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 [2,4,9]. Certain brands of 5-ASA are also licensed for the maintenance of remission in Crohn's ileo-colitis[1,3].
The medications that contain 5-ASA include sulfasalazine, mesalazine, olsalazine and balsalazide. 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[2] 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[16].

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]:
The four currently available 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 different formulations.
Therefore, it is recommended to **prescribe the medicine by brand name**[1].

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 [1,7].

Dosages and route of administration[1]:
Depending on the location of inflammation in the bowel, the 5-ASA can be given:
- Orally - tablets, granules, and suspensions
- Rectally – suppositories, foam, and enemas

Please see Table 2 and Table 3 for more information on oral and rectal dosing of the currently available 5-ASA products.

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

Table 1 Aminosalicylates - available products

Medication	Release mechanism[4]	Brand	Formulation	Site of action[4,7]
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	Suppositories Tablets (400mg tablets discontinued April 2024)	Terminal ileum & large bowel (colon & rectum)
		***Restricted for patients who are unable to switch to Octasa® brand**		
	Mezavant® and Ipocol® brands of mesalazine are non-formulary medicines.			
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, existing patients may continue)*		Salazopyrin®	Tablets, EC tablet Suspension Suppositories	Colon
Olsalazine is non-formulary				

Table 2 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)	500mg four times a day	Max 8g daily (1-2g four times daily)	Active CD: 1-2g four times daily
* may be continued for existing patients			

Table 3 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 [4,9].

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 [3, 13].

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.	
If results are stable repeat FBC, U&E and LFT once yearly (6-monthly monitoring may be required in some patients).		

Explicit criteria for review and discontinuation of the medicine:

Table 5 Actions to be taken[10]**:**

Side effect	Action
Nausea, dizziness, headache, worsening diarrhoea	If troublesome, reduce or stop treatment and consider alternative Refer to hospital specialist team.
WBC < 4.0 x 10^9/l	Monitor carefully – if WBC continues to fall, withhold until discussed with the Gastroenterologist
Neutrophils < 2.0 x 10^9/l	Monitor carefully – if neutrophil count continues to fall, withhold until discussed with Gastroenterologist
Platelets < 150 x 10^9/l	Monitor carefully – if platelet count continues to fall, withhold until discussed with Gastroenterologist
Severe abdominal pain	Check amylase level. Withhold and 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)	Withhold until discussed with the specialist team; Ultrasound liver.
Rise of creatinine level above the normal range (or rise of > 20% compared to baseline)	Withhold until discussed with the specialist team; 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 Gastroenterologist
Unexplained acute widespread rash	Withhold; seek urgent specialist (preferably Dermatological) advice

Contraindications[1,8]:

- 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 [1,8]:

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.

Precautions[1,8]:

- **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)

Clinically relevant medicine interactions and their management[1,8]:

- 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.
- Ipocol®, and 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[1]. 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.

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