Recommendations for the optimal use of mesalazine in the management of patients with mild to moderate ulcerative colitis

Abstract

The 2021 National report from IBD UK included responses from over 10 000 patients with inflammatory bowel disease, over 70% of whom reported having at least one flare in the last 12 months. As the first-line treatment for patients with mild and moderate ulcerative colitis, the action and delivery mechanisms of mesalazine are crucial for successful management of the disease. The choice of the most appropriate formulation of mesalazine and securing patient concordance and adherence to treatment remains a challenge for healthcare professionals. This article details the outcome of a roundtable discussion involving a group of gastroenterology consultants and specialist nurses which considered the importance of ensuring that patients have individualised mesalazine therapy before escalation to other treatments and gives recommendations for the management of patients with mild or moderate ulcerative colitis.

Key words: Inflammatory bowel disease; Mesalazine; Ulcerative colitis

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Introduction

Ulcerative colitis is a form of inflammatory bowel disease which, unlike Crohn's disease, affects only the colon. Ulcerative colitis and Crohn's disease are both chronic immune-mediated diseases, causing inflammation of the mucosal lining. The aim of treatment is to stop this inflammation. Patients may progress from mild to moderate, then to severe ulcerative colitis, depending on the appropriateness of and response to initial therapy and on their adherence and self-management of the disease. Ulcerative colitis is defined as mild when there are fewer than four bowel movements per day with minimal or no blood, severe if there are six or more bowel movements per day with blood and at least one of fever, tachycardia, elevated inflammatory markers or anaemia, and moderate if neither the mild nor severe criteria are met (Truelove and Witts, 1955). Clinical symptoms of mild and moderate ulcerative colitis include a gradual onset of abdominal pain, rectal bleeding and diarrhoea (Baumgart and Sandborn, 2007).

The aim of treatment is to induce remission of the active inflammation in ulcerative colitis, following which the patient may be put on long-term maintenance therapy (which is often lifelong) to reduce the risk of relapse, as this is a chronic relapsing and remitting disease. Disease location will affect the selection of the initial treatment (Harbord et al, 2017; National Institute for Health and Care Excellence, 2019). Adherence to therapy is also important, while non-adherence means that patients with ulcerative colitis are not getting the maximum benefit from their maintenance therapy (Kane et al, 2001). More than one third of 363 patients with ulcerative colitis, reviewed in 11 Leicestershire general practices, showed inadequate maintenance therapy with mesalazine, requiring therapy modification by healthcare professionals (Palin, 2014). One problem leading to non-adherence is patients lacking knowledge about available formulations and dosing of mesalazine, as nearly 85% of ulcerative colitis patients interviewed were unaware of a once-daily dose alternative (Palin, 2014).

Mesalazine is one of the aminosalicylic acid (5-ASA) drugs, formulated and marketed for oral and rectal use. It acts topically to induce and maintain remission in patients with

The content of the article was developed by the authors at a meeting initiated and sponsored by Dr Falk Pharma UK. Prescribing information for Salofalk formulations can be found at the end of the article.

Job code UI--2100113 Date of preparation: September 2021

How to cite this article:
Akbar A, Arnott I, Kennedy NA et al. Recommendations for the optimal use of mesalazine in the management of patients with mild to moderate ulcerative colitis. Br J Hosp Med. 2021. https://doi.org/10.12968/hmed.2021.0399

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ulcerative colitis. Panellists at this roundtable meeting discussed individualised therapy, the importance of adherence and patient self-management for patients with mild or moderate ulcerative colitis. They also developed practical recommendations for the optimal use of mesalazine to prevent disease escalation and to support adherence with mesalazine. The article highlights the importance of choosing appropriate formulations and encouraging patient engagement to maximise success before escalation. This is important to help to try and keep patients in remission to prevent relapse and unnecessary visits to hospital.

The annual prevalence of ulcerative colitis increased from 390 per 100 000 population in 2000 to 570 per 100 000 in 2017, with an average increase of 2.5% per annum (King et al, 2020). An estimated 10% of patients present with severe ulcerative colitis, meaning that the majority of patients with mild to moderate ulcerative colitis are suitable for mesalazine therapy. Of these, around 50% are on maintenance therapy in a community setting (Langholz et al, 1991, 1994). The 2021 National report from IBD UK included responses from over 10 000 patients with inflammatory bowel disease. Over 70% of these reported having at least one flare in the last 12 months, with 14% having had more than five flares in that period (IBD UK, 2021).

