Amber with Guidance (Amber-G) = To be recommended or initiated by a specialist with follow up prescribing and monitoring by primary care clinicians.*
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Barnsley Hospital NHS Foundation Trust | South West Yorkshire Partnership NHS Foundation Trust | South Yorkshire Integrated Care Board

Sulfasalazine for ulcerative colitis and Crohn's disease

The details of side-effects, cautions, contraindications and interactions are not a complete list and the current BNF (https://www.medicinescomplete.com/#/) and the SPC (https://www.medicines.org.uk/emc/) remain authoritative.

Background Information	• Induction and maintenance of remission of ulcerative colitis; treatment of active Crohn's Disease. • Sulfasalazine is a combination of 5-aminosalicylic acid ('5-ASA') and sulfapyridine. Sulfapyridine acts as a carrier to the colonic site of action. • To be recommended or initiated by the specialist team with follow up prescribing and monitoring by primary care clinicians. • The Amber-G guideline covers the care of adults only.
BNF therapeutic class	1.3 Inflammatory Bowel Disease Aminosalicylates https://doi.org/10.18578/BNF.848009552
Indication	• Licensed indication for the management of ulcerative colitis and Crohn's disease. • Sulfasalazine and its metabolites exert immunomodulatory effects, antibacterial effects, effects on the arachidonic acid cascade and alteration of activity of certain enzymes. The net result is a reduction in activity of inflammatory bowel disease. • Aminosalicylates may be considered for mild-moderate first presentation of inflammatory exacerbation of proctosigmoiditis or left-sided ulcerative colitis. These drugs are also effective at maintaining remission. • The enteric coated tablets are also licensed for Rheumatoid Arthritis and have an Amber classification for this indication. A Shared Care Guideline for the treatment of rheumatoid arthritis with sulfasalazine is available.
Dosage and administration	For the treatment of acute attacks of ulcerative colitis and Crohn's disease the dose is 1-2g four times a day until remission occurs. Specialist to advise on this. With induction of remission reduce the dose gradually to 500mg four times daily and continue this as maintenance therapy. The duration of treatment and frequency of review will be determined by the specialist, based on clinical response and tolerability. Termination of treatment will be the responsibility of the specialist team. Both plain and enteric coated tablets are licensed for use in ulcerative colitis and Crohn's disease. These are both available in 500mg tablets. Adequate fluid intake should be ensured during treatment as sulfasalazine causes crystalluria and kidney stone formation.
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 & SPC for comprehensive information. Sulfasalazine is contraindicated in; • Patients with a known hypersensitivity to sulfasalazine, its metabolites or any of the excipients as well as sulfonamides or salicylates.

	• Patients with porphyria. Sulfasalazine should not be given to patients with impaired hepatic or renal function or with blood dyscrasias unless the potential benefit outweighs the risk. Sulfasalazine should be given with caution to patients with severe allergy or bronchial asthma. Since sulfasalazine may cause haemolytic anaemia, it should be used with caution in patients with G-6-PD deficiency. Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency, potentially resulting in serious blood disorders (e.g. macrocytosis and pancytopenia), this can be normalised by administration of folic acid or folinic acid (leucovorin).
Pregnancy, breast feeding and fertility	Pregnancy- Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency- adequate folate supplements (5mg) should be given to mother and to women trying to conceive where it is deemed appropriate to continue taking sulfasalazine. The British Society of Gastroenterology advise that sulfasalazine is low risk for use in pregnancy. Information for healthcare professionals: USE OF SULFASALAZINE IN PREGNANCY (medicinesinpregnancy.org) Information for patients and carers: bumps - best use of medicine in pregnancy (medicinesinpregnancy.org) Low levels of drug are found in breast milk, this can cause bloody stools in the infants which has been found to be reversible on stopping the sulfasalazine. The British Society of Gastroenterology advise that sulfasalazine is thought to be low risk in breastfeeding an infant. Inform patients of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient is planning to become pregnant, becomes pregnant or is planning to breastfeed. Paternal exposure- Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of the drug appears to reverse these effects within 2 to 3 months.
Adverse Drug Reactions	• The details below are not a complete list and the BNF and SPC remain authoritative. Listed side-effects are common (1 in 10 to 1 in 100) • Blood and Lymphatic System disorders Leucopenia • Psyciatric Disorders Insomnia • Nervous System Disorders Dizziness, headache and taste disorders • Ear and labyrinth Disorders Tinnitus • Respiratory Disorders Cough • Gastrointestinal Disorders Nausea, abdominal pain, diarrhoea, vomiting, loss of appetite and stomatitis • Skin Disorders Skin reactions, rash • Musculoskeletal and Connective Tissue Disorders Arthralgia • Renal and Urinary Disorders Proteinuria • General Disorders Fever • Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme: www.mhra.gov.uk/yellowcard
Monitoring	• Baseline tests (to be undertaken by specialists if providing first prescription OR to be undertaken in primary care following a recommendation to prescribe by secondary care); FBC, U&Es, LFTs, Creatinine /calculated GFR, folate and serum albumin.

