What are the differences between different brands of mesalazine tablets?

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Background

Mesalazine is an aminosalicylate that is used routinely to induce and maintain remission in chronic inflammatory bowel disease – ulcerative colitis (UC) and Crohn's disease (1). Mesalazine is commonly given as a gastro-resistant, delayed release preparation to target delivery of the drug to the diseased area of the bowel to provide topical anti-inflammatory therapy. Asacol MR, Mezavant XL, Octasa MR, Pentasa Slow Release, Salofalk and Zintasa are all delayed-release mesalazine tablet formulations. The delayed release mechanism commonly used on the tablets is enteric coating (EC) (1-13).

Available formulations have differences in licensed indications, tablet strengths, dose frequency, interactions, pharmaceutical, pharmacological and pharmacokinetic properties. This Q&A will provide an overview of these differences to help prescribers determine the most appropriate choice of mesalazine preparation based on aspects such as indication (i.e. acute disease or maintenance of remission), disease location, dosage regimen and anticipated compliance (i.e. once-daily or multiple-daily dosing) and cost.

Answer

Licensed indications

All 12 mesalazine tablet preparations are licensed for the treatment of mild to moderate acute exacerbations of UC and all except Salofalk 1g tablets are licensed for maintenance of UC remission (2-11). Asacol MR and Octasa MR 400mg and 800mg strengths are also licensed for the maintenance of remission in Crohn's ileo-colitis (2, 3, 5, 6). Ipocol tablets were previously available but were discontinued in March 2017 (14).

Tablet strength, dose and frequency

A list of the licensed preparations including strengths, indications and corresponding licensed doses can be found in Appendix 1.

Recommended dosing

For treatment of acute disease, the total daily dose should generally be taken in 2 or 3 doses throughout the day, with exception to Mezavant XL (2, 3, 5-13). Octasa MR, Mezavant XL and Pentasa Slow Release can be taken once daily (4-9). For maintenance of remission, depending on the licensing of the product, the total daily dose can be taken in 2 or 3 doses throughout the day (10-13), once daily (4, 7-9) or by either method (2, 3, 5, 6). The NICE guidelines for the management of UC recommends to consider once-daily dosing for maintenance of remission, although they do state that this dosing regimen may be associated with more side-effects (15).

The British Society of Gastroenterology guidelines for inflammatory bowel disease recommends that, for mild to moderate UC, oral mesalazine 2-3g daily should be used, which can be increased to 4-4.8g daily in acute flares with addition of topical mesalazine. The guidelines recommend against the use of mesalazine in the induction of remission and maintenance of Crohn's disease (16).

Monitoring

Renal function should be measured prior to treatment starting and then periodically once treatment is commenced (2-13). The SPCs vary in their recommendations for frequency of testing – see table 1.

Table 1 – Suggested renal monitoring frequency in SPCs

Brand	Renal monitoring frequency
Asacol Zintasa	Prior to treatment starting, then periodically during treatment: every 3 months for the first year, then 6 monthly for the next 4 years and annually thereafter, based on individual patient history.
Mezavant XL	Prior to treatment starting, then at least twice a year while on treatment.
Octasa, Salofalk, Pentasa	Prior to treatment starting, then 14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. In the absence of an acute renal reaction monitoring intervals can be extended to every 3 months.

The Specialist Pharmacy Service website has published recommendations for drug monitoring in primary care, including mesalazine (17). This provides the following advice:

Tests prior to starting treatment: Renal function, urea and electrolytes, liver function tests, full blood count and urine dipstick.

Monitoring until patient is stabilised: Renal function, urea and electrolytes, liver function tests, full blood count and urine dipstick. These tests should be monitored 14 days after starting treatment and then a further 2 or 3 tests at intervals of 4 weeks. If results are normal, then tests can be reduced to every 3 months

Ongoing monitoring: There is no national standard for long term monitoring. It is left to the discretion of the physician and should take into account the person's risk factors. For renal function, it is suggested to monitor every 6 months for the first 4 years then annually, or more frequently if there are risk factors for renal impairment. For urea and electrolytes, liver function tests and full blood count, it is suggested that these are monitored every 6 months or annually depending on patient's individual risk factors.

Pharmaceutical / Pharmacological

To ensure that mesalazine is targeted to the terminal ileum and colon, the tablet formulations have various coatings or protective characteristics that release mesalazine under various conditions. The site of drug release is an important factor in determining the most appropriate choice of preparation based on the disease location within the gastrointestinal tract.– see table 2 (2-13, 18-21).

Eudragit L and S methacrylic acid polymers are the preferred choice of coating polymers for enteric coated tablets as they allow targeted release of the drug into specific areas of the intestine. The polymers are sometimes combined to adjust the dissolution pH, and thus to achieve the required GI-targeting for the drug. Eudragit L dissolves at pH >6 and Eudragit S dissolves at pH >7. In practical terms, the jejunum is pH 6–7 and the ileum/colon has a pH > 7.0 (2-6, 10, 11, 19, 22).

A comparison of the efficacy and safety of Eudragit-L and ethylcellulose coated mesalazine tablets in patients with mild to moderately active UC concluded that both preparations were well tolerated and equally effective in achieving remission over 8 weeks (23).

