NHS
Somerset
Clinical Commissioning Group

Somerset Healthcare Community
Shared Care Protocol:

Immunomodulatory therapies in rheumatology/gastroenterology and dermatology conditions

- ***Azathioprine in dermatology/gastroenterology/rheumatology patients;***
- ***Hydroxychloroquine in dermatology/ rheumatology patients;***
- ***Leflunomide in rheumatology patients;***
- ***Mercaptopurine in gastroenterology patients;***
- ***Methotrexate tablets and subcutaneous injection in dermatology / gastroenterology /rheumatology patients***
- ***Penicillamine in rheumatology patients;***
- ***Sodium aurothiomalate in rheumatology patients;***
- ***Sulfasalazine in gastroenterology/ rheumatology patients***

This shared care protocol (SCP) sets out details for the sharing of care for patients requiring azathioprine tablets, hydroxychloroquine tablets, leflunomide tablets, mercaptopurine tablets, methotrexate tablets, subcutaneous methotrexate injection, penicillamine tablets or sulfasalazine tablets. It should be read in conjunction with the relevant Summary of Product Characteristics (SPC), available at http://www.medicines.org.uk/emc) as well as the 'BSR and BHPR guideline for the prescription and monitoring of non-biologic Disease Modifying Anti-Rheumatic Drugs'

As outlined in NHS England Guidance 2018 (07573), 'Responsibility for Prescribing Between Primary & Secondary/Tertiary Care': When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP concerned (and the patient) to share their care.
This document provides information on drug treatment for the shared commitment between the consultant and GP concerned. GPs are invited to participate. If the 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. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

N.B. If the GP decides not to participate in shared care for a particular patient, they must inform the relevant specialist in writing, within 2 weeks of receipt of a request to share care.

For further information please click on the links below or visit:

British National Formulary

Summary of Product Characteristics

NICE Guidance

The Green Book

General Information and Index

This shared care guideline has been written to bring the shared care guidelines for all immunomodulatory therapies which can be prescribed under shared care arrangements in Somerset for dermatology, gastroenterology and rheumatology into a single document. The monitoring parameters set out are based on the BSR and BPHR guideline for the prescription and monitoring of Disease Modifying Anti-Rheumatic Drugs, although there are a few variations due to specialist recommendations. There is an information page for each drug, which should be read along with the shared care responsibilities and monitoring section on pages 11-16.

NICE guideline 100 (NG100) 'Rheumatoid arthritis in adults: management' states:
1.2.1. Treat active RA in adults with the aim of achieving a target of remission or low disease activity if remission cannot be achieved (treat-to-target). Achieving the target may involve trying multiple conventional disease-modifying anti-rheumatic drugs (cDMARDs) and biological DMARDs with different mechanisms of action, one after the other.

Index:

Further support

- Medicines Information department, Musgrove Park Hospital: 01823 342253
- Medicines Information department, Yeovil District Hospital: 01935 384327
- Prescribing & Medicines Management Team, NHS Somerset CCG: 01935 384123

Azathioprine information

Azathioprine is an immunosuppressive pro-drug, which is cleaved rapidly in the liver to 6-mercaptopurine.

The main toxic effect is myelosuppression, although hepatotoxicity is also well recognised. Azathioprine is metabolised by the enzyme thiopurine methyltransferase (TPMT). It has been established that approximately 89% of the population has a normal TPMT activity requiring normal doses of azathioprine (2.0-2.5 mg/kg/day), 11% have intermediate TPMT activity and are at a higher risk of adverse drug reaction on standard doses of azathioprine and 0.3% are deficient or have no detectable TPMT activity and are at risk of suffering life-threatening complications even when treated with low doses of azathioprine. TPMT activity can be measured phenotypically and genotypically.

Azathioprine- licensed indications relevant to shared care:

Adult patients in the treatment of:

- Systemic lupus erythematosus;
- Dermatomyositis and polymyositis;
- Polyarteritis nodosa;
- Generalised myasthenia gravis
- Pemphigus vulgaris;
- Auto-immune chronic active hepatitis;
- Severe or moderately severe inflammatory bowel diseases (IBD; Crohn's disease or ulcerative colitis), in patients who are intolerant to steroids or who are dependent on steroids and in whom the therapeutic response is inadequate despite treatment with high doses of steroids. I'm sure this is a licensed indication but I think maintenance is unlicensed

Azathioprine- unlicensed indications relevant to shared care:

- Maintenance of remission of Crohn's disease or ulcerative colitis

Azathioprine dose (posology & method of administration) (click for details in SPC)

- Lower doses if there is significant renal or hepatic impairment.
- If allopurinol is prescribed concomitantly, the dose of azathioprine must be reduced to 25% of the original dose or avoided; Concomitant administration of other xanthine oxidase inhibitors, such as febuxostat, should be avoided.

