## Sulfasalazine for patients within adult services

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| Clinical content last reviewed: | November 2023 | Next review date: | November 2025 |

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| **Version** | **Date published** | **Changes since previous version** |
| RDTC v1.0 | 08/03/24 | * Section 5: advice on viral screening at baseline amended to recommend following local policy * Section 6: advice on shingles vaccination updated to reflect new schedule * Section 7: brief note added on taking care when prescribing or dispensing sulfasalazine vs. sulfadiazine * Section 9: interaction added - bulvertide |
| RDTC v1.1 | 26th November 2024 | * Advice on shingles vaccine clarified to reflect potential eligibility of patients aged 50 years or older taking immunosuppressive therapy |

**Local review and adoption**

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| **Local approval** | **Date** |
| Local content added |  |
| Approved for use by xx ICB |  |
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Clinical content has been reviewed and updated by the RDTC on the date indicated above. Every effort is made to keep the content up to date. These templates are provided to the North West and North East and Yorkshire ICBs for localisation and approval through standard ICB processes. The most recent version is available on the RDTC website at <https://rdtc.nhs.uk/prescribing-support-document/shared-care-protocol-sulfasalazine-in-adults/>.

Information requiring local completion is highlighted.

This document is intended for use by NHS healthcare professionals and cannot be used for commercial or marketing purposes.

**Shared Care Protocol**

## Sulfasalazine for patients within adult services

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| Background | Sulfasalazine is a disease modifying antirheumatic drug (DMARD) used to treat a number of rheumatological conditions, and to induce and maintain remission in certain inflammatory gastrointestinal diseases.  This shared care protocol does not cover the treatment of people less than 18 years old. |
| Licensed and agreed off-label indications | The licensed indications for sulfasalazine are:   * Rheumatoid arthritis (EC tablets only) * Ulcerative colitis * Active Crohn’s disease   Sulfasalazine is also used off-label for other chronic inflammatory disorders including:   * Seronegative spondyloarthropathies such as psoriatic arthritis * Sarcoidosis   These indications are off-label. The specialist must specify the indication for each patient when initiating shared care and clearly state when use is off-label.  This shared care protocol applies to adults aged 18 and over. |
| Locally agreed indications | *To be completed locally* |
| Initiation and ongoing dose regime | Transfer of monitoring and prescribing to primary care is normally after at least 12 weeks, and when the patient’s dose has been optimised and with satisfactory investigation results for at least 12 weeks however this may be longer in some circumstances (see section 5).  The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.  All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.  Termination of treatment will be the responsibility of the specialist. Initial stabilisation: Treatment of acute attacks of ulcerative colitis and Crohn’s disease:  Oral: 1-2g four times daily until remission. The night-time interval between doses should not exceed 8 hours.    Rheumatoid arthritis (using enteric coated (EC) tablets):  500mg daily, increasing by 500mg each week until 2-3g per day in divided doses is reached according to response. Only the enteric coated tablets are licensed in rheumatoid arthritis; use of other formulations is off-label.    For other indications take specialist advice.  **The initial stabilisation period must be prescribed by the initiating specialist.** Maintenance dose (following initial stabilisation): Ulcerative colitis and Crohn’s disease:  Oral: Usual maintenance dose 500mg four times daily.    Rheumatoid arthritis and other indications (using EC tablets):  2-3g daily in 3-4 divided doses.    **The initial maintenance period must be prescribed by the initiating specialist.** Conditions requiring dose adjustment: In patients with GFR less than 10 mL/min, start at very low dose and monitor. |
| Baseline investigations, initial monitoring, and ongoing monitoring to be undertaken by specialist | Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in the immediate future will prescribing and monitoring be transferred to primary care. Baseline investigations:  * Urea and electrolytes (U&Es) including creatinine and creatinine clearance (CrCl) * Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), & albumin * Full blood count (FBC) * Height and weight * Blood pressure (BP) * Assess for co-morbidities which may influence DMARD choice * Screening for viral infections as per local policy, e.g. HIV, hepatitis B and C, varicella zoster, Epstein Barr virus, cytomegalovirus * Screening for lung disease, including tuberculosis, should be undertaken at clinician discretion on a case by case basis. * Provide or request appropriate vaccination prior to treatment initiation, according to local arrangements (e.g. pneumococcal, influenza, COVID-19)   Initial monitoring and at dose change:  To be repeated every 2 weeks until the dose has been stable for 6 weeks, then monthly for three months. After which, the transfer of prescribing to primary care should normally only take place when the patient has received a stable dose for at least 12 weeks and their blood and physical tests results have been satisfactory. It is anticipated that this should be around 16 weeks after initiation of the medicine, but may be sooner in some indications.   * Blood pressure * FBC * U&Es, including creatinine and CrCl * AST and/or ALT, albumin, and bilirubin * Rheumatology patients: C-reactive protein (CRP) &/or erythrocyte sedimentation rate (ESR)   Following a dose change repeat every 2 weeks until the dose has been stable for 6 weeks, then revert to previous schedule. Ongoing monitoring: The specialist will retain the responsibility for monitoring the patient’s ongoing response to treatment, and advise if a dose change or treatment cessation is appropriate. This should usually be undertaken annually.  After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in [section 6](#six_monitoring) remains appropriate. |

