SHARED CARE GUIDELINE

Lancashire & South Cumbria Medicines Management Group

Drug: Sulfasalazine

Introduction	**Indications**: Licensed: Rheumatoid arthritis; ulcerative colitis, Crohn's disease in adults and children Unlicensed: Sero-negative spondyloarthropathy including psoriatic arthritis and psoriasis. **Background:** Following oral administration around 90% of a dose reaches the colon where bacteria split the drug into sulfapyridine and 5-aminosalicylic acid (mesalazine). Overall the drug and its metabolites exert immunomodulatory effects, antibacterial effects, effects on the arachidonic acid cascade and alteration of activity of certain enzymes. The net result clinically is a reduction in activity of the inflammatory bowel disease. The enteric coated Sulfasalazine is licensed for the treatment of rheumatoid arthritis, where the effect resembles penicillamine or gold. Clinical response cannot be expected before 3 months. **Definitions:** Stable dose – the dose will be titrated to achieve efficacy at the lowest dose. Once efficacy achieved and provided the patient can tolerate the dose, this will be termed "stable dose" Stable bloods – results of blood tests remain below the "alert" thresholds as set by national guidelines and have stayed at similar levels for at least two consecutive tests. N.B. The patient can continue to have active disease despite being on a stable dose or having stable bloods, so the "patient" is not referred to as "stable"
Form	Tablets: 500mg Tablets EN: 500mg Suppositories: 0.5g Liquid: 250mg/5ml
Dose & Administration	A typical dose regimen for rheumatoid arthritis is 500mg daily increasing by 500mg daily at weekly intervals to a maximum 2g-3g/day in divided doses. Occasionally doses above 3g/day are prescribed Treatment of acute attacks of ulcerative colitis is 1-2g four times a day until remission achieved. Maintenance falls back to 500mg four times a day. Night time interval between doses should **not** exceed 8 hours
Secondary Care Responsibilities	• Confirm the diagnosis. • Check for absence of pregnancy in women of child-bearing age and ensure the patient understands the importance of contraception. • Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands which warning signs and symptoms to report. • Advise patient on adequate fluid intake to prevent crystalluria and kidney stone formation. • Perform pre-treatment screening[5]: height, weight, blood pressure, FBC, LFT, albumin and, creatinine/ calculated GFR • Patients should be assessed for co-morbidities, including evaluation for respiratory disease and screening for occult viral infection. • Ensure that the patient understands not to expect improvement from the treatment straight away. • Provide the patient with prescriptions for Sulfasalazine (ensure EN tablets for rheumatoid arthritis) until on stable dose and undergoing 3 monthly monitoring. Provide the patient with a monitoring and dosage record booklet and ensure that the patient knows when and where to attend for monitoring. Encourage the patient to take responsibility for ensuring that results of tests are entered in the monitoring booklet. • Make arrangements for shared care with the patient's GP. • Review the patient regularly to monitor the patient's response to therapy. • Advise the GP on frequency of monitoring, management of any dose adjustments and when to stop treatment. • Ensure that clear backup arrangements exist for GPs to obtain advice.
Primary Care Responsibilities	• Provide the patient with prescriptions for Sulfasalazine (ensure EN tablets for rheumatoid arthritis) once on stable dose and undergoing 3 monthly monitoring • Monitor at the recommended frequencies (see MONITORING below) and ensure that test results are recorded in the monitoring booklet. • Report any adverse events to the consultant or specialist nurse and stop treatment on their advice or immediately if an urgent need arises (see MONITORING below). • Report any worsening of control of the condition to the consultant or the specialist nurse. • Follow recommended immunisation programme