Initial and maintenance therapy: the current situation

Initiation

The European Crohn's and Colitis Organisation consensus (Harbord et al, 2017) stated that 'mild to moderately active left-sided ulcerative colitis should initially be treated with an aminosalicylate enema ≥1 g/day [EL1] combined with oral mesalazine ≥2.4 g/day [EL1], which is more effective than oral or topical aminosalicylates or topical steroids alone'. Disease location affects the selection of the initial treatment, with guidance from the National Institute for Health and Care Excellence (2019) and the European Crohn's and Colitis Organisation consensus (Harbord et al, 2017) recommending that treatment should be selected according to the site of disease. In the UK, a high percentage of symptomatic patients are initially prescribed mesalazine. Participants felt that patients with mild to moderate ulcerative colitis that was inadequately controlled on initial mesalazine therapy should mainly receive an increased dose of mesalazine as the first step, topical treatment as the second step, and steroids as the third step. Participants felt that a change of therapy generally only happens in the second or third step.

Adherence has been shown to be closely linked to drug formulation. The majority of patients prefer oral mesalazine to rectal therapy, and up to 68% of patients with ulcerative colitis who are prescribed rectal enemas do not adhere to therapy (D'Incà et al, 2008; Lakatos, 2009; Katz et al, 2010).

Maintenance

As well as being used as initial therapy, mesalazine is also recommended for maintenance therapy (Lamb et al, 2019). Risk factors for non-adherence with mesalazine maintenance therapy include being in remission for more than 2 years, patients having frequent endoscopy, taking multiple concomitant medications, being prescribed frequent daily doses and being male or single (Kane at al, 2001; Taylor and Irvine, 2011; Stansfield, 2016). To optimise mesalazine treatment, there are different options to choose from, depending on whether the patient has left-sided or extensive disease (Figure 1) or distal disease (Figure 2). With good response to the selected drug, disease symptoms, mesalazine dose, calprotectin level and blood tests are monitored with the option of adding or changing to topical treatment if necessary (Yamamoto et al, 2015). Monitoring involves measuring C-reactive protein and faecal calprotectin levels. This is usually performed post-commencement, and then every 6 months unless there is a flare. Stable patients can move to annual monitoring. Clinic could be virtual or if and when required for symptoms or surveillance. In patients who have a poor response to mesalazine, adherence is discussed before choosing from dose maximisation, introducing a topical treatment or changing therapy (Kane at al, 2001). Table 1 outlines some questions to ask patients at each stage of the treatment pathway to encourage adherence with treatment.

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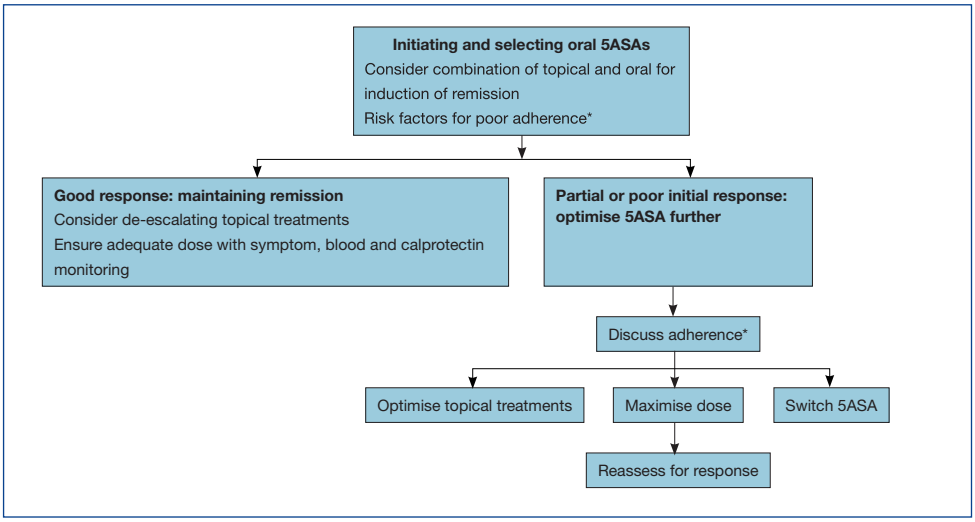

Figure 1. Optimising 5-aminosalicylic acid (5ASA) treatment in patients with left-sided or extensive disease. *Risk factors for poor adherence include pill burden and multiple daily dosing in addition to unmodifiable patient-related factors (Kane et al, 2001).