Table 2 – Formulation & release characteristics of MR mesalazine tablets

Brand	Formulation	Optimal drug release pH	Site of drug release
Asacol MR	400mg: Enteric coated with Eudragit S 800mg: Enteric coated with Eudragit S and Eudragit L	>7 >6-7	Terminal ileum & large bowel
Mezavant XL	Film coated with Eudragit S and Eudragit L	>6-7	Colon
Octasa MR	Enteric coated with Eudragit S	>7	Terminal ileum & colon
Pentasa Slow Release	Ethylcellulose coated microgranules	Release not pH dependant*	Duodenum to rectum
Salofalk	Enteric coated with Eudragit L	>6	Terminal ileum & colon
Zintasa	Enteric coated with Eudragit S	>7	Terminal ileum & colon

* Release of mesalazine from Pentasa slow release tablets is time dependant as opposed to pH dependant. The ethyl cellulose coated microgranules enter the duodenum within an hour of administration. Mesalazine is then continuously released from microgranules throughout the gastrointestinal tract in any enteral pH conditions (24).

Pharmacokinetics

A systematic review of the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of UC concluded that the systemic exposure to 5-aminosalicylate (5-ASA) as measured by urinary excretion of total 5-ASA and faecal excretion of 5-ASA is comparable for all oral mesalazine formulations and pro-drugs. This review was conducted in 2003 and the preparations included were Asacol 400mg MR, Pentasa Slow Release and Salofalk (25).

Octasa MR 400mg is a generic version of Asacol 400mg MR. The in vitro dissolution profile of Octasa MR is virtually identical to that of Asacol 400mg MR – see table 3 (20). Octasa MR has not been compared to other mesalazine MR preparations in patient studies because to obtain a licence as a generic medicine, the product only needs to demonstrate bioequivalence to the brand leader (20, 26).

Table 3 - Release characteristics of Asacol 400mg MR & Octasa MR tablets

	Asacol 400mg MR	Octasa MR
pH 1.0-1.2 for 2 hours	0% release	0% release
pH 6.4 for 1 hour	<1% released	<1% released
pH 7.2 for 1 hour	~98% released in 30 - 60 minutes	~99% released in 30 - 60 minutes

pH 1.0-1.2 mimics the conditions in the stomach, pH 6.4 – 6.5 mimics the conditions in the small bowel and pH 7.2 - 7.5 mimics the conditions in the terminal ileum/colon (19).

Interactions

The summaries of product characteristics (SPCs) for Asacol MR and Zintasa states that the tablets should not be given with lactulose or similar preparations which lower stool pH and may prevent release of mesalazine (2, 3, 13). None of the other mesalazine tablet SPCs highlight this interaction. This is a theoretical interaction and there is currently no evidence to suggest that an interaction of clinical importance would be expected to occur. There have been no published reports to date of any interaction with ispaghula husk, lactulose or lactitol (27).

Choice of preparation

The NICE guidelines for the management of UC do not differentiate between different aminosalicylate preparations. They recommend to consider once-daily dosing for maintenance of remission but also add that this may result in more side-effects. Although associated with greater adherence, once daily dosing with mesalazine may result in more side-effects and therefore (15). Similarly, the BSG guidelines line for inflammatory bowel disease reinforce that once daily dosing is as effective as divided dosing regimens. Because of this and adherence issues with mesalazine, the guidelines recommend once daily dosing should be considered as a standard dosing regimen for all mesalazine use. Other factors to base prescribing decisions on include patient preference and cost (18).

Two Cochrane reviews have also been published about the use of mesalazine in the treatment of UC (one focussing on induction of remission and the other focussing on maintenance of remission) and both reviews state that there is no apparent difference in efficacy or safety between the different mesalazine preparations (28, 29).

From a cost perspective, PrescQIPP have published a cost-analysis of mesalazine tablets. They state that, for 400mg and 800mg preparations, Octasa tablets are the least costly. Therefore, it is recommended that patients on generic mesalazine or Asacol tablets (400mg and 800mg strengths) should be reviewed to determine whether it is suitable to switch to Octasa tablets. The switch should be tailored to the individual patient, and conducted and managed in conjunction with their gastroenterologist (30).