## Ongoing monitoring requirements to be undertaken by primary care

If monitoring results are forwarded to the specialist team, please include clear clinical information on the reason for sending, to inform action to be taken by secondary care.

| **Monitoring** | **Frequency** |
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| * FBC * U&Es including creatinine and CrCl * ALT and/or AST and albumin * Rheumatology patients: CRP and/or ESR | Monthly  After 12 months no routine monitoring is required for the majority of patients. Annual serum creatinine or eGFR may be considered. **The decision to discontinue monitoring should be following advice from the specialist for the individual patient.** |
| * Patients aged 60-79 years old are eligible for the shingles vaccine (herpes zoster). Patients aged 50 years or older and taking immunosuppressive therapy may also be eligible. Specialist input may be required. Refer to [Green Book Chapter 6 (Contraindications and special considerations)](https://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6) and [Green Book Chapter 28a (Shingles)](https://www.gov.uk/government/publications/shingles-herpes-zoster-the-green-book-chapter-28a) for further details. * **Annual** influenza ([The Green Book, Chapter 19](https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19)) vaccinations are recommended * COVID-19 vaccination is safe and recommended (see [Green Book Chapter 14a](https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a)). * Repeat pneumococcal vaccine may be indicated. See [Green Book Chapter 25](https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25) for advice. | * Shingles vaccination: single course (two doses). * Influenza vaccination: annual. It is advisable to add the patient to the influenza vaccine list. * COVID-19 vaccination as per national schedule. |

## Pharmaceutical aspects

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| Route of administration: | Oral |
| Formulation: | 500mg tablets  500mg enteric coated (EC) tablets  250mg/5mL oral suspension  Licensed indications vary with formulation. See relevant [summary of product characteristics](https://www.medicines.org.uk/emc/search?q=sulfasalazine) for full details. |
| Administration details: | EC tablets should be swallowed whole and not crushed or broken. |
| Other important information: | Plain tablets and oral suspension are only licensed for use in ulcerative colitis or active Crohn’s disease.  EC tablets are licensed for use in rheumatoid arthritis as well as ulcerative colitis and active Crohn’s disease. Their use in ulcerative colitis and Crohn’s disease is usually recommended if the patient experiences gastro-intestinal intolerance with the plain tablets.  Sulfasalazine may cause a yellow-orange discolouration of body fluids and skin. Certain types of extended wear soft-contact lenses may be permanently stained.  Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include urea, ammonia, LDH, α-HBDH and glucose. It is possible that alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), or thyroxine may also show interference when sulfasalazine treatment is given at high doses. Consult with the testing laboratory regarding the methodology used. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings.  Sulfasalazine has been confused with sulfadiazine; care must be taken to ensure the correct drug is prescribed and dispensed. |

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| Cautions and contraindications | This information does not replace the Summary of Product Characteristics (SPC), and should be read in conjunction with it. Please see [BNF](https://bnf.nice.org.uk/drugs/sulfasalazine/) and [SPC](https://www.medicines.org.uk/emc/search?q=sulfasalazine) for comprehensive information.  **Contraindications:**   * Known hypersensitivity to sulfasalazine, its metabolites or any of the excipients as well as sulfonamides or salicylates. * Porphyria.   **Cautions:**   * Hepatic or renal impairment. * Pre-existing blood dyscrasias. * Severe allergy or bronchial asthma. * Glucose-6-phosphate dehydrogenase (G6PD) deficiency due to risk of haemolytic anaemia. * Folic acid deficiency. * Adequate fluid intake should be maintained during treatment to avoid crystalluria and kidney stone formation. * Slow acetylator status increases the risk of sulfapyridine-related adverse drug reactions (ADRs) which can present as a drug-induced lupus-like syndrome. |
| Significant drug interactions | The following list is not exhaustive. Please see [BNF](https://bnf.nice.org.uk/drugs/sulfasalazine/) & [SPC](https://www.medicines.org.uk/emc/search?q=sulfasalazine) for comprehensive information and recommended management.   * **Digoxin**: Reduced absorption may be seen when used concomitantly with sulfasalazine. * **Sulfonamides** are chemically similar to some oral hypoglycaemic agents and may cause hypoglycaemia. Patients receiving sulfasalazine and hypoglycaemic drugs should closely monitor blood glucose. * **Azathioprine and 6-mercaptopurine**: Possible risk of bone marrow suppression and leucopenia * **Folate** absorption and metabolism may be reduced by sulfasalazine. * **Darolutamide, tepotinib and voxilaprevir** may increase exposure to sulfasalazine, manufacturer advises avoid. * **Bulevirtide**: efficacy may be affected by sulfasalazine. |

## Adverse effects and management

As well as responding to absolute values in laboratory tests, a rapid change or a consistent trend in any value should prompt caution and extra vigilance**.** For information on incidence of ADRs see relevant SPCs.

**Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit** [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

Advice based on shared care guidelines published by NHS England, and checked against current guidance.

| **Adverse effect** | **Management** |
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| **Full blood count**   * White cell count less than 3.5 x109/L * Lymphocytes less than 0.5 x109/L * Neutrophils less than 1.6 x109/L * Platelets less than 140 x109/L * Unexplained eosinophilia; greater than 0.5 x109/L * Unexplained fall in albumin; less than 30g/L | Withhold treatment and discuss with specialist. |
| Mean cell volume greater than 105 fL | Consider interruption in treatment.  Check serum folate, B12, alcohol history and TSH and treat any underlying abnormality. If results of these additional investigations are normal discuss with specialist team urgently. |
| Signs or symptoms of bone marrow suppression, e.g. unexplained bleeding or bruising, severe sore throat, purpura, mouth ulcers. | Check FBC immediately, withhold treatment while awaiting results, and discuss with the specialist team. See haematological monitoring above. |
| Acute infection | During serious infections (e.g. requiring intravenous antibiotics or hospitalisation) temporarily withhold sulfasalazine until the patient has recovered. Consider additional investigations (e.g. FBC), if clinically appropriate. |
| **Liver function tests:**  ALT and/or AST greater than 100units/L  And/or a sudden increase (e.g. doubling of baseline)  Jaundice | Withhold and discuss with specialist team.  Check any other reason for risk of hepatic dysfunction such as alcohol history and drug interactions, including OTC or complementary medication. |
| **Renal function**  Creatinine increase of greater than 30% from baseline in the last 12 months **or** CrCl reduces to less than 60mL/min | Use clinical judgement and repeat in 1 week  If still more than 30% from baseline, withhold and discuss with specialist. |
| **Gastrointestinal disorders**  Nausea, vomiting, diarrhoea or unintentional weight loss | Review for reversible causes. Advise patient to take with food. If no improvement contact specialist team. |
| **Other symptoms**   * Skin/mucosal reaction, e.g. serious rash or itch * Diffuse alopecia * Breathlessness or cough * Peripheral neuropathy | Consider withholding treatment and discussing with specialist.  For widespread rash, discontinue and discuss with specialist urgently. |