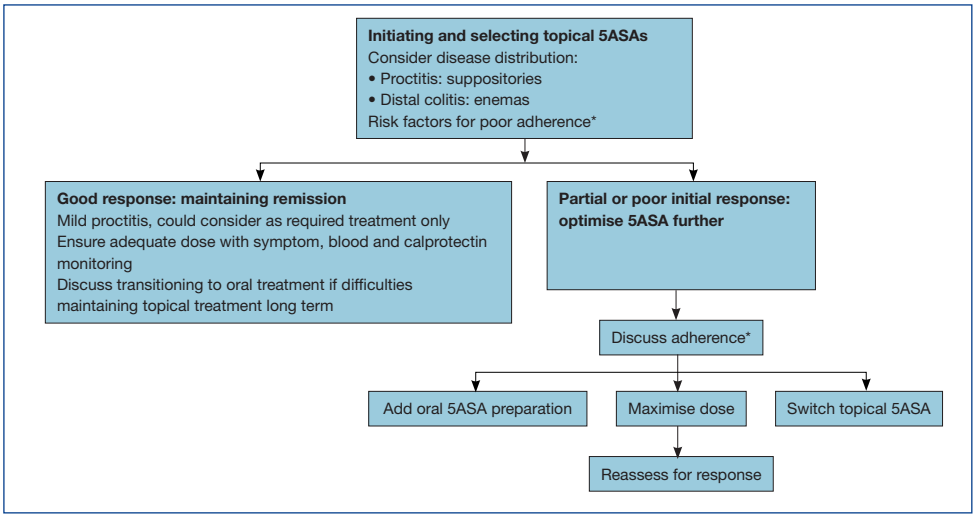

Figure 2. Optimising 5-aminosalicylic acid (5ASA) treatment in patients with distal disease. *Risk factors for poor adherence include pill burden and multiple daily dosing in addition to unmodifiable patient-related factors (Kane et al, 2001).

Table 1. Questions for patients to help optimise adherence

Initiating mesalazine	Do you have any difficulties or issues with taking suppositories or enemas?
	What is your daily routine like? (if the patient is working or busy, once-daily medication would probably be better)
	Are you taking any other regular medication? (adherence more likely if fits in with current schedule)
Taking the medication (tablets)	Is frequency of tablets a problem? (work pattern, night shifts)
	Is the number of pills a problem?
	Does the size of the tablets make them difficult to swallow?
Partial or poor response	Have you missed any doses?
	Have you seen any improvement in your symptoms? (allows you to manage expectations)
	Do you have any problems with the formulation? Do you think you might prefer granules or tablets?
Good response	How are your symptoms now? (use a scoring system, eg partial Mayo scoring index, to assess the patient's response – this give objective details for comparison in future)

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Table 2. 5-aminosalicylic acid (5ASA) formulations and their mechanism of action

Formulation	Drug release mechanism
Azo-bonded prodrugs, eg sulphasalazine (Azulfidine, Pyralin, Salazopyrin), olsalazine (Dipentum), basalazide (Colazide, Colazal)	The active ingredient is bound to a transporter molecule or another drug molecule via an azo bond that is cleaved by bacteria in the colon
pH dependent formulations of mesalazine, eg Asacol, Octasa, Mezavant, Salofalk tablets	Capsules or tablets are coated with an enteric, acid-resistant film coating that resists gastric breakdown until they reach pH of approximately ≥7.0 in the terminal ileum or right-sided colon onwards. 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
Time dependent formulations of mesalazine, eg Pentasa tablets and granules	Microspheres of mesalazine are encapsulated in an ethylcellulose membrane that breaks down gradually over time
Multi-matrix system containing mesalazine, eg Lialda, Mezavant XL, Mezavant	Lipophilic and hydrophobic matrices are enclosed in a pH dependent coating (pH>7) and, when exposed to intestinal fluid, swell to form a gel that slowly releases mesalazine throughout the colon
Dual release mechanisms for mesalazine, eg Salofalk granules	The dual release mechanism allows both controlled and extended release. In stage 1, there is pH-controlled release via gastro-resistant Eudragit L coating, allowing release of mesalazine starting at pH>6 from the terminal ileum. In stage 2, there is extended release via the insoluble polymer matrix core, allowing homogenous continuous mesalazine release during transit throughout the entire colon

From Iacucci et al (2010), Leifeld et al (2011), Ye and van Langenberg (2015), British National Formulary (2021)

Formulations of mesalazine

Mesalazine can be delivered to the colon orally or rectally. Oral formulations are available as tablets or granules, and there are five main oral formulations of mesalazine (Iacucci et al, 2010; Leifeld et al, 2011; Ye and van Langenberg, 2015; Khan et al, 2020) (Table 2). Rectal formulations are available as suppositories, liquid enemas or foam enemas (Table 3).