Azathioprine dose in rheumatology indications:

- A typical dose regimen may be**:** 1mg/kg/day increasing after 4 to 6 weeks to 2-3mg/kg/day
- It may take up to 3 months to see a clinical response.

Azathioprine dose in inflammatory bowel disease:

- The target dose is **2–2.5 mg/kg daily** for IBD, but lower doses are used in hepatology**;**
- Start at 50 mg once daily (adults) and increase to achieve target dose within 4-6 weeks.
- As clinical response is not usually expected for 12-16 weeks, azathioprine is often commenced with oral steroids for more immediate relief of symptoms with the steroid dose being tapered as the immunosuppressant begins to be effective.

Azathioprine - Contraindications (click for details in SPC)

Azathioprine - Special warnings and precautions for use (click for details in SPC)

Live vaccines including oral polio, oral typhoid, intranasal influenza, varicella zoster, yellow fever, BCG and rubella (including MMR) should be administered with caution in patients taking azathioprine. The Green Book states that many adults with chronic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, psoriasis, glomerulonephritis) will be on stable long term low dose corticosteroid therapy (defined as up to 20mg prednisolone per day for more than 14 days in adults or 1mg/kg/day in children under 20kg) either alone or in combination with other immunosuppressive drugs. Long term stable low dose corticosteroid therapy, either alone or in combination with low dose **non-biological** oral immune modulating drugs (e.g. azathioprine 3.0mg/ kg/day), are **not** considered sufficiently immunosuppressive and these patients **can** receive live vaccines. **N.B. Green Book advice is new, from 2017 some literature and patient information leaflets and websites still state that patients on Azathioprine should not receive**

live vaccines- this could cause confusion

Azathioprine - Interactions (click for details in SPC)

Azathioprine in pregnancy and lactation (click for details in SPC)

- Careful assessment of risk versus benefit should be carried out before and during pregnancy/ breastfeeding but do not stop these drugs without consulting hospital specialist clinician or IBD nurse. Risks of continuing azathioprine are usually outweighed by benefits.
- There have been reports of premature birth and low birth weight following maternal exposure to azathioprine, particularly in combination with corticosteroids. There have also been reports of spontaneous abortion following either maternal or paternal exposure.
- Azathioprine and/or its metabolites have been found in low concentrations in foetal blood and amniotic fluid after maternal administration of azathioprine.
- Leucopenia and/or thrombocytopenia have been reported in a proportion of neonates whose mothers took azathioprine throughout pregnancies. Extra care in haematological monitoring is advised during pregnancy.
- 6-Mercaptopurine has been identified in the colostrum and breast-milk of women receiving azathioprine treatment.

BSR Guidelines state:

- Azathioprine is compatible throughout pregnancy at ⩽2 mg/kg/day
- Azathioprine is compatible with breastfeeding .
- Azathioprine is compatible with paternal exposure.

Azathioprine- Adverse effects (click for details in SPC)

Hydroxychloroquine information

Hydroxychloroquine is a disease-modifying anti-rheumatic drug used in the treatment of rheumatoid arthritis and systemic and discoid lupus erythematosus.

Hydroxychloroquine - licensed indications relevant to shared care:

Adult patients in the treatment of:

- Active rheumatoid arthritis
- Systemic and discoid lupus erythematosus
- Dermatological conditions caused or aggravated by sunlight

Hydroxychloroquine dose (posology & method of administration) (click for details)

Adults (including the elderly):

- The minimum effective dose should be employed; dose should not exceed 5mg/kg/day (calculated from ideal body weight, **NOT** actual body weight) and will be either 200mg or 400mg/ day.
- **In patients able to receive 400mg daily:** Initially, 400mg daily in divided doses, reducing to 200mg when no further improvement is evident. The maintenance dose should be increased to 400mg daily if the response lessens.
- No dose adjustment is required in patients above 65 years of age.
- In patients with hepatic or renal disease, and in those taking drugs known to affect those organs, estimation of plasma hydroxychloroquine levels should be undertaken in patients with severely compromised renal or hepatic function and dosage adjusted accordingly.