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| Advice to patients and carers The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual drugs. | **The patient should be advised to report any of the following signs or symptoms to their primary care prescriber without delay**   * Sore throat, mouth ulcers, fever, malaise, swollen lymph nodes, or unexplained bleeding or bruising * Progressive skin rash with blisters or oral ulcerations – see below * Nausea, vomiting, diarrhoea, jaundice, dark urine and unintentional weight loss. * Hair loss * Breathlessness, infection or cough * Symptoms of peripheral neuropathy e.g. pins and needles, numbness or burning pain in extremities   **The patient should be advised:**   * Life-threatening skin reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of sulfasalazine. The highest risk for occurrence is within the first weeks of treatment. Patients should be advised to report a progressive skin rash often with blisters or mucosal lesions, or any other sign of hypersensitivity. * During a serious infection, sulfasalazine should be temporarily discontinued until the patient has recovered from the infection. * Tell anyone who prescribes them a medicine that they are taking sulfasalazine. Always ask a pharmacist before purchasing any medicines over the counter, including herbal remedies, and ask if they are safe. * That vaccination in line with current national advice (e.g. for COVID-19, influenza) is safe and recommended. * Sulfasalazine may cause a harmless yellow-orange discolouration of body fluids and skin. Certain types of extended wear soft-contact lenses may be permanently stained. * To maintain adequate fluid intake during treatment to reduce the risk of crystalluria and kidney stones, especially in patients with moderate to severe renal impairment.   Patient information:   * General information: [nhs.uk](https://www.nhs.uk/medicines/sulfasalazine/) * General information: [patient.info](https://patient.info/medicine/sulfasalazine-salazopyrin-sulazine%20) * Rheumatology: [Versus Arthritis](https://www.versusarthritis.org/about-arthritis/treatments/drugs/sulfasalazine/%20%20) |
| Pregnancy, paternal exposure and breastfeeding | All patients should be informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed.  The [BSR guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids](https://academic.oup.com/rheumatology/article/62/4/e48/6783012) advises the following:  Pregnancy:  Sulfasalazine, with folate supplementation (5 mg/day), is compatible throughout pregnancy.  Information for healthcare professionals: [UK Teratology Information Service (UKTIS)](https://uktis.org/monographs/use-of-sulfasalazine-in-pregnancy/)  Information for patients and carers: [Best Use of Medicines in Pregnancy (BUMPs)](https://www.medicinesinpregnancy.org/Medicine--pregnancy/Sulfasalazine/%20)    Breastfeeding:  Sulfasalazine is compatible with breastfeeding in healthy, full-term infants.  There have been reports of bloody stools or diarrhoea in infants who were breastfeeding from mothers on sulfasalazine. In cases where the outcome was reported, bloody stools or diarrhoea resolved in the infant after discontinuation of sulfasalazine in the mother.    Information for healthcare professionals: [UK Drugs in Lactation Advisory Service (UKDiLAS)](https://www.sps.nhs.uk/medicines/sulfasalazine/)    Paternal exposure:  Men taking sulfasalazine may have reduced fertility, due to oligospermia and impaired mobility, which may take 2-3 months to return to normal following treatment cessation. |
| Specialist contact information and arrangements for referral | *To be completed locally* |
| Additional information | Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient’s GP or their contact details. |
| References | 1. British National Formulary. Accessed via <https://bnf.nice.org.uk/> on 15/11/23. 2. Salazopyrin En tabs. Date of revision of the text 10/2023. Accessed via <https://www.medicines.org.uk/emc/product/6686/smpc> on 15/11/23 3. Salazopyrin tablets. Date of revision of the text 10/2023. Accessed via <https://www.medicines.org.uk/emc/product/3838/smpc> on 15/11/23 4. Sulfasalazine 250mg/5mL oral suspension. Date of revision of the text 21.11.20. Accessed via <https://www.medicines.org.uk/emc/product/413/smpc> on 15/11/23 5. British Society of Rheumatology and British Health Professionals in Rheumatology. 2017. Guidelines for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Accessed via <https://academic.oup.com/rheumatology/article/56/6/865/3053478>. 6. British Society for Rheumatology. Guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology, Volume 62. Ossie 4. April 2023, pages e48-e88. Accessed via <https://academic.oup.com/rheumatology/article/62/4/e48/6783012>. 7. UK Teratology Information Service. Use of sulfasalazine in pregnancy. Version 3 October 2020. Accessed via https://uktis.org/monographs/use-of-sulfasalazine-in-pregnancy/ on 15/11/23 8. Best Use of Medicines in Pregnancy. Last updated September 2020, accessed via <https://www.medicinesinpregnancy.org/Medicine--pregnancy/Sulfasalazine/> on 15/11/23 9. Menter, MD et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. JAAD: 2009: 61: 3: 451-485. DOI: <https://doi.org/10.1016/j.jaad.2009.03.027> 10. The Renal Drug Database. Sulfasalazine (sulphasalazine). Reviewed 01/03/2018. Accessed via <https://renaldrugdatabase.com/monographs/sulfasalazine-sulphasalazine> on 15/11/23. |
| To be read in conjunction with the following documents | * Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from <https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/> * NHSE guidance – Responsibility for prescribing between primary & secondary/tertiary care. Available from <https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/> * General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from <https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care> * NICE NG197: Shared decision making. Last updated June 2021. <https://www.nice.org.uk/guidance/ng197/>. |