Fallingborg et al (1989) demonstrated that the pH in the terminal ileum and colon does not reach 7 in 25% of healthy controls. Patients with ulcerative colitis have significantly more acidic pH than healthy controls and some patients might not reach a pH of 7 (Bosworth et al, 2009). Therefore, using a drug with a coating which delays mesalazine release until pH≥7 may reduce the amount of drug available (Bosworth et al, 2009). The transit time during which the colonic pH is above 7 is significantly reduced in patients with ulcerative colitis vs healthy controls (Bosworth et al, 2009). If a patient does not respond to treatment with the initial mesalazine preparation, consider trying a different preparation which may be released at a different site in the colon before trying a completely different drug.

The British National Formulary (2021) states that: 'There is no evidence to show that any oral preparation of mesalazine is more effective than another, however, the delivery characteristics of oral mesalazine may vary.'

As shown in Table 2, the differences in formulation of different mesalazine preparations can be used to try and improve delivery of the active ingredient to the site of inflammation. Owing to their 1 mm diameter, Salofalk granules have a much larger surface area than a similar dose given as tablets, which may optimise mesalazine delivery in the distal area of

Table 3. Topical 5-aminosalicylic acid (5ASA) formulations

Formulation	Drug
Suppository	Mesalazine (Asacol, Octasa, Pentasa, Salofalk)
Liquid enema	Mesalazine (Pentasa, Salofalk)
Foam enema	Mesalazine (Salofalk)

From British National Formulary (2021)

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the colon. Significantly more patients with left-sided or distal colitis achieved endoscopic remission with Salofalk granules than with Salofalk tablets (Leifeld et al, 2011).

Not all patients are able to or want to use rectal therapy. However, by choosing rectal delivery of mesalazine (Table 3), patients will benefit from increased topical action targeting the inflammation in the colon more specifically. This also minimises systemic absorption from the small intestine, which occurs when the drug is delivered orally as tablets and granules (Harris and Lichtenstein, 2011).

Individualised therapy before escalation

Individualised therapy would be recommended for patients who are newly diagnosed, patients with mild to moderate disease who are relapsing on their current mesalazine maintenance therapy and patients with disease confined to the rectum and left side of the colon. This process can be carried out by consultants, GPs, junior doctors or inflammatory bowel disease nurse specialists. According to the meeting's panellists, the aims of individualising treatment in this way are to alleviate symptoms of ulcerative colitis, which automatically improve daily quality of life, to be able to induce and maintain remission and finally to prevent disease progression and complications. Depending on the location of ulcerative colitis, the type of mesalazine used could vary from rectal suppositories for patients with proctitis to oral and/or rectal formulation for those with distal and extensive colitis. This individualised therapy works best if patients fully understand their healthcare professionals' recommendation of a particular drug and how it works.

Successful individualised treatment will improve outcomes of maintenance therapy in patients with mild or moderate ulcerative colitis and by reducing change of drug (formulation or type) to improve adherence, the substantial cost burden for the NHS will improve too. Both the active ingredient and the delivery system determine the efficacy of any medication, and the latter has a pivotal role in controlling the drug's pharmacological effect by influencing rate of release, site and duration of action, and side-effect profile. Panellists emphasised that all these parameters were important to consider during individualised therapy to prevent escalation. A Swiss study on the management of active ulcerative colitis, which made treatment recommendations for different clinical scenarios, concluded that in future personalised medicine will help to improve the treatment of patients with ulcerative colitis (Burri et al, 2020).

When initial therapy with mesalazine fails, two main pathways can be followed to address persistent symptoms in patients with mild or moderate ulcerative colitis. The first pathway involves maximising the dose of mesalazine, extending treatment duration, adding topical therapy or changing to a new formulation of mesalazine (Figure 3), and the second pathway involves discussing adherence issues (Table 1) (Taylor and Irving, 2011).