Immunisations	Annual flu vaccine is recommended Pneumococcal vaccination recommended In patients exposed to chicken pox or shingles, if required, passive immunisation should be considered for varicella. Refer to Green book: Varicella: the green book, chapter 34 - Publications - GOV.UK
Common Drug Interactions	• Sulfasalazine possibly reduces absorption of digoxin. • Oral hypoglycemic agents • Bone marrow suppression and leucopenia have been reported when sulfasalazine given with azathioprine or mercaptopurine. This list is not exhaustive, please refer to SPCs and BNF
Cautions	• Glucose-6-phosphate dehydrogenase deficiency: May cause hemolysis. • Renal impairment (moderate): Risk of toxicity including crystalluria, ensure high fluid intake. • Pregnancy and breastfeeding[6]. Sulfasalazine with folate supplementation (5 mg/day) is compatible throughout pregnancy, sulfasalazine should be used during pregnancy only if clearly needed. • Men taking sulfasalazine may have reduced fertility but no evidence that conception is enhanced by stopping the medication for three months prior to conception, unless conception delayed by >12 months when other causes of infertility should also be considered. • Severe infections – temporarily stop treatment Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of sulfasalazine. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. **Sulfasalazine should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.** Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking various drugs including sulfasalazine. **It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Sulfasalazine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.**
Contraindications	• Infants under the age of 2 years. • Patients with a known hypersensitivity to sulfasalazine, its metabolites or any of the excipients as well as sufonamides or salicylates. • Patients with porphyria.

This guidance does not replace the SPC's, which should be read in conjunction with this guidance.

MONITORING AND ADVERSE EFFECTS

Treatment Status	FBC	LFT	Albumin	Creatinine/ calculated GFR	ESR or CRP
Initial monitoring until on stable dose for 6 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 3 months (for RA only)
For next three months	Every month	Every month	Every month	Every month	Every 3 months (for RA only)
Thereafter, *	Every 3 months	Every 3 months	Every 3 months	Every 3 months	

After 12 months on a stable dose, no routine monitoring is required.

Dose increases should be monitored by FBC, creatinine / calculated GFR, albumin and LFTs every 2 weeks until on stable dose for 6 weeks and then revert to previous schedule.

The team responsible for prescribing the medication should also hold responsibility for monitoring
i.e. prescribing to be carried out in Primary care only once patient on stable dose and undergoing 3 monthly monitoring

***Please note:** If the patient is also being treated with **leflunomide**, increased monthly monitoring is required, as specified in the leflunomide shared care guidance. (Where other biologic/DMARDs are used in combination with sulfasalazine, the standard monitoring requirements, as outlined above, continue to apply).

As per secondary care responsibilities, for clarity the frequency of monitoring should be specified in the initial shared care request.

In the event of the following adverse laboratory results or patient reported symptoms, withhold sulfasalazine until discussed with specialist team and repeat the test after two weeks:

- WCC < 3.5 x 10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 1.6 x 10^9/L or less than the lower limit of reference range as per lab
- Platelets < 140 x 10^9/L or less than the lower limit of reference range as per lab
- AST/ALT > 100U/l
- MCV > 105Fl
- Creatinine increase >30% over 12 months and / or calculated GFR <60ml/min
- Unexplained eosinophilia >0.5 x 10^9/l
- Unexplained reduction in albumin <30g/l
- Abnormal bruising or **severe** sore throat
- Rash or oral ulceration
- As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes.

Other adverse effects:

- Nausea/dizziness/headache. If possible continue, may have to reduce dose or stop if symptoms severe. Discuss with specialist team.
- Loss of appetite, raised temperature, leucopenia, hypoglycaemia, insomnia, taste distortion, tinnitus, cough, pruritus, arthralgia, proteinuria are all relatively common
- Impaired folate absorption
- Oligospermia (reversible on discontinuing salazopyrin)

