

Why do carers make mistakes?

The drug is packaged in packs of 28 or 100. When patients are prescribed smaller quantities, the dose warning information is often separated from the tablets. In addition folic acid is often prescribed with methotrexate; these are taken daily and can add to the confusion. There is evidence that even when patients are given clear written information that they should take this drug on a weekly basis, they can assume that this must be incorrect. For this reason verbal communication with patients is essential. Methotrexate is a powerful drug. Patients and carers are not always sufficiently informed of the symptoms they should look out for that would indicate toxicity.

Patient information

Patients should be given information about methotrexate, including written information in the form of the purple methotrexate booklet, and allowed time to understand it or discuss it with their families before starting treatment. The weekly dosing and the importance of monitoring must be stressed.

Dosage and administration

For both oral and SC methotrexate, the usual dose range is 2.5mg-25mg ONCE WEEKLY on the SAME DAY EACH WEEK.

Dose is titrated over two to three weeks initially and dosage must be made clear to the patient by specialist team. Initial target dose is 20mg.

- Oral: **oral methotrexate should be prescribed as multiples of 2.5mg tablets.**
  - Methotrexate is also available as tablets containing 10mg of methotrexate. The 10mg tablets of methotrexate are to be used only in oncology and in haematology for patients with malignant disease. The prescriptions must be endorsed as such by the prescriber in secondary care. There should be no prescribing of 10mg tablets in primary care.
- Subcutaneous (sc) methotrexate route is used if:
  - There has been a good response to oral methotrexate but patients suffer severe GI side effects
  - Poor response to oral preparation due to suspected reduced absorption.
  - To avoid confusion for patients due to differences between injection devices, brand prescribing should be used as per current formulary.

To limit the side effects of methotrexate, all patients should receive folic acid 5mg orally at least once weekly and at least 24 hours after taking methotrexate.

Special patient groups: Dose reduction is required for elderly patients and for patients with hepatic or renal impairment.

All prescriptions should avoid the use of "as directed" in prescribing; a specific dose must be put on each prescription. Patients often understand their dose by number of tablets rather than "mg". Quantity and frequency of dose should be regularly discussed with the patient.

Repeat prescriptions should be retained separately for prescriber review prior to authorising.

The label on prescribed/dispensed methotrexate tablets should state the instructions clearly, for example: 'methotrexate 2.5mg tablets: (number of tablets) to be taken as a single dose ONCE A WEEK on XXXDAY'.

The label on prescribed/dispensed methotrexate subcutaneous injection should state the instructions clearly, for example: 'methotrexate ……..injection: (dose) to be taken injected subcutaneously ONCE A WEEK on XXXDAY'.

Contraindications and precautions

Refer to product SPC for methotrexate tablets or the prescribed brand of methotrexate injection.

Patients receiving methotrexate must **not** receive immunization with live vaccines.

Pregnancy and lactation (BSR guidelines September 2016)

Methotrexate is teratogenic and can affect male and female fertility. Women of child-bearing age should use a reliable method of contraception during treatment and at least four months after stopping methotrexate treatment.

When planning a pregnancy it is important to discuss medication with the Rheumatology team.

There is limited evidence that methotrexate at low doses in male patients may be compatible with paternal exposure. Male patients should use contraception and discuss conception with the Rheumatology team when planning a pregnancy.

Methotrexate is not recommended in breast-feeding women.

Alcohol intake

Methotrexate is contraindicated in patients who abuse alcohol.

Ideally not more than 1 unit/day should be consumed. Alcohol consumption should be discussed with patients on or starting methotrexate and limited to the minimum acceptable amount.

Adverse effects

Refer to individual product SPCs for methotrexate.

