

A review of mesalazine MR formulations in ulcerative colitis

There are six modified-release preparations of mesalazine currently licensed in the UK. In this article, the North Central London Formulary and Medicines Management Group propose a prescribing strategy that could potentially save the NHS several million pounds over the next five years.

Inflammatory bowel disease is a non-specific term for conditions that cause inflammation of the intestines, including ulcerative colitis (UC) and Crohn's disease. In UC, the affected tissue is localised to the large intestine (colon) and rectum (see background box).

There are six modified-release mesalazine preparations currently licensed in the UK for the treatment of mild to moderate acute exacerbations of UC, and maintenance of remission. These are:

- Asacol MR (Proctor & Gamble Pharmaceuticals)
- Ipocol (Sandoz)
- Mesren MR (Ivax)
- Mezavant XL (Shire)
- Pentasa (Ferring)
- Salofalk (Dr Falk).

Asacol MR is the current market leader in oral 5-aminosalicylates; Mesren MR and Ipocol are generic versions of this product.

Asacol MR, Ipocol, Mesren MR and

Background

Ulcerative colitis (UC) causes characteristic ulceration or open sores along the wall of the large intestine, which may result in rectal bleeding. Current guidelines for the management of mild to moderate UC recommend that, following non-pharmacological interventions such as dietary modification, the standard, first-line pharmacological intervention should be an oral aminosalicylate such as mesalazine (5-aminosalicylic acid).^{1,2} Patients who experience frequent relapses of UC are advised to take an aminosalicylate for life to reduce the risk of relapse.³

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Mezavant XL comprise mesalazine encapsulated within a protective coating of the methacrylate copolymer Eudragit-S. In Salofalk, the coating used is Eudragit-L. Methacrylate copolymers are pH-dependent and do not disintegrate in acidic conditions. These delivery systems therefore provide pH-dependent release of the active drug at the mid to terminal ileum and colon, at pH 7 (Asacol MR, Mesren MR, and Mezavant XL) and pH 6 (Ipocol).

Pentasa contains mesalazine within ethylcellulose coated microspheres, providing slow, continuous release throughout the whole intestine (duodenum to rectum) and is therefore excluded from this review.

Adherence A recent patient survey has identified that the ideal aminosalicylate therapy would not only be effective, but also require fewer tablets to be taken and less frequent dosing.⁴ Kane et al⁵ conducted

a prospective study to determine the effects of non-adherence among patients with quiescent UC (i.e. in remission). At the end of the 12 month period, it was concluded that patients who were non-adherent with their medication (refilling less than 80% of their prescriptions, as indicated by pharmacy records), had a risk of recurrence that was more than five-fold greater than in adherent patients (hazard ratio = 5.5; 95% CI 2.3–13, $p < 0.001$).

Licensing a generic product

Under current European regulations, a new generic product needs to demonstrate 'essential similarity' to the innovator product. Essential similarity requires the product to demonstrate "the same qualitative and quantitative composition in terms of active principles and bioequivalence."⁶ These guidelines are not directly applicable to modified-release preparations because of the problems with confirming comparable efficacy (e.g. time-dependent, site-specific release profile as well as bioequivalence) and requires approval of a generic MR product by brand name.⁷

Comparative studies

Asacol MR versus Mezavant XL

Mezavant XL is the most recently licensed modified-release mesalazine formulation, with a patented multi-matrix release system permitting less frequent dosing (once or twice-daily) with fewer tablets. Clinical trials have demonstrated the efficacy of this agent over placebo for the induction and maintenance of remission in UC.^{8–11}

Prantera C et al¹² recently undertook a multicentre, randomised, double-blind, double-dummy, parallel-group study that investigated the efficacy and safety

of Mezavant XL compared with Asacol MR for the maintenance of left-sided UC in adults. A total of 334 patients were randomised equally to receive either Mezavant XL (two 1.2g tablets in the morning and one placebo tablet in the evening) or Asacol MR (two 800mg tablets in the morning and one 800mg tablet in the evening) for a period of 12 months.

