Aminosalicylates in Inflammatory Bowel Disease in Adults

Traffic light classification - Amber 2
Information sheet for Primary Care Prescribers
THIS IS NOT A SHARED CARE PROTOCOL

This document is intended to guide healthcare professionals to manage adults (over 18 years old) with inflammatory bowel disease (IBD) who are newly started on or those who are already on 5-aminosalicylate (5-ASA) treatment.

Therapeutic Summary
5-aminosalicylates are recommended for the treatment of mild to moderate ulcerative colitis (UC) and the maintenance of remission in ulcerative colitis. Certain brands of 5-ASA are also licensed for the maintenance of remission in Crohn's ileo-colitis (CD).
The medications that contain 5-ASA include mesalazine, balsalazide, sulfasalazine and olsalazine. They have different modes of action (See Table 1 for the individual mode of action).
The newer 5-ASAs i.e., mesalazine, olsalazine and balsalazide are better tolerated than sulfasalazine because of the lack of 'sulfa' related side effects. In Nottinghamshire, **mesalazine** is recommended as the first choice of 5-ASA therapy for patients with IBD.

Indications:
- treatment of mild to moderate UC, acute attack
- maintenance of remission of UC
- maintenance of remission in CD and active disease.
  (Only certain brands are licensed)

Medicines Initiation:
Treatment with 5-ASAs will be initiated in Secondary Care and the hospital will provide a minimum of 14 days of treatment on discharge.

Products available[1]:
5-ASA medications are used in several formulations, targeted at specific areas of the bowel as shown in Table 1.

There are differences in licensed indications, dose frequency, interactions, pharmaceutical, pharmacological, and pharmacokinetic properties between products available. Therefore, it is recommended to **prescribe aminosalicylates by brand name**.

Octasa® and Pentasa® brands are generally preferred for new patients as they are more cost-effective.

There is very little difference in terms of efficacy between mesalazine preparations so the choice of the formulation should depend on factors that may aid adherence to therapy and the proximal extent of the inflammation.

Dosages and route of administration:
Depending on the location of inflammation in the bowel, the 5-ASA can be given via oral or rectal route. Further information on dosing for oral preparations can be found in Table 2 and for rectal in Table 3.

NOTE: If no symptomatic improvement is evident after 2 weeks on the maximum dose of either oral or rectal medication, treatment escalation is necessary.

Table 1. Aminosalicylates – products available

Medication	Release mechanism[4]	Brand	Formulation		Site of action[4,]
			oral	rectal	
Mesalazine	Time-controlled release	Pentasa®	Tablets Granules	Enema Suppositories	Duodenum to rectum
	pH-dependent release/resin coated	Octasa®	Tablets	Suppositories	Terminal ileum & colon
		*Salofalk®	Tablets Granules M/R	Enema Foam Enema Suppositories	Terminal ileum & colon
		*Asacol® *Asacol® MR	Tablets (400mg tablets discontinued April 2024)	Suppositories Foam enema	Terminal ileum & large bowel (colon & rectum)
		***Restricted for patients who are unable to switch to Octasa® brand**			
	Mezavant® brand of mesalazine is non-formulary.				
Balsalazide	Delivery by carrier molecules, with the release of 5-ASA after splitting by bacterial enzymes in the large intestine	Colazide®	Capsules	-	Colon
Sulfasalazine (Non-formulary, only existing patients may continue)		Salazopyrin®	Tablets, EC tablet Suspension	Suppositories	Colon
Olsalazine is non-formulary					

Table 2. Aminosalicylates - oral formulations

Name	Maintenance dose for UC	Treatment dose for active UC	Use in CD
Pentasa® (tablets/granules)	2g daily	4g daily (in 2-4 divided doses)	
Octasa®	1.2-2.4g once daily (or in divided doses)	2.4-4.8g once daily (or in divided doses)	Maintenance of remission: 1.2-2.4g once daily, alternatively daily in divided doses
Salofalk® (tablets/granules)	500mg three times daily	1.5-3g daily, preferably in the morning (or 0.5-1g three times daily)	
Asacol® MR tablets **(Discontinued April 2024 – patients should be switched to another brand. Octasa® is first line and equivalent in dose and availability)**	1.2-2.4g daily (in divided doses)	Max 4.8g daily (in divided doses)	Maintenance of remission: up to 2.4g daily in divided doses
Balsalazide	1.5g twice daily (max. per dose 3g) Max. 6g per day	2.25g three times a day Maximum dose for 12 weeks.	
Olsalazine (Non-formulary)	500mg twice daily after food	1g daily in divided doses taken after meals. The dose may be titrated upwards over one week to a maximum of 3g daily. A single dose should not exceed 1g.	
*Sulfasalazine (Non-formulary, existing patients may continue)	500mg four times a day	Max 8g daily (1-2g four times daily)	Active CD: 1-2g four times daily