Hydroxychloroquine - Contraindications (click here for details in SPC)

Hydroxychloroquine - Special warnings and precautions (click here for details in SPC)

Hydroxychloroquine - Interactions (click here for details in SPC)

Hydroxychloroquine in Pregnancy and Lactation (click here for details in SPC)

BSR guidelines state:

- Hydroxychloroquine remains the antimalarial of choice in women planning a pregnancy with rheumatic disease in need of treatment and should be continued during pregnancy.
- Hydroxychloroquine is compatible with breastfeeding.
- Men should not be discouraged from taking hydroxychloroquine while trying to conceive

Hydroxychloroquine - Adverse effects (click here for details)

Leflunomide information

Leflunomide is a disease-modifying anti-rheumatic drug (**normally used in** after Methotrexate/Sulphasalazine treatment is contra-indicated, not tolerated or ineffective). The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

Leflunomide - licensed indications relevant to shared care:

Adult patients in the treatment of:

- active rheumatoid arthritis
- active psoriatic arthritis

Leflunomide- Dose (posology & method of administration) (click for details in SPC)

Adults:

- **Rheumatoid Arthritis:** The recommended maintenance dose of leflunomide is 10 mg to 20 mg once daily. Patients may be started on leflunomide 10 mg or 20 mg depending on the severity (activity) of the disease.
- **Active psoriatic arthritis:** The recommended maintenance dose for psoriatic arthritis is leflunomide 20 mg once daily.
- There is no dose adjustment recommended in patients with mild renal insufficiency.
- No dosage adjustment is required in patients above 65 years of age.

Leflunomide- Contraindications (click here for details in SPC)

Leflunomide- Special warnings and precautions for use (click here for details in SPC)

Leflunomide- Interactions (click here for details in SPC)

Leflunomide in Pregnancy and Lactation (click here for details in SPC)

- Based on limited evidence, leflunomide may not be a human teratogen but it is still not recommended in women planning pregnancy.
- Women on leflunomide considering pregnancy should stop and undergo cholestyramine washout before switching to alternative medication compatible with pregnancy.
- There is no human evidence of increased congenital abnormalities on leflunomide if washout is given. Therefore, if accidental conception occurs on leflunomide, the drug should be stopped immediately and cholestyramine washout given until plasma levels are undetectable Contact the rheumatology department urgently for advice about wash out.
- No data exist on excretion into breast milk, therefore breastfeeding is not recommended.
- Based on very limited evidence, leflunomide may be compatible with paternal exposure.

Leflunomide- Adverse effects (click here for details)

Mercaptopurine information

Mercaptopurine is a cytotoxic purine analogue which interferes with nucleic acid synthesis. The drugs mercaptopurine and azathioprine (a prodrug of mercaptopurine) are commonly used unlicensed at low doses to treat inflammatory bowel disease (IBD). Mercaptopurine is an option where Azathioprine has been beneficial but side effects are affecting tolerability. The decision as to whether the patient is initiated on either Azathioprine or Mercaptopurine lies with the consultant.

Mercaptopurine - licensed indications relevant to shared care:

- N/A

Mercaptopurine - unlicensed indications relevant to shared care:

- Adults in the treatment of severe acute Crohn's disease or ulcerative colitis, maintenance of remission of Crohn's disease or ulcerative colitis

Mercaptopurine - Dose (posology & method of administration) (click for SPC)

Adults over 18 years:

- Mercaptopurine is usually commenced at 25mg per day (half a 50mg tablet); dose is gradually increased to achieve the target dose, if tolerated.
- Responsible consultants will give instructions to individual patients and inform GPs regarding the target dose and rate of increase.
- Typically, target dose is 1–1.5 mg/kg daily; some patients may respond to lower doses. Tablets are scored to facilitate division of tablets into two halves, if required. A tablet cutter may be useful.
- If allopurinol is prescribed concomitantly, the dose of mercaptopurine must be reduced to 25% of the original dose or avoided; Concomitant administration of other xanthine oxidase inhibitors, such as febuxostat, should be avoided.
- As a clinical response is not usually expected for up to 12 weeks, mercaptopurine is often commenced with oral steroids for more immediate relief of symptoms, with the steroid dose being tapered as the mercaptopurine begins to take effect.
- Mercaptopurine should be administered at least 1 hour before or 3 hours after food or milk.

Mercaptopurine- Contraindications (click for details in SPC)

- Hypersensitivity to azathioprine or mercaptopurine.

Mercaptopurine - Interactions (click for details in SPC)

Mercaptopurine - Special warnings and precautions for use (click for details in SPC)

- Mercaptopurine is also known as 6-mercaptopurine (6-MP). This should not be used on prescriptions because historically it has been associated with an increased risk of prescribing and pharmacy dispensing errors.

Live vaccines including oral polio, oral typhoid, intranasal influenza, varicella zoster, yellow fever, BCG and rubella (including MMR) should be administered with caution in patients taking mercaptopurine. The Green Book states that many adults with chronic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, psoriasis, glomerulonephritis) will be on stable long term low dose corticosteroid therapy (defined as up to 20mg prednisolone per day for more than 14 days in adult or 1mg/kg/day in children under 20kg) either alone or in combination with other immunosuppressive drugs. Long term stable low dose corticosteroid therapy, either alone or in combination with low dose **non-biological** oral immune modulating drugs (e.g. 6-mercaptopurine 1.5mg/kg/day), are **not** considered sufficiently immunosuppressive and these patients **can** receive live vaccines. **N.B. Green Book advice is new, from 2017 some literature and patient information leaflets and websites still state that patients on Mercaptopurine should not receive live vaccines- this could cause confusion**

Mercaptopurine in pregnancy and lactation (click for details in SPC)

- Despite the concerns raised in the SPC, the European Crohn's and Colitis Organisation (ECCO) Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease review does not conclude that Mercaptopurine needs to be discontinued (van der Woude et al, JCC 2015; 9(2) 107-124, see section 5.2.3 p113). In summary, controlled studies and a meta-analysis in 2013 (Hutson et al, J Obst Gynaecol. 2013 Jan 33(1):1-8) conclude that thiopurines do not pose an increased risk for adverse pregnancy outcome, compared with pregnancy outcomes of IBD patients without this treatment. Other studies have reported an increased rate of spontaneous miscarriage, preterm delivery, low birth weight which could have been caused by the underlying disease rather than the use of thiopurines.

- Very small amounts of Azathioprine and Mercaptopurine metabolites have been identified in breast milk in several case reports. The available data show no increased infection risks for the observed breastfed babies of 11 mothers taking Azathioprine compared with those of 12 mothers who were not taking any sort of immunosuppressive therapy. The ECCO consensus statement 6B (6B, see p115) states 5ASA derivatives, thiopurines, anti TNFs and corticosteroids are of low risk for breast-fed infants.

Mercaptopurine - Adverse effects (click for details in SPC)

Methotrexate information

Methotrexate inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines. It is used in low doses for the treatment of active rheumatoid arthritis in adult patients, severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, Psoralen combined with Ultraviolet A (PUVA) treatment, and retinoids, and severe psoriatic arthritis in adult patients. It is also used in patients with inflammatory bowel disease (small bowel Crohn's).

Methotrexate - licensed indications relevant to shared care:

Methotrexate tablets

- treatment of severe cases of uncontrolled psoriasis, unresponsive to conventional therapy.
- treatment of adults with severe, active, classical or definite rheumatoid arthritis

Methotrexate subcutaneous injection

- treatment of active rheumatoid arthritis in adult patients
- treatment of severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, psoralens and ultraviolet A (PUVA), and retinoids, and severe psoriatic arthritis in adult patients.
- mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines (N.B. Some injectable preparations only)

Methotrexate - unlicensed indications relevant to shared care:

- treatment of severe Crohn's Disease
- generalised myasthenia gravis
- dermatomyositis; connective tissue disease (SLE, myositis and vasculitis); blistering conditions; sarcoidosis; lymphomatoid papulosis.

Methotrexate- Dose (posology & method of administration) (click for details in SPC)

Adults over 18 years:

- Methotrexate dose is usually titrated at regular intervals until target dose / response is achieved.
- Maximum weekly dose of methotrexate tablets should not exceed 25mg unless there has been prior agreement between consultant and GP.
- Methotrexate must be used with caution in renal failure or hepatic impairment; elderly patients should be

given a smaller test dose and titrated at a slower rate.
- Folic acid tablets 5mg to be taken once EACH WEEK on the day before or the day after methotrexate to limit side effects, e.g. gastrointestinal and haematological toxicity.

Methotrexate – Contraindications (click for details in SPC)

Methotrexate – Special warnings and precautions for use (click for details in SPC)

- Live vaccines including oral polio, oral typhoid, intranasal influenza, varicella zoster, yellow fever, BCG and rubella (including MMR) should be administered with caution in patients taking methotrexate. The Green Book states that many adults with chronic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, psoriasis, glomerulonephritis) will be on stable long term low dose corticosteroid therapy (defined as up to 20mg prednisolone per day for more than 14 days in adult or 1mg/kg/day in children under 20kg) either alone or in combination with other immunosuppressive drugs. Long term stable low dose corticosteroid therapy, either alone or in combination with low dose **non-biological** oral immune modulating drugs (e.g. methotrexate 25mg per week in adults or up to 15mg/m2 in children), are **not** considered sufficiently immunosuppressive and these patients **can** receive live vaccines. **N.B. Green Book advice is new, from 2017 some literature and patient information leaflets and websites still state that patients on Methotrexate should not receive live vaccines- this could cause confusion.**

Note that the dose is a **weekly** dose. To avoid error with low-dose methotrexate, it is recommended that:
- the patient is carefully advised of the **dose** and **frequency** and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (2.5 mg) should be prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).
- In most patients, subcutaneous methotrexate will replace current oral methotrexate and monitoring should be continued as already being done by the GP without any change. The monitoring for subcuataneous and oral methotrexate is the same (i.e. a straight switch from the current monitoring)

Methotrexate – Interactions (click for details in SPC)

Methotrexate in pregnancy and lactation (click for details in SPC)

BSR guidelines state:

- Methotrexate at any dose should be avoided in pregnancy and stopped 3 months in advance of conception.
- In women treated with low-dose methotrexate within 3 months prior to conception, folate supplementation (5 mg/day) should be continued prior to and throughout pregnancy.
- In the case of accidental pregnancy on low-dose methotrexate, the drug should be stopped immediately, folate supplementation (5 mg/day) continued and a careful evaluation of foetal risk carried out by local experts.
- Methotrexate cannot be recommended in breastfeeding because of theoretical risks and insufficient outcome data.
- Based on limited evidence, low-dose methotrexate may be compatible with paternal exposure.

Methotrexate - Adverse effects (click for details in SPC)

Penicillamine

Penicillamine is an anti-rheumatic drug, mainly used in the treatment of rheumatoid arthritis.

Penicillamine – Licensed indications relevant to shared care:

- Severe active rheumatoid arthritis, including juvenile forms

Penicillamine - Dose (posology & method of administration) (click for details in SPC)

Adults over 18 years, rheumatoid Arthritis: 125mg to 250mg daily for the first month. Increase by the same amount every four to twelve weeks until remission occurs. The usual maintenance dose is 500 to 750mg daily.

The minimum maintenance dose to achieve suppression of symptoms should be used and treatment should be discontinued if no benefit is obtained within 12 months. Improvement may not occur for some months.

The elderly: 20mg/kg/day in divided doses adjusting the dose to minimal level necessary to control disease.

Penicillamine- Contraindications (click here for details in SPC)

Special warnings and precautions for use (click here for details in SPC)

Renal insufficiency: Extra precautions should be taken to monitor for adverse effects in patients with Wilson's disease and renal insufficiency.

Tablets should be taken at least half an hour before meals. Indigestion remedies or products containing iron or zinc should not be taken within 2 hours of the penicillamine dose.

Penicillamine - Interactions (click here for details in SPC)

Penicillamine in Pregnancy and Lactation (click here for details in SPC)

- Penicillamine should not be administered to patients with Rheumatoid Arthritis who are pregnant, and therapy should be stopped when pregnancy is diagnosed or suspected, unless considered to be absolutely essential by the physician.
- Due to the lack of data on 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.

Penicillamine - Adverse effects (click here for details)

Sodium Aurothiomalate

Sodium Aurothiomalate (gold injection) is an anti-rheumatic drug used in the treatment of rheumatoid arthritis. The earliest initial response is seen at 6 – 12 weeks.

Sodium Aurothiomalate – Licensed indications relevant to shared care

- Myocrisin is used in the management of active progressive rheumatoid arthritis and progressive juvenile chronic arthritis especially if polyarticular or seropositive

Sodium Aurothiomalate - Dose (posology & method of administration) (click for details in SPC)

Adults over 18 years:

- An initial test dose of 10 mg should be given in the first week followed by weekly doses of 50 mg until signs of remission occur. At this point 50 mg doses should be given at two week intervals until full remission occurs. With full remission the interval between injections should be increased progressively to three, four and then, after 18 months to 2 years, to six weeks.

- Administration: should only be administered by deep intramuscular injection followed by gentle massage of the injection area.

Sodium Aurothiomalate – Contraindications (click for details in SPC)

Sodium Aurothiomalate – Special warnings and precautions for use (click for details in SPC)

- ***Renal insufficiency:*** Extra precautions should be taken to monitor for adverse effects in patients with Wilson's disease and renal insufficiency.
- Tablets should be taken at least half an hour before meals. Indigestion remedies or products containing iron or zinc should not be taken within 2 hours of the penicillamine dose.

Sodium Aurothiomalate – Interactions (click for details in SPC)

Sodium Aurothiomalate in pregnancy and lactation (click for details in SPC)

- The safety of sodium aurothiomalate in the foetus and the newborn has not been established. Female patients receiving Myocrisin should be instructed to avoid pregnancy. Pregnant patients should not be treated with Myocrisin.
- Lactating mothers under treatment with sodium aurothiomalate excrete significant amounts of gold in their breast milk and should not breast feed their infants.

