Shared Care Guideline

Sulfasalazine - in rheumatic diseases

Executive Summary

- Sulfasalazine is used as a disease-modifying agent to induce and maintain remission of rheumatoid arthritis (RA).
- Enteric-coated tablets are recommended to reduce the risk of adverse drug reactions.
- The starting dose is 500mg once a week, increasing by 500mg per week to a dose of 1G twice a day (or higher if clinically appropriate).
- Clinical response usually starts within approximately 3 months.
- Sulfasalazine is usually considered safe in pregnancy (maximum dose 2g/day, folic acid 5mg daily supplementation for the mother) and in breastfeeding of a healthy full-term infant.
- Sulfasalazine can be prescribed to men of childbearing potential although there may be transient reversible oligospermia. Conception may be enhanced by stopping sulfasalazine for 3 months prior to conception.
- Most adverse drug reactions occur within 6 months of starting treatment. Some undesirable effects are dose-dependent and symptoms may be alleviated by dose reduction.
- The most common adverse drug reactions are nausea, headache, rash, loss of appetite and raised temperature.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here.

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here.
1. Scope
Cross-boundary: Trust and general practice in adult patients.

2. Aim
To provide guidance in the use of sulfasalazine as a disease-modifying agent in the treatment of rheumatoid arthritis.

3. Introduction
Sulfasalazine is used as a disease modifying agent to induce and maintain remission in rheumatoid arthritis and psoriatic arthritis. It is potentially toxic and therefore the drug must be monitored, particularly in the first three months of treatment. This shared care guideline outlines the responsibility of primary and secondary care clinicians using sulfasalazine in rheumatic diseases.

4. Abbreviations
- ALT alanine transaminase
- BCG bacillus Calmette–Guérin
- DMARD disease-modifying anti-rheumatic drug
- ESR erythrocyte sedimentation rate
- FBC full blood count
- G-6-PD glucose-6-phosphate dehydrogenase
- GP general practitioner
- LFTs liver function tests
- MCV mean cell volume
- MMR measles, mumps and rubella vaccine
- SmPC summary of medicinal product characteristics
- TSH thyroid stimulating hormone
- WBC white blood cell count

5. Dose and Administration
Sulfasalazine 500mg enteric coated tablets are recommended as gastrointestinal intolerance is more likely to occur with plain tablets.

- The starting dose is 500 mg daily for one week, increasing by 500 mg each week up to a maximum of 2 g daily. This is usually taken in two divided doses (1g twice a day).
- Higher doses may be used if required, for example 1 g three times a day. Very occasionally the dose may exceed 3 g daily.
- Clinical response usually starts in approximately three months.

Further information can be found in the British National Formulary and the Summary of Medicinal Product Characteristics (SmPC) (https://www.medicines.org.uk/emc/product/6686 ).
6. **Adverse Effects**

   About 75% of adverse drug reactions occur within three months of starting therapy, and over 90% by six months. Some undesirable effects are dose-dependent and symptoms can often be alleviated by reducing the dose.

**Very common** (≥1/10)

- Gastric disturbances
- Nausea

**Common** (≥1/100 to < 1/10);

- Abdominal pain
- Arthralgia
- Conjunctival and scleral injection
- Cough
- Diarrhoea
- Dizziness
- Fever
- Headache
- Insomnia
- Leucopenia
- Proteinuria
- Pruritis
- Stomatitis
- Taste disorders
- Tinnitus
- Vomiting

**Uncommon** (≥1/1000 to < 1/100).

- Alopecia
- Convulsions
- Depression
- Dyspnoea
- Elevation of LFTs
- Facial oedema
- Thrombocytopenia
- Urticaria
- Vasculitis
- Vertigo
Frequency unknown

- Blood and lymphatic system: agranulocytosis, aplastic anemia, haemolytic anemia, Heinz body anaemia, hypoprothrombinaemia, lymphadenopathy, macrocytosis, megaloblastic anemia, methaemoglobinaemia, neutropenia, pancytopenia
- Cardiac: allergic myocarditis, cyanosis, pericarditis
- Gastrointestinal: aggravation of ulcerative colitis, pancreatitis, parotitis
- General: yellow discoloration of skin and body fluids
- Hepatobiliary: hepatic failure, fulminant hepatitis, hepatitis
- Skin and subcutaneous tissue: epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), toxic pustuloderma, erythema, exanthema, exfoliative dermatitis, periorbital oedema, lichen planus, photosensitivity
- Immune system: anaphylaxis, polyarteritis nodosa, serum sickness
- Infections: pseudomembranous colitis
- Investigations: induction of autoantibodies
- Metabolism and nutrition: loss of appetite
- Musculoskeletal: systemic lupus erythematosus
- Nervous system: aseptic meningitis, ataxia, encephalopathy, peripheral neuropathy, smell disorders
- Psychiatric: hallucinations
- Renal and urinary: nephrotic syndrome, interstitial nephritis, crystalluria*, haematuria
- Reproductive: reversible oligospermia
- Respiratory: fibrosing alveolitis, eosinophilic infiltration, interstitial lung disease