The primary objectives of this study were to compare the proportion of patients who, at the end of the study period, were in (a) clinical remission, and (b) clinical and endoscopic remission (modified intention-to-treat population). Secondary objectives included time to relapse and assessment of the safety and tolerability of both preparations.

At month 12, 68.0% and 65.9% of patients treated with Mezavant XL and Asacol MR, respectively, were in clinical remission ($p=0.69$). Furthermore, 60.9% and 61.7% of patients treated with Mezavant XL and Asacol MR, respectively, were in clinical and endoscopic remission ($p=0.89$). Both treatments were similarly tolerated with no notable differences in the incidence of treatment-emergent adverse events. The authors concluded that both agents had a similar efficacy and safety profile.

pH	Proportion of mesalazine released		
	Asacol MR	Mesren MR	Ipocol
1.0–1.2 for 2 hours	0%	0%	0%
6.4 for 1 hour	<1%	<1%	13–41%
7.2 for 1 hour	~98% (in 30–60 minutes)	~99% released (in 30–60 minutes)	59% (in 30–60 minutes)

Table 1: *In vitro* release characteristics of Asacol MR, Mesren MR and Ipocol¹⁴

Asacol MR versus Ipocol

Forbes et al¹³ conducted a multicentre, randomised controlled trial comparing Asacol MR with Ipocol in patients with UC, using a non-inferiority design (margin of 15%). A total of 88 patients with mild to moderate active UC were randomised to one of the two preparations at a daily dose of 2.4g for eight weeks. The primary efficacy endpoint was improvement of UC symptoms as scored against the modified St. Mark's colitis activity score. The use of oral or topical steroids was permitted if the patient's condition deteriorated sufficiently to warrant such treatment, but the patient was then withdrawn from the trial and classified as a treatment failure.

No significant difference in improvement between baseline and week eight was observed between the two groups

(improvement scores of -2.3 with Ipocol and -1.5 with Asacol MR). Furthermore, a similar proportion of patients entered clinical remission at the end of the study (26% in the Ipocol group and 29% in the Asacol MR group; non-significant).

A larger proportion of patients in the Asacol MR group required oral prednisolone than in the Ipocol group (12% versus 7%; non-significant), but fewer patients taking Asacol MR required topical steroids (11% versus 17%; non-significant). The authors concluded that while Ipocol was not pharmaceutically identical to Asacol MR, it still offered a safe and similarly effective alternative.