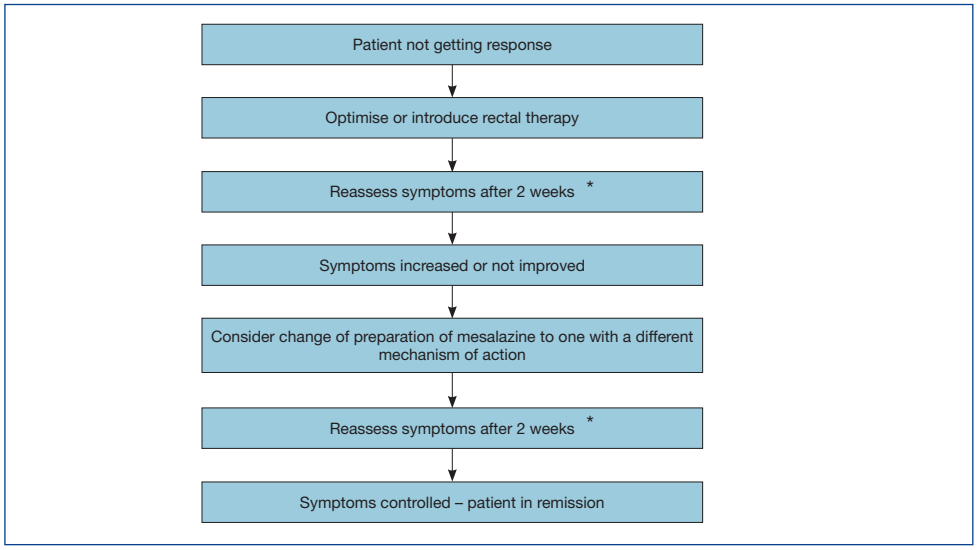

Figure 3. Addressing persistent symptoms in patients taking oral therapy for mild or moderate ulcerative colitis. *at each 2 week review, consider topical steroids.

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Focusing on the different formulations of mesalazine and the effect this will have on the site of action and therefore efficacy, and supporting patients in understanding this and making the decision about how to progress treatment, should help to improve adherence. Feedback from inflammatory bowel disease specialist nurses highlighted the difficulties for patients in openly communicating their concerns and causes of non-adherence, which makes it harder to accurately assess the outcome of maintenance therapy. So, part of this individualised therapy is to ensure open and clear communication between healthcare professionals and patients.

Practical solutions to improve the management of ulcerative colitis

Patients who are treated with once-daily dosing of mesalazine should have better adherence to treatment and improved self-management of ulcerative colitis. In the UK, following initial therapy, symptomatic patients with ulcerative colitis are often followed up by inflammatory bowel disease nurses. Cost to the NHS and inadequate maintenance therapy are two major reasons highlighted by panellists for producing guidance for inflammatory bowel disease nurses and GPs to support them in individualising treatment for patients with mild or moderate ulcerative colitis before drug escalation. In 31 Worcestershire general practices, from a total population of 285 000, there were 279 patients with ulcerative colitis whose management was reviewed. It was found that maintenance therapy was inadequate because of non-adherence (29%), taking multiple daily doses (75%) or additional treatment needed (45%). Out of the 279 reviewed patients, 29% had to sign off work, 49% had to book visits to GPs and 5% needed steroid courses (Aldulaimi et al, 2016).

A prompt response to treatment helps to encourage patient adherence to therapy, so using induction therapy which resolves patients' ulcerative colitis symptoms as quickly as possible is a major benefit. Once-daily Salofalk Granules were at least as fast in achieving symptom resolution as three times daily mesalazine dosing, although differences in the studies performed means that the results are not directly comparable (Kruis et al, 2009).

Of the patients reviewed in Leicestershire general practices, who had inadequate mesalazine maintenance therapy, about 67% of them changed to Salofalk granules (Palin, 2014). A 6-month review of these patients demonstrated that, according to the Walmsley index, 70% had improved their ulcerative colitis score, 30% had no change and there was no worsening of symptoms among any of the patients. The majority of patients reported that they preferred the once-daily dosing regimen (Palin, 2014). This demonstrates the importance of managing this stage of treatment of ulcerative colitis. Maintaining their knowledge of current treatments for ulcerative colitis allows healthcare professionals to reduce the incidence of inadequate maintenance therapy.

Optimising mesalazine is preferable before escalation to steroids or biologics, which bring with them additional side effects and costs. Changing products with different release characteristics should be considered, as this provides a practical solution to improve adherence and delivery of the active mesalazine. Depending on the presentation of the patient's ulcerative colitis, tablets may not be able to act at the site of inflammation because of proximal constipation slowing transit through the colon or diarrhoea that reduces time of release. Also, reducing the amount of drug entering the bloodstream means that patients gain the maximum benefit from direct action of mesalazine on the site of inflammation. Mesalazine within Salofalk Granules is released at pH >6 (Electronic Medicines Compendium, 2021), so it is unaffected by the differing pH of the gastrointestinal tract, and the inner matrix core ensures continuous release throughout the colon.

Practical solutions require taking the right step at the right time and the panellists gave some practical tips for healthcare professionals to help support patients' adherence with medication and improve outcomes (Table 4).

Another practical solution for patient management of ulcerative colitis would be via education and support networks. With practical guidance in place, patients with ulcerative colitis could be offered tailored care and advice on how to achieve individualised optimisation before disease escalation.