Table 3. Aminosalicylates - rectal formulations

Name	Maintenance dose for UC	Treatment dose for active UC	Use in CD
Pentasa® Suppository	1g daily	Max 1g at night for up to 2-4 weeks. Continue for 2 weeks after symptomatic relief occurs then taper to stop	unlicensed
Pentasa® liquid enema (retention)	1g at night	1g at night	unlicensed
Octasa® Suppository	1g at night	1g at night	unlicensed
Salofalk® Enema	2g at night	2g at night	unlicensed
Salofalk® Rectal Foam	unlicensed	2g at night (or in 2 divided doses)	unlicensed
Salofalk® Suppositories	unlicensed	Max. 0.5-1g, 2-3 times a day, adjusted according to the response.	unlicensed
Asacol® Suppository	0.75- 1.5g daily in divided doses. Last dose to be administered at bedtime	0.75- 1.5g daily in divided doses. Last dose to be administered at bedtime	unlicensed
Asacol® Foam Enema	unlicensed	1-2g daily for 4-6 weeks	unlicensed
Sulfasalazine suppositories (Non-formulary)	0.5-1g twice daily Administered alone or in conjunction with oral therapy, morning, and night after a bowel movement	0.5-1g twice daily	Active Crohn's disease 0.5–1g BD

Duration of treatment:
Lifelong maintenance therapy is recommended for all patients with UC, especially those with left-sided disease or extensive disease who relapse more than once a year. Those with distal disease who have been in remission for 2 years should have a discontinuation assessment performed. However, it is suggested that maintenance therapy reduces the risk of colorectal cancer.

There is limited evidence to support the use of 5ASAs in CD, however current BSG guidelines recommend their use in mild ileocolonic disease. The 5-ASA medicines are of little benefit for either inducing remission or maintaining medically induced remission. They may be of use for the maintenance of surgically induced remission.

Recommended monitoring schedule:

Table 4. Monitoring requirements

Pre-treatment	Baseline	FBC, U&E, LFT
Monitoring	1 month	FBC, U&E, LFT
	3 months	FBC, U&E, LFT
	Every 6 months for one year or until stable	FBC, U&E, LFT
Following dose change	Repeat FBC, LFT, and U&E 1 month after a dose increase, then as above.	
Ongoing, once results and dose are stable	FBC, U&E and LFT once yearly (6-monthly monitoring may be required in some patients i.e. with renal impairment).	

Please note, for any existing patients on sulfasalazine for IBD initiated by Gastroenterology Specialist, the monitoring requirements and responsibilities would be expected to be in line with those for rheumatology patients. For further information see the local Shared Care Protocol and monitoring summary.

Explicit criteria for review and discontinuation of the medicine:

Table 5. Side effects and actions to be taken

Side effect	Action
Progressively more severe and recurrent headache, disturbed vision, ringing or buzzing in the ears, back pain, or neck pain, nausea, dizziness, or worsening diarrhoea.	If troublesome, reduce or stop treatment and consider alternative. Contact the IBD helpline for advice from the Specialist team. In patients taking mesalazine, consider if those could be symptoms of idiopathic intracranial hypertension. If so, consider discontinuation and contact the IBD helpline to discuss referral to Specialist for investigations (i.e. blood pressure monitoring and ophthalmology examination). For further information see Drug Safety Update on mesalazine and idiopathic intracranial hypertension.
WBC < 4.0 x 10^9/l	Monitor carefully – if WBC continues to fall, withhold until discussed with the IBD helpline.
Neutrophils < 2.0 x 10^9/l	Monitor carefully – if neutrophil count continues to fall, withhold until discussed with the IBD helpline.
Platelets < 150 x 10^9/l	Monitor carefully – if platelet count continues to fall, withhold until discussed with the IBD helpline.
Severe abdominal pain	Check amylase level. Withhold until discussed with the IBD helpline, consider ultrasound or CT scanning.
> 2-fold rise above the upper limit of the normal reference range for ALT (0-45 U/L), AST (0-35 U/L)	Stop and discuss with the IBD helpline. Ultrasound liver.
Rise of creatinine level above the normal range (or rise of > 20% compared to baseline)	Stop and discuss with the IBD helpline. Urinalysis for proteinuria etc, renal ultrasound, nephrology opinion.
Abnormal bruising or severe sore throat	Check FBC immediately and withhold until the result is available. Discuss with the IBD helpline.
Unexplained acute widespread rash	Stop and seek urgent Specialist advice (preferably Dermatological).