Further information can be found in the British National Formulary and the Summary of Medicinal Product Characteristics (https://www.medicines.org.uk/emc/product/6686).

7. Cautions

- Sulfasalazine should not be prescribed for patients with known impaired hepatic or renal function or with blood dyscrasias unless the benefits outweigh the risks.
- Patients must be warned to report a sore throat or signs of bruising / bleeding.
- Sulfasalazine should not be prescribed for patients with known (or suspected) G6PD deficiency because of the risk of haemolytic anaemia.
- Sulfasalazine can cause folic acid deficiency potentially resulting in serious blood disorders (eg macrocytosis and pancytopenia). Supplementation with folic acid or folinic acid may be required.
- Sulfasalazine may cause crystalluria and kidney stone formation. Adequate fluid intake should be ensured during treatment.
Hypoglycemia may occur in patients receiving sulfonamides including sulfasalazine due to chemical similarity with some oral hypoglycaemic agents. Close monitoring of blood glucose is required in patients with diabetes mellitus.

Sulfasalazine should be used with caution in patients with severe allergy or bronchial asthma.

If sulfasalazine is used in pregnancy, the dose must not exceed 2g/day and folate supplements should be given to the mother due to the risk of folate deficiency (folic acid 5mg daily).

Sulfasalazine can be prescribed to men of childbearing potential although there may be transient reversible oligospermia. Conception may be enhanced by stopping sulfasalazine 3 months prior to conception.

Sulfasalazine is split by intestinal bacteria to sulfapyridine and 5-amino salicylate so adverse drug reactions to either sulfonamide or salicylate are possible. Patients with slow acetylator status are more likely to experience adverse drug reactions related to sulfapyridine.

Annual influenza vaccination and a single dose of pneumococcal vaccine are recommended.

Live vaccines should be avoided (ie oral polio, MMR, BCG and yellow fever and oral typhoid).

Passive immunisation with Varicella zoster immunoglobulin should be considered in non-immune patients exposed to active chicken pox or shingles.


8. Contraindications
- Known hypersensitivity to sulfasalazine and its metabolites
- Known hypersensitivity to sulfonamides or salicylates.
- Patients with porphyria.
- Children under 2 years

Further information can be found in the British National Formulary and the Summary of Medicinal Product Characteristics (SmPC) (https://www.medicines.org.uk/emc/product/6686)

9. Interactions
- Digoxin: absorption of digoxin may be reduced leading to sub-therapeutic levels.
- 6-mercaptopurine and azathioprine: increased risk of bone marrow suppression and leucopenia
- Methotrexate: increased risk of gastrointestinal adverse effects.
- Sulfonamides: increased risk of hypoglycemia

Further information can be found in the British National Formulary and the Summary of Medicinal Product Characteristics (SmPC) (https://www.medicines.org.uk/emc/product/6686)
10. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

| Pre-treatment by the hospital rheumatology team. | • Check ESR, FBC, creatinine/eGFR, ALT and/or AST and albumin  
• Check for known or suspected G6PD deficiency (do not prescribe if confirmed) |
| Initiation to stabilisation monitoring by the hospital rheumatology team (or GP if in agreement). | • Check ESR, FBC, creatinine/eGFR, ALT and/or AST and albumin every:  
  o two weeks until on stable dose for 12 weeks then  
  o once on stable dose, monthly FBC, creatinine/eGFR, ALT and/or AST and albumin for 3 months  
  o thereafter FBC, creatinine/eGFR, ALT and/or AST and albumin at least every 12 weeks*  
• Look out for downward trends as well as absolute levels of blood counts. |
| On-going monitoring by GP once stable. | • ESR, FBC, LFTs, U&Es once every three months.  
• If dose and monitoring are stable after one year, blood monitoring can be reduced to every six months.  
• Ask about rash and oral ulceration at each visit. |

Legend: ALT: alanine transaminase; AST: aspartate transaminase; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; FBC: full blood count; LFTs: liver function tests; U&Es: urea and electrolytes.