- Common: gastrointestinal effects (nausea, vomiting, diarrhoea, reduced appetite, stomatitis, oral ulcers); if severe or persistent, seek specialist advice. Ulcerative stomatitis can be a toxic effect and require interruption of therapy as haemorrhagic enteritis and intestinal perforation may result.
- Liver toxicity including elevated transaminases, cirrhosis and periportal fibrosis can occur. Monitor LFTs and limit alcohol intake.
- Leucopenia, anaemia, pancytopenia, thrombocytopenia: GPs should be alert to any unexplained warning signs and ensure monitoring carried out (see "Monitoring" section, above).
- Acute or chronic interstitial pneumonitis often associated with eosinophilia has been reported.
- Possible activation of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C)
- Malignant lymphomas may occur in patients receiving low dose methotrexate in which case stop treatment.
- Methotrexate can cause dizziness, fatigue, blurred vision and eye-irritation which may affect the ability to drive or operate machinery safely.

Drug interactions

This list is not exhaustive, for additional information, and further interactions, consult the BNF and individual product SPCs for methotrexate. Concurrent use with other haematostatic, nephrotoxic or hepatotoxic drugs will increase the risk of toxicity.

- Concurrent administration of drugs with anti-folate properties e.g**. co-trimoxazole, trimethoprim and sulphonamides** is **contraindicated** due to increased risk of haematological toxicity.
- There is an increased risk of toxicity with **other antibiotics** including doxycycline, penicillins, tetracycline and possibly ciprofloxacin and neomycin.
- Increased risk of toxicity with **NSAIDs** (including high-dose aspirin) – advise patients not to use over the counter products containing NSAIDs or aspirin.
- Excretion of methotrexate may be reduced by **proton-pump inhibitors** increasing risk of toxicity.
- Excretion of methotrexate has been reported as being increased by **levetiracetam** leading to potentially toxic levels. Advice when administered with levetiracetam is to monitor blood levels of both drugs.

Mycophenolate Mofetil (Cellcept®)

Dosage and administration

Usual range: 500mg – 2g per day (max 3g per day) in two divided doses.

Patient specific guidance will be provided to the GP by the specialist.

Contraindications and precautions

Refer to product SPC for Cellcept®.

Patients receiving mycophenolate must **not** receive immunization with live vaccines.

Contraception

Women with childbearing potential should use **two** reliable forms of contraception simultaneously **before starting CellCept therapy, during therapy, and for six weeks after stopping the therapy**; unless abstinence is the chosen method of contraception. Mycophenolate is contraindicated in pregnant women and in women of child-bearing potential who are not using reliable contraception.

Male patients of reproductive potential should therefore be made aware of the potential risks of fathering a child. The available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate, however a risk cannot be fully excluded.

As a precautionary measure for male patients, it is recommended that the patient **or** their female partner **use reliable contraception during treatment and for at least 90 days after cessation** of treatment.

Pregnancy and lactation

Refer to individual product SPCs for Cellcept®.

Mycophenolate mofetil is a powerful human teratogen and should not be used in pregnancy.

Mycophenolate mofetil should not be given to women who are breastfeeding.

Adverse effects

Refer to individual product SPCs for Cellcept®.

- Commonly gastrointestinal effects (vomiting, abdominal pain, diarrhoea, nausea); if severe or persistent, seek specialist advice.
- Leucopenia, anaemia and thrombocytopenia: GPs should be alert to any unexplained bruising or bleeding (see “Monitoring” section, above).
- Patients receiving mycophenolate mofetil are at increased risk of developing lymphomas and other malignancies, particularly of the skin. To minimise the risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Drug interactions

This list is not exhaustive, for additional information, and further interactions, consult the BNF and individual product SPCs for Cellcept®.

- It is recommended that CellCept® should not be administered concomitantly with **azathioprine** because such concomitant administration has not been studied.
- Some **indigestion remedies** and **iron** preparations may reduce the absorption of mycophenolate. These should not be taken within 2 hours of taking the mycophenolate.
- **Colestyramine** may decrease absorption of mycophenolate. Mycophenolate should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption.
- **Rifampicin:** Plasma concentration of active metabolite of mycophenolate reduced by rifampicin which may make mycophenolate less effective. Avoid concomitant administration or monitor closely.