Contraindications:

- Hypersensitivity to salicylates
- Hypersensitivity to sulfonamide/co-trimoxazole
- Hypersensitivity to the active substance or any of its excipients
- Severe renal impairment (GFR <30ml/min)
- Severe liver impairment
- Patients with G6PD or porphyria (only with sulfasalazine)

Side effects:

The most common and dose-related side effects are headaches, rash, nausea, epigastric pain, and diarrhoea.

Side effects that occur rarely include:

- **Skin disorders** (Steven Johnson Syndrome, lupus erythematosus-like syndrome)
- **Blood disorders** (agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinaemia, neutropenia, and thrombocytopenia)
- **Lung disorders** (fibrosing alveolitis, eosinophilia)
- **Renal impairment** (interstitial & nephritic syndrome)

Others include acute pancreatitis, hepatitis, myocarditis, pericarditis, alopecia, and peripheral neuropathy.

Sulfasalazine is associated with a reversible reduction in male fertility, yellow-orange discolouration of the skin, urine, and other body fluids, and staining of soft contact lenses.

Sulfasalazine can also reduce the body's ability to absorb folates (B vitamins) which are essential for blood cell formation. Some people taking sulfasalazine may need a folic acid replacement.

Mesalazine has been linked to idiopathic intracranial hypertension (IIH). Although reported very rarely, patients should be advised to look for signs and symptoms of IIH including severe or recurrent headache, visual disturbances or tinnitus and seek medical advice promptly.

Precautions:

- **Renal impairment -** (See Table 4 Monitoring) avoid in patients with severe renal failure. Discontinue treatment if renal function deteriorates. Discuss with the renal team if appropriate.
- **Blood disorder -** patients should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever, or malaise that occurs during treatment.
- **Hepatic impairment**
- **Elderly** – use with caution in elderly >70 years old.
- **History of allergy or asthma** (sulfasalazine, balsalazide).
- **Glucose 6 phosphate dehydrogenase deficiency** (sulfasalazine may cause haemolysis).
- Previously diagnosed or suspected **idiopathic intracranial hypertension** (mesalazine has been linked with incidence of IIH).

Clinically relevant medicine interactions and their management:

- Concurrent use of other known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal toxicity.
- Sulfasalazine may reduce the absorption of digoxin and folate.
- Concomitant treatment in patients receiving azathioprine can increase the risk of blood dyscrasias.
- Salofalk® should not be given with lactulose or similar preparations which lower the stool pH and may prevent the release of mesalazine.

For further information about cautions, side effects and interactions for individual medicine, please see individual summary product characteristics accessible via medicines.org.uk.

Pregnancy Breastfeeding and Fertility:

Careful assessment of risk versus benefit should be carried out before use during pregnancy and breastfeeding. Consult specialists for further advice. Only continue treatment if the potential benefits outweigh the potential risks.

Consider folate acid supplementation during pregnancy in high-risk individuals such as those taking sulfasalazine. Sulfasalazine has been safely used in pregnancy but a folic acid supplement of 5mg a day should be prescribed to those trying to conceive and during pregnancy.

Patients are advised to avoid breastfeeding unless essential whilst on sulfasalazine. Small amounts of the medicine may be excreted in breast milk although these are not thought to be a risk to a healthy, full-term infant.

Sulfasalazine can be prescribed to men with child procreating potential although there may be transient reversible oligospermia and infertility. Pregnancy may still occur, and contraception is needed.

Patient information:

Patients should be counselled on the risks and benefits of their treatment where appropriate. The patient should be told the indication for their treatment and intended duration and advised on what side effects to look out for.

References for clinicians:

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5. Summary of Product Characteristics for individual preparations available at www.medicines.org.uk
6. European Crohn's and Colitis Organisation: Guidelines on Therapeutics 2019: medical treatment. Journal of Crohn's and Colitis 2020; 14: 1:4-22. Available at https://doi.org/10.1093/ecco-jcc/jjz180.
7. Drug Monitoring database from Specialist Pharmacy Service. Available at https://www.sps.nhs.uk/home/tools/drug-monitoring/.
8. Using mesalazine tablets appropriately. Specialist Pharmacy Services. Available at https://www.sps.nhs.uk/articles/using-mesalazine-tablets-appropriately/.