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Table 4. Practical tips to encourage adherence with medication

Issue	Suggested discussion with patient
Healthcare professionals should explain to patients the site in the bowel where the drugs work	Your disease is near the end of your bowel, so the best way to get the medicine to work is to either use an enema or a drug which isn't released until it reaches that part of your bowel. A topical therapy gets to the area of inflammation quicker and more directly so could be more effective that way
If treatment is uncomfortable or difficult to administer, eg enema, patients are less likely to adhere. Would foam be better retained and leak less?	Would you be happy and able to use an enema or a suppository?
Control is important for adherence as it allows patient choice	Rectal therapy can be given 'last thing before you go to sleep'
Practicalities of administering rectal therapy can be a problem, particularly for older patients, or those who live on their own	Do you have problems in putting in the enema or suppository? Do not worry too much if it feels like the enema has come straight out, as some will have been retained and coated the mucosa
	Consider different types of suppositories: some have a hard coating and tablet shape, others are more bullet shaped to ease insertion and have a waxy, softer coating
	Discuss the different applicators (is squeezing a bottle going to be difficult or would squeezing a collapsible corrugated device be better?), and show pictures of the enema bottles if possible
Timing of treatment	Lying down at bedtime is a good time for enemas. Retain the enema for as long as possible, but any time is ok
If a patient says that tablets go straight through them (pill in pan), that is a good indicator to look at different formulations and help explain how they work to encourage better outcomes and therefore adherence	If you see tablets or parts of tablets when you go to the toilet, that might mean that the drug isn't reaching the parts that need treatment, so we should think about using a different type of drug instead
Managing expectations is important – patients should not expect complete recovery within 1 week of starting treatment	Advise 'I will give you this dose, and you should expect one symptom to be measurably better after 2 weeks, and much better after 3 weeks. If this doesn't happen, then call us'
Check that the patient is taking the drug properly	When do you take your tablets and how many do you take each time? Do you have any problems taking the tablets?
Check that the patient has received the correct dose that was prescribed and the correct length of prescription – some settings can only prescribe 2 weeks' worth	Have you been taking the tablets for at least 4 weeks?

Conclusions

In both the initial and maintenance therapy for patients with mild and moderate ulcerative colitis, it is important to focus on the action and delivery mechanisms of mesalazine to target the site of inflammation and prevent treatment escalation to steroids or biologics. Individualised therapy, well managed by doctor and inflammatory bowel disease nurse specialists, should prevent disease progression and complications. In addition, practical solutions during maintenance therapy should lower the cost burden for the NHS, and increase healthcare professionals' confidence in managing and supporting these patients to optimise adherence and improve outcomes.

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Key points

- Importance in respecting ulcerative colitis patient's choice of drug formulation to maximise adherence, agreeing on acceptable regimen and delivery pathway.
- The choice of drug formulation plays a crucial role in targeting the site of inflammation in patients with mild or moderate ulcerative colitis.
- Appropriate initial choice of therapy by doctors will help to maximise treatment adherence by patients with ulcerative colitis.
- Healthcare professionals need to manage 5-ASA dosing during the first step of the disease, switching to new formulations and brands of mesalazine with different release characteristics to optimise before stepping up, alternate therapy or applying a combination of therapy if necessary to optimise outcomes.
- Patients must be supported to understand and communicate their preferred mesalazine formulation and any concerns which affect adherence.

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Conflicts of interest

Dr A Akbar has received speaker or advisory board fees from Dr Falk Pharma and Tillotts Warner Chilcott; Dr S Whiteoak has received sponsorship from Dr Falk Pharma, AbbVie, MSD, Pharmacosmos, Takeda, Janssen, speaker fees from Dr Falk Pharma, Kyowa Kirin, AbbVie, Pharmacosmos, Janssen, Pfizer, Norgine, and advisory board fees from Dr Falk Pharma, AbbVie, Takeda; Ms A Fraser has received speaker or advisory board fees, travel and accommodation from Takeda UK Ltd, Dr Falk Pharma, Abbvie Ltd, Ferring, Pharmacosmos, Allergan, Janssen, speaker or advisory board fees from Gilead, and speaker fees from Tillotts, Sheild and Actavis; Professor C Probert has received speaker fees from Celltrion and Dr Falk Pharma; payment for advisory board attendance from Celltrion and Dr Falk Pharma, and support for attendance to other meetings from AbbVie; Mr G Scott has attended advisory boards for Dr Falk Pharma, Tillotts and Ferring; Ms S Laird has taken part in a roundtable discussion with Fresenius Kabi Ltd; Dr I Arnott has received support from Takeda, Ferring, Vifor, Galapagos and Tillots; Dr J Nolan has recieved honoraria from Dr Falk; Dr NA Kennedy has received honoraria for advisory boards and/or speaking from Allergan, Amgen, Celltrion, Falk, Ferring, Janssen, Mylan, Pharmacosmos, Takeda, Tillotts; support for attending meetings from AbbVie, Falk, Janssen; research grants to institution from AbbVie, Biogen, Celgene, Celtrion, Galapagos, MSD, Napp, Pfizer, Pharmacosmos, Roche and Takeda; Ms A Lewis, Dr S Peake, Miss A Cheshire and Ms K Sugrue have no conflicts of interest.