Dosage and administration

Week 1: 500mg each evening
Week 2: 500mg twice daily
Week 3: 500mg in the morning and 1 gram in the evening
Week 4: 1 gram twice daily

The dose may be increased to 3 grams (1.5 grams twice daily or 1 gram three times daily) if no response (after 3 months). Tablets should not be crushed or broken.

Use doses at the lower end of the range for patients with hepatic or renal impairment.

Contraindications and precautions

Refer to product SPC for sulfasalazine.

Contraindications: hypersensitivity to sulphonamides or salicylates, porphyria

Ensure adequate fluid intake as sulfasalazine causes crystalluria and kidney stone formation

Limit alcohol intake to within national recommendations

Use with caution in:

- Patients with severe allergy or bronchial asthma.
- Patients with G-6-PD deficiency as sulfasalazine may cause haemolytic anaemia

Pregnancy and lactation (BSR guidelines September 2016)

When planning a pregnancy, women of child bearing potential are advised to use a reliable method of contraception until discussion with the rheumatology team about pregnancy planning. There is no evidence that sulfasalazine is teratogenic, but the possible risks and benefits to the mother and child should be discussed and folate supplementation should be prescribed.

Sulfasalazine may cause reversible oligospermia and infertility in men. Consider as a possible contributing cause if conception is delayed by more than 12 months.

Sulfasalazine is compatible with breastfeeding in healthy, full-term infants.

Adverse effects

Refer to individual product SPCs for sulfasalazine.

- Leukopenia, thrombocytopenia
- Insomnia, depression, dizziness, headache, taste disorders, convulsions, tinnitus, vertigo
- Vasculitis, cough, dyspnoea, arthralgia
- Gastric distress, nausea, abdominal pain, diarrhoea, vomiting, stomatitis
- Elevation of liver enzymes, proteinuria
- Pruritus, alopecia, urticaria, fever, facial oedema

Epidermal necrolysis, Stevens-Johnson Syndrome and drug rash with eosinophilia and symptoms (DRESS) have been reported but less frequently.

Interactions

Interactions with sulfasalazine are generally due to increased risk of myelosuppression or hepatoxicity when used with other agents which also increase these risks. See BNF or SPC.

- Azathioprine and mercaptopurine: sulfasalazine inhibits TPMT enzyme. Risk of bone marrow suppression and leucopenia with concurrent use of azathioprine or mercaptopurine.
- Digoxin: concomitant use results in reduced absorption of digoxin
- Hypoglycaemic agents: Hypoglycaemia has occurred in patients receiving sulfonamides. Patients receiving hypoglycaemic agents and sulfasalazine should be closely monitored.

Shared Care Agreement Letter – Consultant Request

Rheumatology Department

plh-tr.rheumatologynurses@nhs.net

University Hospitals Plymouth NHS Trust

Patient Details

Date:

Dear Dr _____

Diagnosed condition: ……

We have today commenced the above patient onto the following drug(s) and dosage: ……..

……

……

We have prescribed the first month of treatment and request your agreement to sharing the care of this patient according to the Western Locality Shared Care Information guidelines for this drug.

The results of any relevant baseline tests and any additional supportive information (target range, date of last blood test etc.) are included below:

A further clinic appointment has been booked for _____ weeks' time, and a full clinic letter will follow.

GPs are invited to participate, but if the GP is not confident to undertake these roles then they are under no obligation to do so. If so, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If asked to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them.

Remember: the doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

If you agree to share the care of this medication, further prescriptions should be issued from your practice.

Many thanks for your co-operation.

Signed:		**Date:**
Consultant name:		

Please sign below and return promptly. Remember to keep a copy of this letter for the patient's records. If this letter is not returned shared care for this patient will not commence.

GP Response **Please return via email to:** plh-tr.rheumatologynurses@nhs.net

I agree / do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: **Date:**

GP name: *Delete as appropriate.

Patient agreement

I understand and agree to my responsibilities as described above.

Signed: **Date:**

Name: