HISTORICALLY ACCEPTED USE

Tertiary and Quaternary Committee

Executive Summary

Date: May 2024

Medicine (INN): Sulfasalazine

Medicine (ATC): A07EC01

Indication/s (ICD10 code/s): Ulcerative colitis (K51)

Patient population/s: Patients diagnosed with Ulcerative Colitis (any severity)

Level of Care: Tertiary and Quaternary

Prescriber Level: Specialist

Current standard of Care: Sulfasalazine (*aminosalicylate)* forms part of a standard regimen for management of Ulcerative Colitis in the public sector and has been utilised for a number of decades. The agent was historically included on Adult Hospital Level Standard Treatment Guidelines until 2015 when amendments were made to refer all patients with Inflammatory Bowel Disease to specialist care. Sulfasalazine has remained on national contract however it was not carried through to the Tertiary and Quaternary EML. Oral mesalazine was added to the TQ EML in 2015 as an alternative to sulfasalazine for special access for those patients with a Sulphur allergy.

Rationale:

Sulfasalazine has been utilised in clinical practice internationally for decades. Newer agents were developed to provide alternatives with better side effect profiles. Thus the majority of trials and systematic reviews use sulfasalazine as the comparator and standard of care.

Induction

- A systematic review by Murray 2020a[1] for induction of remission in patients with active ulcerative colitis focussed on oral mesalazine versus placebo and oral mesalazine versus sulfasalazine.
- There is high-certainty evidence that mesalazine is superior to placebo (Failure to induce complete global or clinical remission 6-12 weeks; RR 0.86, 95% CI [0.82 to 0.89], i^2=25%, P < 0.00001, n= 2387, 11 studies) and moderate-certainty evidence that oral mesalazine is not superior to sulfasalazine (Failure to induce complete global or clinical remission 4-8 weeks; RR 0.90 95% CI [0.77 to 1.04], i^2=0%, P = 0.15 n=526, 8 studies).
- There was moderate certainty of evidence in favour of sulfasalazine over oral mesalazine for adverse events (4-8 weeks, RR 0.48 95% CI [0.36 to 0.63], i^2=0%, P < 0.00001, n=909, 12 studies), and low certainty of evidence that there is no difference in serious adverse events (RR 1.36, 95% CI [0.28 to 6.52], i^2=37%, P = 0.70, n=107, 2 studies).

Maintenance

- Murray 2020b[2] also explored oral mesalazine compared to placebo and compared to sulfasalazine for maintenance of remission in patients with ulcerative colitis.

[1] Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD000543. DOI: 10.1002/14651858.CD000543.pub5.

[2] Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020 Aug 28;8(8):CD000544. doi: 10.1002/14651858.CD000544.pub5. PMID: 32856298; PMCID: PMC8094989.

» There is high-certainty evidence that mesalazine is superior to placebo (Failure to maintain clinical or endoscopic remission at 6-12 months; RR 0.68 95% CI [0.61 to 0.76], i^2=10%, P < 0.00001, n=1555, 8 studies) and high-certainty evidence that oral mesalazine is inferior to sulfasalazine (Failure to maintain clinical or endoscopic remission at 6–18 months, RR 1.14 95% CI [1.03 to 1.27], i^2=17%, P = 0.01 n=1655, 12 studies).

» There was moderate-certainty evidence that there was no difference in adverse events between oral mesalazine and placebo and between mesalazine and sulfasalazine.

Evidence based guideline recommendations:

Guideline	Recommendations
Ulcerative colitis: management NICE guideline [NG130] Published: 03 May 2019[3]	<u>Treating mild-to-moderate ulcerative colitis</u> **Proctitis** 1.2.1 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of proctitis, offer a topical aminosalicylate as first-line treatment. [2019] *In May 2019, this was an off-label use of some topical aminosalicylates for children and young people. See NICE's information on prescribing medicines.* 1.2.2 If remission is not achieved within 4 weeks, consider **adding an oral aminosalicylate. [2019]** **Proctosigmoiditis and left-sided ulcerative colitis** 1.2.6 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of proctosigmoiditis or left-sided ulcerative colitis, offer a topical aminosalicylate as first-line treatment. 1.2.7 If remission is not achieved within 4 weeks, consider: • **adding a high-dose oral aminosalicylate** to the topical aminosalicylate or • switching to a high-dose oral aminosalicylate and a time-limited course of a topical corticosteroid. [2019] **Extensive disease** 1.2.11 To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of extensive ulcerative colitis, offer a topical aminosalicylate **and a high-dose oral aminosalicylate as first-line treatment**.

[3] Ulcerative colitis: management. NICE guideline [NG130]Published: 03 May 2019. Available: https://www.nice.org.uk/guidance/ng130/chapter/Recommendations

Historically accepted use Criteria

	Criteria	Comment
1	The medicine is included in the WHO Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES: X / NO: Anti-inflammatory medicines (17.3) and Disease-modifying anti-rheumatic drugs (29.2)
2	The medicine is currently registered by SAHPRA for the indication.	YES: X / NO: Registration since 1994, SAHPRA Database
3	There is evidence of long-established (prior to 1996*) safe and effective use of the medicine for the recognised indication in the public health sector.	YES: X / NO: Comment: Registered in 1994, part of standard regimen
4	There have been no new reported safety or efficacy concerns (Please mark 'yes' if in agreement with statement).	YES: X / NO: Comment: Note Appeal in 2015 for alternative for patients with sulphur allergy – special access can be granted for mesalazine
5	The budget impact is not expected to have an incremental increase, that a de novo review is justified (Please mark 'yes' if in agreement with statement).	YES: X / NO: Comment: Costs - Salazopyrin EN 500mg TAB 100 tablets = R309.57 (2-4g daily = R186 to R743 per month)[4] Agent already on contract and was previously part of standard of care in Adult Hospital Level STGs
6	Equitable access across the country is essential, and is limited only by the availability of adequately trained staff and availability of equipment.	YES: X / NO: Comment

** The Essential Drugs Programme (EDP) of South Africa was established in terms of the National Drug Policy (NDP) which was implemented in 1996*

Recommendation

It is recommended that sulfasalazine, oral be included on the Tertiary Essential Medicines List for use in patients with ulcerative colitis.

[4] Medicine Health Product List (MHPL). May 2024.