All results to be recorded in a patient-held record.

The following table includes advice on what action to take if test results rise or fall below defined limits or if the patient reports one of the adverse events below:

<table>
<thead>
<tr>
<th>Test results</th>
<th>Action</th>
</tr>
</thead>
</table>
| • Leucopenia WBC < 3.5 x10⁹/L, or  
• Neutropenia < 1.5 x10⁹/L, or  
• Thrombocytopenia platelets <150 x10⁹/L, or  
• LFTs > 2 x upper limit of normal (ULN) | STOP SULFASALAZINE and inform rheumatologist or rheumatology practitioner: see contact list below |
| • MCV > 105fl | Check B12, folate and TSH levels. If abnormal, treat any underlying abnormality. If normal, discuss with the hospital rheumatology team. |
### Symptoms/side effects

<table>
<thead>
<tr>
<th>Symptom Description</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal bruising/ bleeding or severe sore throat</td>
<td>Check FBC immediately and withhold sulfasalazine until results available. Discuss with specialist team if necessary. Send the patient to A&amp;E if considered high risk.</td>
</tr>
<tr>
<td>Fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness</td>
<td>Check FBC and LFTs immediately and withhold sulfasalazine until results available. Discuss with specialist team if necessary.</td>
</tr>
<tr>
<td>Significant infection</td>
<td>Urgent FBC looking for neutropenia. If present, withhold sulfasalazine and discuss with specialist team. Send the patient to A&amp;E if considered high risk.</td>
</tr>
<tr>
<td>Unexplained acute widespread rash</td>
<td>Stop sulfasalazine and seek urgent specialist advice – preferably dermatological. Send the patient to A&amp;E if severe (e.g. Stevens-Johnson syndrome).</td>
</tr>
<tr>
<td>Oral ulceration</td>
<td>Withhold sulfasalazine and discuss with specialist team.</td>
</tr>
<tr>
<td>Nausea, dizziness, headache</td>
<td>If possible, continue sulfasalazine. May have to consider dose reduction, or stop sulfasalazine if symptoms are severe. Discuss with the hospital rheumatology team.</td>
</tr>
</tbody>
</table>

**Legend:** LFTs: liver function tests; MCV: mean cell volume; ULN: upper limit of normal; WBC: white blood cell count.

### 11. Shared Care Responsibilities

#### a. Hospital specialist:
- Send a letter to the GP requesting shared care for the patient. Agreement to shared care will be assumed unless GP advises otherwise.
- Ensure accurate details of the patient’s prescription are communicated.
- Inform the GP after each clinic attendance if there is any change to treatment and/or monitoring.
- Inform the GP of patients who do not attend clinic appointments.
- Provide any advice to the patient/carer when requested.
- Initiate treatment and prescribe the first month of treatment.
- Carry out routine clinic follow-up on a regular basis.
- Send a letter to the GP after each clinic attendance ensuring current dose and most recent test results are stated.
- Evaluate any reported adverse effects by the GP or patient.
- Advise the GP on review, duration or discontinuation of treatment where necessary.
- Ensure that backup advice is available at all times.

#### b. General Practitioner:
- Agree to shared care guideline if requested by the hospital specialist.
• Report any adverse events and adverse drug reactions to the hospital specialist, where appropriate.
• Request advice from the hospital specialist when necessary.
• Refer the patient to an emergency care centre if the patient has a severe / high risk adverse drug reaction.
• Monitor the patient’s overall health and well-being.
• Prescribe the drug treatment as described.
• Monitor blood results (ESR, FBC, LFTs, U&Es, creatinine) in line with recommendations from the hospital specialist.
• Help in monitoring the progression of disease.

c. **Patient or parent/carer:**
• Report to the hospital specialist or GP if they do not have a clear understanding of their treatment.
• Do not exceed the recommended dose.
• Patients must attend their scheduled test appointments to assist health professionals to provide effective, safe, appropriate treatment.
• Inform other clinical staff involved in their care that they are receiving treatment.
• Report any adverse effects to the hospital specialist or GP.
• Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any outstanding queries.
• Share any concerns they have in relation to treatment with sulfasalazine.