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Prescribing Information (refer to full SPC before prescribing):
Presentation: Salofalk gastro-resistant prolonged-release granules containing 500mg, 1g, 1.5g or 3g mesalazine per sachet. **Salofalk gastro-resistant tablets** containing 250mg, 500mg (UK only) or 1g (UK only) of mesalazine. **Salofalk 1g/actuation rectal foam** containing 1g mesalazine per actuation. **Salofalk enema 2g** (UK only) enema containing 2g mesalazine in 59ml of suspension. **Salofalk 4g enema** (IE only) enema containing 4g mesalazine in 60ml of suspension. **Salofalk Suppositories** containing 250mg (IE only), 500mg (UK only) or 1g mesalazine. **Indications**: **granules**: treatment of acute episodes and maintenance of remission of ulcerative colitis. **Tablets: 250mg (UK)**: treatment of mild to moderate acute exacerbations and maintenance of remission of ulcerative colitis. **250mg (IE):** management of ulcerative colitis and in the treatment of Crohn's disease. **500mg**: treatment of acute episodes and maintenance of remission of ulcerative colitis 1g: treatment of acute episodes of mild to moderate ulcerative colitis. **Enema 2g:** treatment and prophylaxis of acute attacks of mild ulcerative colitis, especially in the rectum/sigmoid colon/descending colon. **Enema 4g**: management of ulcerative colitis, alone or, particularly in the acute phase, with corticosteroids. **1g rectal foam**: treatment of active, mild ulcerative colitis of the sigmoid colon and rectum. **250mg suppositories (IE):** management of ulcerative colitis, alone or, particularly in the acute phase, with corticosteroids. **500mg (UK only) and 1g suppositories:** treatment of mild and moderate attacks of ulcerative colitis in the rectum. **Dosage**: **granules**: adults: acute episodes: once daily 1 sachet of 3g granules, 1 or 2 sachets of 1.5g granules, 3 sachets of 1g granules or 3 sachets of 500mg granules (equivalent to 1.5–3g mesalazine daily), preferably taken in the morning. Alternatively, take in three divided doses. Maintenance: 1 sachet of 500mg granules 3 times a day (1.5g mesalazine daily). Where needed, 3g per day in a single morning dose. **250mg tablets**: adults and elderly: acute treatment 6 -12 tablets daily in 3 divided doses. Maintenance: 6 tablets daily in 3 divided doses. **500mg tablets**: 1 or 2 tablets 3 times daily. Maintenance: 1 tablet 3 times daily. **1g tablets**: 1 tablet three times a day. **Children (all formulations):** there is only limited documentation for an effect in children (age 6-18 years). Dosage in children 6 years and older - oral formulations: active disease – on individual basis starting with 30-50mg/kg/day either once daily (granules) or in divided doses (tablets and granules). Maximum 75mg/kg/day. Total dose should not exceed recommended adult dose. Maintenance - on individual basis starting with 15-30mg/kg/day in divided doses. Total dose should not exceed recommended adult dose. Generally recommended that half the adult dose may be given to children up to a body weight of 40kg and the normal adult dose to those above 40kg. **2g, 4g enema:** adults and elderly: 1 enema a day at bedtime. **1g Rectal Foam:** adults: 2 administrations once a day at bedtime. Divided dose is also possible (1 administration night and morning). Suppositories 250mg: 2 suppositories 3 times a day; maintenance - 1 suppository 3 times a day. **500mg suppositories:** adults and elderly: 1–2 suppositories, 2–3 times daily. **1g suppositories:** adults and elderly: 1 suppository once daily. **Method of administration: Oral**: **Granules**: taken on the tongue and swallowed, without chewing, with plenty of liquid. **Tablets**: taken whole without chewing, one hour before meals with liquid. **Rectal**: Read the SmPC and/or patient information leaflet for administration details. **Contra-indications**: hypersensitivity to salicylates or any of the excipients. Severe impairment of renal or hepatic function. **Warnings/Precautions**: blood tests and urinary status should be determined before and during treatment. Caution is recommended in patients with impaired hepatic function. Not to be used in patients with impaired renal function. Mesalazine-induced renal toxicity should be considered if renal function deteriorates during treatment. Patients with pulmonary disease, in particular asthma, should be very carefully monitored. Patients with a history of reaction to preparations containing sulphasalazine should be kept under close medical surveillance. Discontinue immediately if there are acute intolerance reactions e.g.,abdominal cramps, acute abdominal pain, fever, severe headache and rash. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported. Discontinue treatment at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity. Tablets may (rarely) be excreted undissolved in patients with the ileocecal valve removed. Cases of nephrolithiasis reported; ensure good hydration. **Salofalk granules**: contain aspartame as a source of phenylalanine. May be harmful to patients with phenylketonuria. Also contain sucrose: 0.02mg (500mg granules), 0.04mg (1000mg granules), 0.06mg (1.5g granules) 0.12mg (3g granules). **Salofalk tablets**: for patients on a sodium-controlled diet: the 250mg/500mg tablets contain 48mg/49mg of sodium - 2.4%/2.5% of maximum daily sodium intake. **Salofalk enema 2g/4g**: sodium benzoate may