This list is not exhaustive, please refer to SPCs and BNF

References

1. Summary of product characteristics. Salazopyrin tablets. Pfizer limited. Last updated on the EMC 24th December 2021. Accessed via: https://www.medicines.org.uk/emc/medicine/3344 [accessed online: 21st June 2022].
2. Summary of product characteristics. Salazopyrin EN tablets. Pfizer limited. Last updated on the EMC 24th December 2021. Accessed via: https://www.medicines.org.uk/emc/medicine/10722 [accessed online: 21st June 2022].
3. Summary of product characteristics. Salazopyrin suppositories. Pfizer limited. Last updated on the EMC 24th December 2021. Accessed via: https://www.medicines.org.uk/emc/medicine/3345 [accessed online: 21st June 2022].
4. Summary of product characteristics. Sulfasalazine 250mg/5ml suspension. Rosemont Pharmaceuticals Limited. Last updated on the EMC 3rd December 2021. Accessed via: https://www.medicines.org.uk/emc/medicine/22489 [accessed online: 21st June 2022].
5. Ledingham et al. BSR/BHPR Non-Biologic DMARD Guidelines, June 2017. Accessed via: https://academic.oup.com/rheumatology/article/56/6/865/3053478
6. Flint et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding, January 2016. Accessed via: https://academic.oup.com/rheumatology/article/55/9/1693/1744535
7. UK Health Security Agency. Immunisation Against Infectious Disease 'The Green Book', 2021. Department of Health and Social Care. London, UK.

RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.

Appendix 1

Shared Care Agreement form

Request by Specialist Clinician for the patient's GP to enter into a shared care agreement

PLEASE NOTE: The use of this form is not compulsory, but the same information must be communicated between the specialist service and primary care in advance of entering into a shared-care agreement.

Part 1 - To be signed by Consultant / Associate Specialist / Speciality Trainee or Specialist Nurse (who must be a prescriber)

Dear Doctor:	Click or tap here to enter text.
Name of Patient:	Click or tap here to enter text.
Address:	Click or tap here to enter text.
	Click or tap here to enter text.
	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Patient NHS Number:	Click or tap here to enter text.
Patient Hospital Number:	Click or tap here to enter text.
Diagnosed Condition:	Click or tap here to enter text.

I request that you prescribe:

(1) Click or tap here to enter text.
(2) Click or tap here to enter text.
(3) Click or tap here to enter text.
(4) Click or tap here to enter text.

for the above patient in accordance with the LMMG shared care guideline(s) (Available on the LMMG website).

Last Prescription Issued:	Click or tap to enter a date.
Next Supply Due:	Click or tap to enter a date.
Date of last blood test (if applicable):	Click or tap to enter a date.
Date of next blood test (if applicable:	Click or tap to enter a date.
Frequency of blood test (if applicable:	Click or tap here to enter text.

I confirm that the patient has been stabilised and reviewed on the above regime in accordance with the Shared Care guideline.

If this is a Shared Care Agreement for a drug indication which is unlicensed or off label, I confirm that informed consent has been received from the patient.

I will accept referral for reassessment at your request. The medical staff of the department are available if required to give you advice.

Details of Specialist Clinicians

Name:	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Position:	Choose an item.
Signature:	Click or tap here to enter text.

(An email from the specialist clinician will be taken as the authorised signature)
In all cases, please also provide the name and contact details of the Consultant.

When the request for shared care is made by a Specialist Nurse, it is the supervising consultant who takes medicolegal responsibility for the agreement.

Consultant	Click or tap here to enter text.

Contact Details	
Telephone Number	Click or tap here to enter text.
Extension	Click or tap here to enter text.
Email Address	Click or tap here to enter text.

Part 2 - To be completed by Primary Care Clinician (GP)

I agree to prescribe and monitor Click or tap here to enter text. for the above patient in accordance with the LMMG shared care guideline(s) commencing from the date of next supply / monitoring (as stated in Part 1 of the agreement form).

Name:	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Signature:	Click or tap here to enter text.

*Please sign and return a copy **within 14 calendar days** to the address above* **OR**

If you **do not** agree to prescribe, please sign below and provide any supporting information as appropriate:

I **DO NOT** agree to enter in to a shared care agreement on this occasion.

Name:	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Signature:	Click or tap here to enter text.
Further information:	Click or tap here to enter text.