Penicillamine - Adverse effects (click here for details)

Sulfasalazine

Sulphasalazine is an effective second line drug for treatment of rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs). It can also be used for the induction and maintenance of remission of ulcerative colitis and for treatment of active Crohn's Disease, but is rarely indicated in IBD as the newer and generally better tolerated 5-aminosalicylate (5-ASA) medications are used instead.

Sulfasalazine – Licensed indications relevant to shared care

- Induction and maintenance of remission of ulcerative colitis; treatment of active Crohn's Disease.
- Treatment of rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs).

Sulfasalazine - Dose (posology & method of administration) (click for details in SPC)

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 daily if no response.
- Tablets should not be crushed or broken. It is recommended that tablets should be taken with water.

Sulfasalazine – Contraindications (click for details in SPC)

Sulfasalazine – Special warnings and precautions for use (click for details in SPC)

Sulfasalazine – Interactions (click for details in SPC)

Sulfasalazine in pregnancy and lactation (click for details in SPC)

- Sulfasalazine with folate supplementation (5 mg/day) is compatible throughout pregnancy.
- Sulfasalazine is compatible with breastfeeding in healthy, full-term infants.
- Men taking sulfasalazine may have reduced fertility. There is no evidence, however, that conception is enhanced by stopping sulfasalazine for 3 months prior to conception unless conception is delayed >12 months when other causes of infertility should also be considered.

Sulfasalazine- Adverse effects (click for details in SPC)

Shared Care Responsibilities

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to, and accepted by, the patient. This provides an opportunity to discuss drug therapy.

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

Specialist responsibilities (all drugs covered by this Shared Care Guideline):-

1. Assess the need for an immunomodulatory therapy.
2. Complete relevant baseline investigations before patient is commenced on an immunomodulatory therapy.
3. Discuss benefits and side effects of treatment with patient or patient's carers including, where appropriate, the risks associated with pregnancy and need for reliable method of contraception.
4. Check that the patient has been vaccinated against flu and pneumococcus (this is recommended)
5. Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection. Baseline HIV status should also be established in those with risk factors.
6. Discuss how the patient / carer can be aware of possible signs hydroxychloroquine toxicity or intolerance
7. Initiate treatment and prescribe medication for the length of time specified below and request GP to continue/commence monitoring:

Immunomodulatory therapy	**Speciality**	**Duration of treatment to be prescribed by consultant before requesting shared care**
Azathioprine	Gastroenterology	Minimum of 3 months- at least until the patient is stable
Azathioprine	Dermatology/ Rheumatology	Issue the first prescription for 4 weeks supply and request GP to continue/commence monitoring. Check response to treatment after 4 weeks.
Hydroxychloroquine	Dermatology/ Rheumatology	Issue the first prescription for 4 weeks supply and request GP to continue/commence monitoring. Check response to treatment after 4 weeks.
Leflunomide	Rheumatology	Issue the first prescription for 4 weeks supply and request GP to continue/commence monitoring. Check response to treatment after 4 weeks.
Mercaptopurine	Gastroenterology	Minimum of 3 months- at least until the patient is stable
Methotrexate	Dermatology/ Gastroenterology/ Rheumatology	Issue the first prescription for 4 weeks supply and request GP to continue/commence monitoring. Check response to treatment after 4 weeks.
Penicillamine	Rheumatology	Issue the first prescription for 4 weeks supply and request GP to continue/commence monitoring. Check response to treatment after 4 weeks.
Sodium aurothiomalate	Rheumatology	Administer test dose and continue to administer as per dosing regime until remission occurs. Once remission occurs, request GP to continue/commence monitoring.
Sulfasalazine	Rheumatology/ Gastroenterology	Issue the first prescription for 4 weeks supply and request GP to continue/commence monitoring. Check response to treatment after 4 weeks.

8. Specify review dates.
9. 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.
10. Follow the patient's response to treatment at the out-patient clinic.

11. Prompt verbal communication followed up in writing to GP of changes in treatment or monitoring requirements, results of monitoring, assessment of adverse events or when to stop. Urgent changes to treatment should be communicated by telephone to GP.
12. Request GP to monitor as required in the monitoring section of this protocol.
13. Advise GP regarding any concerns about monitoring or, adverse effects, at any stage.
14. Reporting adverse events via the yellow card system.