Summary

- Asacol MR, Mezavant XL, Octasa MR, Pentasa Slow Release, Salofalk and Zintasa are all licensed for treatment of mild to moderate ulcerative colitis and maintenance of remission in ulcerative colitis. Asacol MR and Octasa MR 400mg and 800mg tablets are also licensed for maintenance of remission in Crohn's ileo-colitis, although the BSG advises against this.
- Asacol MR and Octasa MR are available in 400mg and 800mg strengths. Octasa is also available in a 1,600mg strength. Mezavant XL contains 1200mg, Pentasa Slow Release contains 500mg and 1,000mg and Salofalk contains 250mg, 500mg and 1,000mg, and Zintasa contains 400mg mesalazine.
- Different preparations recommend different doses (including frequency) based on both strength of tablet and indication of use. These are listed in Appendix 1.
- Asacol MR, Octasa MR, and Zintasa are similar in terms of formulation, optimal pH for drug release and site of drug release. Mezavant XL, Pentasa Slow Release and Salofalk have slightly different formulations and optimal pH for drug release. Pentasa also has a slightly different site of drug release too.
- Renal function should be measured prior to treatment starting and then periodically once treatment is commenced. The SPCs vary in their recommendations for frequency of testing.
- Independent reviews have concluded that there is very little difference in terms of efficacy or safety between mesalazine MR preparations so choice should depend on factors that may aid adherence to therapy; for example, less frequent dosing has been shown for some preparations to be as effective as multiple daily dosing. NICE recommends considering once-daily dosing for maintenance of remission in ulcerative colitis, although this may result in more side-effects.
- The British National Formulary states that there is no evidence to show that any one oral preparation of mesalazine is more effective than another; however, the delivery characteristics of oral mesalazine preparations may vary. If it's necessary to switch a patient to a different brand of mesalazine, the patient should be advised to report any changes in symptoms.
- From a cost perspective, Octasa 400mg and 800mg tablets are preferred to Asacol or generic mesalazine 400mg and 800mg tablets. Any switch to Octasa needs to be tailored to the individual needs of the patient.

Limitations

There are other mesalazine products available (e.g. enemas, suppositories, granules and foam) which this Q&A has not addressed. A separate Q&A comparing the differences between non-oral mesalazine preparations can be found here

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Quality Assurance

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Search strategy
- British National Formulary online; Martindale, The Complete Drug Reference; Stockleys Drug Interactions. Accessed via www.medicinescomplete.com, search term: mesalazine
- DrugDex, search term: mesalazine
- Electronic Medicines Compendium, accessed via www.emc.medicines.org.uk, search term: mesalazine
- NICE Evidence, Cochrane Library, accessed via http://www.evidence.nhs.uk/, search term: mesalazine
- Medline, 1946 to date, search terms: MESALAMINE/ AND DELAYED-ACTION PREPARATIONS/ [Limit to: Publication Year 2018-Current]

- Embase, 1972 to date, search terms: MESALAZINE/ AND SUSTAINED-RELEASE PREPARATIONS/ [Limit to: Publication Year 2018-Current]

Appendix 1: Licensed indications and dosages of mesalazine tablets (2-13)

Brand	Strength	Licensed indication	Licensed dose
Asacol MR	400mg	For the treatment of mild to moderate acute exacerbations of UC.	2.4g daily in divided doses.
		For the maintenance of remission of UC.	1.2 to 2.4g tablets once daily or in divided doses.
		For the maintenance of remission of Crohn's ileo-colitis.	
	800mg	For the treatment of mild acute exacerbations of UC.	2.4g daily in divided doses.
		For the treatment of moderate acute exacerbations of UC.	4.8g daily in divided doses.
		For the maintenance of remission of UC.	Up to 2.4g once daily or in divided doses.
		For the maintenance of remission of Crohn's ileo-colitis.	Up to 2.4g daily in divided doses.
Mezavant XL	1,200mg	For treatment of mild to moderate acute exacerbations of UC.	2.4 to 4.8g once daily. The highest dose of 4.8g is recommended for patients not responding to lower doses of mesalazine.
		For the maintenance of remission of UC.	2.4g once daily.
Octasa MR	400mg	For the treatment of mild acute exacerbations of UC.	2.4g once daily or in divided doses.
		For the treatment of moderate acute exacerbations of UC.	2.4g to 4.8g daily in divided doses. 2.4g may be taken once daily or in divided doses. Above 2.4g daily should be taken in divided doses.
		For the maintenance of remission of UC.	1.2g to 2.4g taken once daily or in divided doses.
		For the maintenance of remission of Crohn's ileo-colitis.	
	800mg	For the treatment of mild acute exacerbations of UC.	2.4g once daily or in divided doses.
		For the treatment of moderate acute exacerbations of UC.	2.4g to 4.8g a day in divided doses. 2.4g may be taken once daily or in divided doses. Above 2.4g daily should be taken in divided doses.
		For the maintenance of remission of UC.	1.6 g to 2.4 g taken once daily or in divided doses.
		For the maintenance of remission of Crohn's ileo-colitis.	
	1,600mg	For the treatment of mild to moderate acute exacerbations of UC.	4.8g daily, either as single dose or in 2-3 divided doses.
		For the maintenance of remission of UC.	1.6g once daily
Pentasa SR	500mg, 1,000mg	For the treatment of mild to moderate acute exacerbations of UC.	Up to 4g once daily or in two or three divided doses.
		For the maintenance of remission of UC.	Recommended dosage of 2g once daily.
Salofalk	250mg, 500mg	For the treatment of mild to moderate acute exacerbations of UC.	1.5g to 3.0g daily in three divided doses.
		For the maintenance of remission of UC.	1.5g in three divided doses.
	1,000mg	For the treatment of mild to moderate acute exacerbations of UC.	3g in three divided doses.
Zintasa	400mg	For the treatment of mild to moderate acute exacerbations of UC.	2.4g daily in divided doses.
		For the maintenance of remission of UC.	1.2 to 2.4g daily in divided doses.