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cause local irritation. Potassium metabisulphite may rarely cause severe hypersensitivity reactions and bronchospasm. **Salofalk foam**: propylene glycol may cause skin irritation, sodium metabisulphite may rarely cause severe hypersensitivity reactions and bronchospasm, cetostearyl alcohol may cause local skin reactions (e.g., contact dermatitis). **Salofalk 500mg suppositories**: cetyl alcohol may cause local skin reactions. **Interactions**: specific interaction studies have not been performed. With concomitant treatment with azathioprine, 6-mercaptopurine or thioguanine consider a possible increase in their myelosuppressive effects. There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin. **Salofalk granules** (additionally): lactulose, or similar preparations which lower stool pH: possible reduction of mesalazine release from granules due to decreased pH caused by bacterial metabolism of lactulose. **Use in pregnancy and lactation**: do not use Salofalk during pregnancy unless the potential benefit outweighs the possible risks. Limited experience in the lactation period. Salofalk should only be used during breast-feeding if the potential benefit outweighs the possible risks; if the breast-fed infant develops diarrhoea, breast-feeding should be discontinued. **Undesirable effects**: headache, dizziness, peri- and myocarditis, abdominal pain, diarrhoea, flatulence, dyspepsia, nausea, vomiting, photosensitivity especially with pre-existing skin conditions, aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia, peripheral neuropathy, allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), acute pancreatitis, impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency, nephrolithiasis, alopecia, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), myalgia, arthralgia, hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis, asthenia, fatigue, changes in hepatic function parameters, hepatitis, cholestatic hepatitis, changes in pancreatic enzymes, eosinophil count increased and oligospermia (reversible). **Salofalk rectal foam** may also cause abdominal distension, anal discomfort, application site irritation and painful rectal tenesmus. **Salofalk enema and suppositories** may also cause constipation. **Legal category:** POM. **Cost** - UK - basic NHS price; IE - Pt W: **Granules**: 500mg (100 sachets) £28.74; 31.47€. 1g (50 sachets) £28.74; 32.87€. 1.5g (60 sachets) £48.85; 51.29€. 3g (60 sachets) £97.70; 104.06€. **Tablets** 250mg (100s) £16.19; 13.48€. 500mg (100s) £32.38. 1g £58.50 (90s). **Enema**: (7) £29.92; 30.36€. **1g/actuation rectal foam**: 14 administrations per container, £30.17; 31.55€. **Suppositories**: 250mg (30) 10.70€. 500mg (30) £14.81. 1g (30) £29.62; 37.88€. **Product licence number: Granules**: 500mg: PL08637/0007; PA573/3/1. 1g: PL08637/0008; PA573/3/2. 1.5g: PL08637/0016; PA573/3/7. 3g: PL08637/0025; PA573/3/6. Tablets: 250mg: PL10341/0004; PA573/4/3; 500mg: PL08637/0019; 1g: PL08637/0027. **Enema 2g**: PL10341/0008. **Enema 4g**: PA573/4/1. 1g/actuation rectal foam: PL08637/0003; PA573/4/5. **Suppositories**: 250mg: PA573/4/2. 500mg: PL10341/0009; 1g: PL08637/0018; PA573/4/4. **Product licence holder: 250mg tablets (UK), 2g enema, 500mg suppositories:** Dr Falk Pharma UK Ltd, Bourne End Business Park, Cores End Road, Bourne End, SL8 5AS. **250mg tablets** (IE), **500mg and 1g tablets, all granules, 1g foam, 250mg, 1g suppositories, 4g enema**: Dr Falk Pharma GmbH, Leinenweberstr.5, D-79108 Freiburg, Germany.
Date of preparation: July 2021

Further information is available on request.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (UK residents) or in Ireland at https://www.hpra.ie/homepage/about-us/report-an-issue/human-adverse-reaction-form Adverse events should also be reported to Dr Falk Pharma UK Ltd at PV@drfalkpharma.co.uk .

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