GP responsibilities (all drugs covered by this Shared Care Guideline):-

1. Accept clinical responsibility for the patient provided the above criteria have been met.
2. Repeat prescribing of an immunomodulatory therapy no sooner than specified in the table above after initiation.
3. Discuss any important test abnormality with the consultant before continuing treatment.
4. Ensure that the patient has received counselling in verbal and written form.
5. Report any suspected adverse reactions to the consultant.
6. Be alert to the possibility of interactions when initiating new drugs.
7. Report any significant events relating to an immunomodulatory therapy to Somerset CCG.
8. Liaise with the hospital consultant regarding any complications of treatment.
9. Undertake blood monitoring and monitor for specific side effects as detailed in the 'Monitoring' section.
10. Report to and seek advice from specialist on any aspect of patient care of concern to GP which may affect treatment. Prompt referral to specialist if there is a change in patient's health status.
11. Stop treatment in case of a severe adverse event or as per shared care guideline.

Patient/ carer responsibilities (all drugs covered by this Shared Care Guideline):-

1. After counselling, to be willing to take the relevant an immunomodulatory therapy as prescribed.
2. Report any concerns in relation to treatment with immunomodulatory therapy.
3. Inform healthcare professionals treating them that they are taking an immunomodulatory therapy.
4. Report any other medication being taken, including over-the-counter products.
5. Report any adverse effects or warning symptoms whilst taking an immunomodulatory therapy such as mouth ulcers, sore throat, fever, epistaxis, rash, unexpected bruising or bleeding, and any unexplained illness/infection (this will vary depending on treatment).

Additional specialist, GP and patient responsibilities listed by drug (page 1 of 2):

Drug	Laboratory monitoring	Other monitoring
AZATHIOPRINE	Specialist	• Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster virus is not necessary if there is a history of previous infection.
	GP	• Ensure that the patient is **NOT** taking allopurinol
	Patient/ Carer	• Report all symptoms and signs suggestive of infection, especially sore throat.
HYDROXYCHLOROQUINE	Specialist	• No additional responsibilities.
	GP	• No additional responsibilities.
	Patient/ Carer	• No additional responsibilities.
LEFLUNOMIDE	Specialist	• No additional responsibilities.
	GP	• No additional responsibilities.
	Patient/ Carer	• No additional responsibilities.
MERCAPTOPURINE	Specialist	• As per azathioprine (above)
	GP	• As per azathioprine (above)
	Patient/ Carer	• As per azathioprine (above)
METHOTREXATE	Specialist	• Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster virus is not necessary if there is a history of previous infection. • Comply with NPSA Alerts for methotrexate. • Provide and complete the initial **Methotrexate patient information and monitoring booklet**. • Make the patient aware that taking aspirin and NSAIDs with methotrexate may cause toxicity. • Exercise caution when initiating methotrexate in patients with impaired renal function.
	GP	• Comply with NPSA alerts for methotrexate. • Prescribe weekly folic acid (5mg orally) to be taken the day after the methotrexate. • Pause methotrexate treatment if eGFR <35 ml/min due to increased risk of toxicity and, before re-initiating, seek advice from specialist if eGFR remains <35 ml/min. • Provide subsequent **Methotrexate patient information and monitoring booklets** • **Do not** co-prescribe Methotrexate with Trimethoprim or Co-trimoxazole due to the risk of severe blood dyscrasias.
	Patient/ Carer	• Report all symptoms and signs suggestive of infection, especially sore throat.
PENICILLAMINE	Specialist	• Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster virus is not recommended.
	GP	• No additional responsibilities.
	Patient/ Carer	• Report all symptoms and signs suggestive of infection, especially sore throat.

Additional specialist, GP and patient responsibilities listed by drug (page 2 of 2):

Drug	Laboratory monitoring	Other monitoring
SODIUM AUROTHIOMALATE (Gold)	Specialist	• Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster virus is not recommended. • Administer a test dose – observe patient for one hour. Take appropriate action if the patient develops a rash.
	GP	• Check patient for rash and ask about mouth ulceration before subsequent doses. Observe patient for 30 minutes after each dose, check for rash. Take appropriate action if symptoms reported.
	Patient/ Carer	• Report any adverse effects or warning symptoms whilst taking Sodium aurothiomalate such as pruritus, mouth ulcers, sore throat or tongue, bleeding gums, fever, metallic taste, epistaxis, rash, unexpected bruising or bleeding, menorrhagia, diarrhoea and any unexplained illness/infection. Breathlessness or cough must also be reported.
SULFASALAZINE	Specialist	• No additional responsibilities.
	GP	• No additional responsibilities.
	Patient/ Carer	• No additional responsibilities.