### 12. Contact numbers for advice and support (of all hospitals that will be using this SCG)

<table>
<thead>
<tr>
<th>Cambridge University Hospitals NHS Foundation Trust</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist</td>
</tr>
<tr>
<td>Medicsines Information department (patient helpline)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rheumatology Department</th>
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<tbody>
<tr>
<td>Decisions to alter or discontinue treatment are usually discussed via the Rheumatology Helpline on 01223 254933. The on-call rheumatology specialist registrar (SpR) may also be contacted via the Addenbrooke’s Contact Centre.</td>
</tr>
<tr>
<td>Specialist</td>
</tr>
<tr>
<td>Jill Bloxham; Julie Isaacson; Tracey Nash, Jane How</td>
</tr>
<tr>
<td>Dr Nick Shenker – Clinic lead Dr Deepak Jadon Dr Ken Poole Dr Gavin Clunie Dr Andra Negoescu Dr Mark Lillicrap Dr Frances Hall</td>
</tr>
</tbody>
</table>
Shared Care Guidelines: Shared Care Guideline: Sulfasalazine—guidelines for its use in rheumatic diseases.
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Ratified March 2020
Review Date March 2022

Dr Natasha Jordan
Dr Ansh Malaviya
Dr Chris Chan
Locums:
Dr Gaaffar Massawi
Dr Carmel Stober
Dr Anoop Kuttikat

Tina Mitchell (NGS; CH; SS; locums) 01223 274561

North West Anglia NHS Foundation Trust – Peterborough Hospitals

<table>
<thead>
<tr>
<th>Specialist</th>
<th>Post</th>
<th>Telephone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines information department (office hours only)</td>
<td></td>
<td>01733 677303</td>
</tr>
<tr>
<td>Lucy Knight, Jo Miller, Daniel Arundel</td>
<td>Rheumatology Nurse Specialists</td>
<td>01733 676766 (nurses helpline)</td>
</tr>
<tr>
<td>Dr R Brier, Dr S Dahiya, Dr W Gunasekera, Dr M Lillicrap, Dr P Sharma, Dr J Pradeep</td>
<td>Consultant rheumatologist</td>
<td>Secretaries: 01733 676762, 01733 676763, 02733 676764</td>
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North West Anglia NHS Foundation Trust - Hinchingbrooke Hospital

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<tr>
<td>Medicines information department (office hours only)</td>
<td></td>
<td>01733 677303</td>
</tr>
<tr>
<td>Gemma Smith, Samantha Connell</td>
<td>Rheumatology Nurse Specialists</td>
<td>01480 847483</td>
</tr>
<tr>
<td>Dr R Brier, Dr S Dahiya, Dr W Gunasekera, Dr M Lillicrap, Dr P Sharma, Dr J Pradeep</td>
<td>Consultant rheumatologist</td>
<td>Secretaries: 01480 416080</td>
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13. Equality and Diversity Statement
This document complies with the Cambridge University Hospital NHS Foundation Trust service Equality and Diversity statement.

14. Disclaimer
It is your responsibility to check that this printed out copy is the most recent issue of this document.

15. Document Management

<table>
<thead>
<tr>
<th>Document ratification and history</th>
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<tr>
<td>Approved by:</td>
<td>CUH Joint drug and therapeutics committee</td>
</tr>
<tr>
<td>Date approved:</td>
<td>17 March 2020</td>
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<tr>
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<td>Cambridgeshire and Peterborough Joint Prescribing Group</td>
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<tr>
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<td>3rd April 2020</td>
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Review Date March 2022
<table>
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<tr>
<th>Obsolete date</th>
<th>June 2022</th>
</tr>
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<tbody>
<tr>
<td>Supersedes which document?</td>
<td>Version 4, June 2017</td>
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</table>
| Authors:                      | Alison Eggleton, Acting Lead Pharmacist for Surgery  
Eilis Rahill, Acting Associate Chief Pharmacist – Clinical Services  
Dr A Ostor, Consultant Rheumatologist (update confirmed with Dr A Malayiva). |
| Owning Provider Trust:        | Cambridge University Hospitals NHS Foundation Trust |
| File name:                    | SCG sulfasalazine Version5 March 2020 |
| Version number:               | 5                       |
| Summary of changes to updated version: | Side effect profile / frequencies reviewed.  
SmPC web reference amended  
Calculated GFR replaced with eGFR  
Advice to GP on action in the event of severe / acute ADRs added.  
Contacts in NW Anglia hospitals added. |

The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Medicinal Product Characteristics [https://www.medicines.org.uk/emc/product/6686 ] and to Rheumatology: Rheumatology Advance Access (Jan 2016) ‘BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids’ [https://academic.oup.com/rheumatology/article/55/9/1693/1744535 ]