- After started or following dose changes (to be undertaken by primary care); FBC, U&Es, Creatinine / calculated GFR, LFTs and serum albumin
  Every 2 weeks until on a stable dose for 6 weeks then monthly for 3 months. . Consider increasing frequency of testing for patients at higher risk of toxicity.

- Routine tests once stable (to be undertaken in primary care); FBC, U&Es, Creatinine / calculated GFR, LFTs and serum albumin
  Every 12 weeks for the first 12 months. Consider checking creatinine / calculated GFR annually. Consider increasing frequency of testing for patients at higher risk of toxicity.

- If patients present with symptoms of potential adverse effects (sore throat, fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness) perform an urgent blood test.

- If any of the following occur, stop sulfasalazine and contact the specialist:

  Full Blood Count
  WCC < 3.7 x 10^9/L
  Neutrophils <1.7 x 10^9/L
  Platelets < 150 x 10^9/L

  Liver Function tests
  AST or ALT > 3 times normal range
  Unexplained reduction in albumin < 30g/L

  Renal Function
  Increase in creatinine >30% in 12 months and/or calculated GFR <60ml/min
  Proteinuria/Blood >1+

  MCV >100f/l continue medication but contact specialist for further advice. Check serum folate, B12, alcohol history and TSH. Treat any underlying abnormality. If results are normal, discuss with specialist team urgently.

Also observe trends in results e.g. gradually decreasing white blood cell count. Contact specialist for advice where persistent unexplained eosinophilia (eosinophils>0.5x 109 /L)

After 12 months, no routine monitoring is required for the majority of patients. The decision to discontinue should be following advice of the specialist.

Stop treatment and discuss with consultant if any of the following develop;

- Rash or itch
- Hair loss
- Severe sore throat/oral ulceration or abnormal bruising/bleeding (check FBC immediately)
- Breathlessness or dry cough
- GI upset (nausea, vomiting or diarrhoea)
- Weight loss
- Peripheral neuropathy

Appropriate to continue treatment in minor infections. In serious infections, temporarily withhold sulfasalazine until recovered.

Interactions	The list below is not exhaustive and includes common interactions only. Please refer to the BNF and SPC for the complete list. • Reduced absorption of digoxin, resulting in non-therapeutic serum levels, has been reported when used concomitantly with oral sulfasalazine. • Sulfonamides bear certain chemical similarities to some oral hypoglycemic agents. Hypoglycemia has occurred in patients receiving sulfonamides. Patients receiving sulfasalazine and hypoglycemic agents should be closely monitored. • Due to inhibition of thiopurine methyltransferase by sulfasalazine, bone marrow suppression and leucopenia have been reported when the thiopurine 6-mercaptopurine or it's prodrug, azathioprine, and oral sulfasalazine were used concomitantly. • Folate absorption may be reduced by sulfasalazine.
Additional information	• Vaccines are safe and recommended with sulfasalazine and should be offered in line with the standard schedule. Refer to Green Book Chapter 6 for further details. • Sulfasalazine may cause a yellow-orange discolouration of body fluids and skin. Certain types of extended wear soft-contact lenses may be permanently stained. • Patients should be counselled to report any unexplained bleeding, bruising, rash, sore throat, fever or malaise.

Contact names and details

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- BHNFT Gastroenterology Department: https://www.barnsleyhospital.nhs.uk/service/gastroenterology/
- https://www.crohnsandcolitis.org.uk/

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Development Process

This guidance has been produced by Laura White, Clinical Pharmacist SY ICB Barnsley Place following an AMBER-G classification status of Sulfasalazine for ulcerative colitis and Crohn's disease by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the gastroenterologists and was ratified by the Area Prescribing Committee on 11th January 2023.