Monitoring

Drug	Baseline Monitoring (minor variations within each specialty)	Laboratory monitoring	Other monitoring	PARAMETERS FOR CONCERN
AZATHIOPRINE	• Height, • Weight, • Blood pressure evaluation-Full blood count(FBC) • U&Es • Urine analysis • Calculated glomerular filtration rate (GFR), • LFTs • ESR and CRP (rheumatology and gastroenterology patients) • Viral serology; Hepatitis B and C serology, HIV test in all high risk groups, EBV serology (in young gastroenterology patients due to start Azathioprine or Mercaptopurine), Varicella serology if history unclear • **Azathioprine and mercaptopurine:** TPMT assay • **Methotrexate:**CXR unless done in last 6 months, & pulmonary function (only in selected service users, e.g. abnormal shadowing on CXR) • **Sodium Aurothiomalate pts-** CXR	Standard monitoring schedule*	None	**WCC < 3.5 x 10^9/L** **Neutrophils <1.6 x 10^9/L** **Unexplained eosinophilia > 0.5 x 10^9/L** **Platelet Count < 140 x 10^9/L** **MCV > 105f/L** **Creatinine > 30% above baseline and/or calculated GFR < 60 ml/min** **ALT and/or AST > 100 units/L (or 2-3 x upper limit of normal)** **Unexplained fall in serum albumin <30 g/L** Withhold drug and discuss with specialist nurse/ responsible consultant straight away. On specialist advice the dose may need to be reduced and bloods rechecked after an appropriate interval, or the drug stopped
HYDROXYCHLOROQUINE		No routine laboratory monitoring	*Annual eye assessment (ideally inc. Optical Coherence Tomography if continued for > 5 years arranged in secondary care).*	
LEFLUNOMIDE		Standard monitoring schedule*	BP and weight at each monitoring visit	
MERCAPTOPURINE		Standard monitoring schedule*	None	
METHOTREXATE		Standard monitoring schedule*	None	
LEFLUNOMIDE/METHOTREXATE Combined		Extend monthly monitoring longer term	BP and weight at each monitoring visit	
PENICILLAMINE		Fortnightly standard monitoring for 8 weeks*, then monthly;	Urinalysis or blood and protein weekly initially and after dose increase; then monthly	
SODIUM AUROTHIOMALATE (Gold)		Standard monitoring schedule*	Urinalysis for blood and protein prior to each dose; Annual CXR	
SULFASALAZINE		Standard monitoring schedule* for 12 monthly then no routine monitoring needed	None	

See next page for standard monitoring schedule

Standard monitoring schedule

Prescribers should consider individual patient needs for additional monitoring as specified in the drugs SPC

For patient starting treatment or after dose increase:	1. **Rheumatology and dermatology patients:** Every 2 weeks until stable for 6 weeks; followed by monthly monitoring for 3 months; then maintenance monitoring, as below. 2. **TST Gastroenterology patients: Every 2 weeks;** until stable for 8 weeks; repeat again in another 4 weeks; then maintenance monitoring, as below..	FBC Creatinine LFT Albumin
Maintenance Monitoring: **Individual Advice will be given for:**	At least every 12 weeks Patients high risk e.g. age > 80, renal impairment, abnormal results, comorbidities, multiple prescriptions, more frequent monitoring is needed	FBC Creatinine LFT Albumin CRP (prior to every secondary care review)

Further support

- Medicines Information department, Musgrove Park Hospital: 01823 342253
- Medicines Information department, Yeovil District Hospital: 01935 384327
- Prescribing & Medicines Management Team, NHS Somerset CCG: 01935 384123

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Drawn up by:	Version 1.0 by Catherine Henley, Medicines Manager, Somerset CCG with advice from Dr Sally Knights, Dr Alex Bourne (YDH Consultant rheumatologists), Dr Cathy Laversuch (TST Consultant Rheumatologist), Teresa Jewell (TST Rheumatology Nurse Specialist), Dr Nicola Hare (TST consultant gastroenterologist)and Dr Rachael Wachsmuth (Consultant Dermatologist). The original azathioprine, leflunomide, methotrexate, sodium aurothiomalate and sulfasalazine shared care guidelines have been combined into this document in response to new BSR monitoring guidance which aligns the monitoring for all immunomodulatory drugs	June 2018
Updated by:	Version 2.0 by Hels Bennett, Medicines Manager, Somerset CCG Updated to reflect new NICE guidance (NG100) & addition of Myasthenia Gravis indication to azathioprine and methotrexate as per PAMM committee & SPF Nov 2020 Minor formatting changes	December 2020
Approved by:	Prescribing & Medicines Management Committee, NHS Somerset	
	Somerset Prescribing Forum, NHS Somerset	
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