Asacol MR versus Mesren MR

Although Asacol MR has not been compared directly in a clinical study with

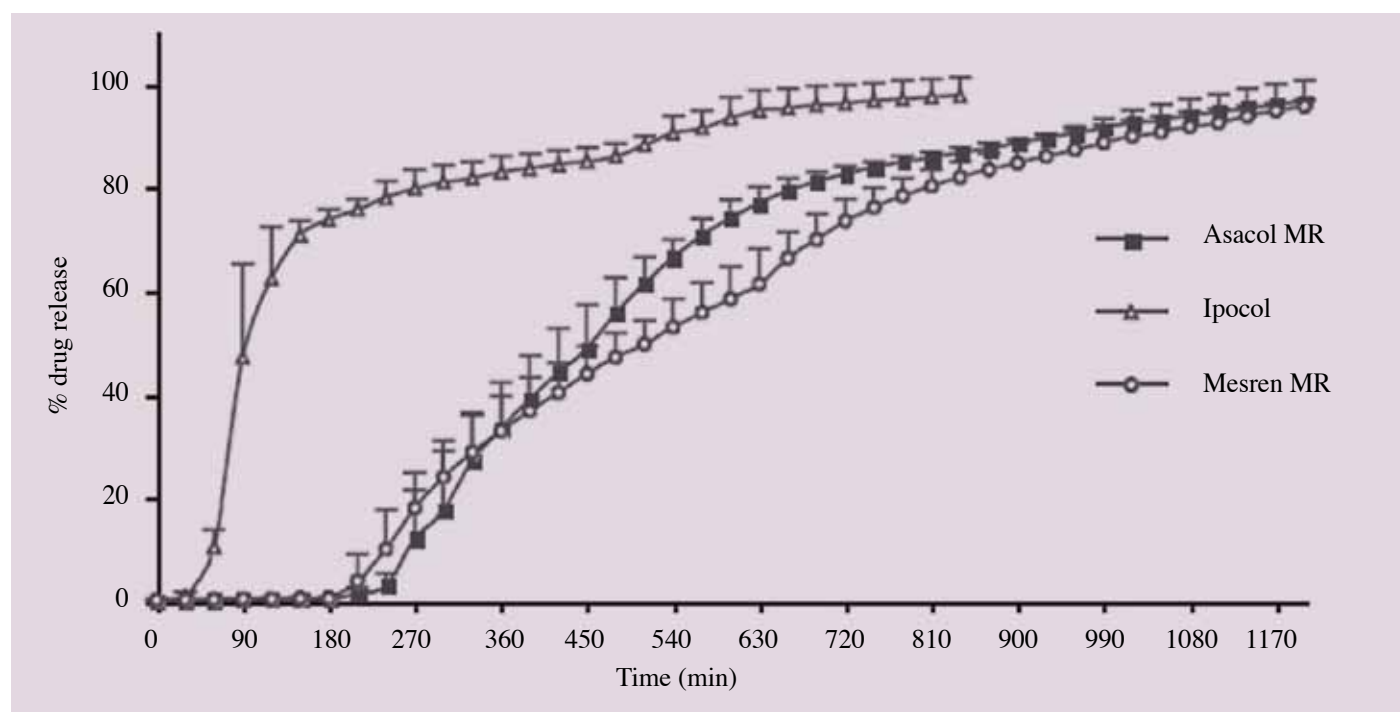


Figure 1: Comparative dissolution profiles of Asacol MR, Mesren MR and Ipocol in physiological Hank's buffer, expressed as mean \pm SD¹⁴

Mesren MR, Fada and Baswit¹⁴ conducted a quantitative analysis of the coating used for Asacol MR, Mesren MR and Ipocol, using scanning electron microscopy. They assessed their dissolution profile in a physiological bicarbonate buffer solution. All three preparations use Eudragit S, as the enteric coating layer, which does not disintegrate in acidic conditions. The coating thicknesses were: Asacol MR 82±11µm, Mesren MR 75±7.5µm, and Ipocol 50±8µm.

Asacol MR and Mesren MR were found to have similar dissolution profiles in physiological buffers such as Krebs and Hank's buffer solutions, unlike Ipocol (see Figure 1, p334). The pH of Hank's buffer solution was adjusted to 6.6. The variation in drug release within and between batches may be attributable to the intra-brand differences in coating thickness.

Table 1 (p334) shows the pH-dependent release profile of Asacol MR, Mesren MR, and Ipocol, showing a near identical *in vitro* dissolution profile of Mesren MR to Asacol MR.

A systematic review of the pharmacokinetic profile of Asacol MR, Pentasa and Salofalk in the management of UC concluded that the systemic exposure was comparable for all three formulations.¹⁵

Prescribing

In 2000, the National Prescribing Centre issued a MeReC bulletin stating that where use of a modified-release preparation of mesalazine is appropriate, it is important that the correct preparation, as intended by the prescriber, is dispensed, and that the drug should therefore be prescribed by brand.¹⁶ The British National Formulary states that the delivery characteristics of enteric coated mesalazine preparations may vary, and that these preparations should not be considered interchangeable.¹⁷

The British Society of Gastroenterology guidelines do not differentiate between different brands of mesalazine, but they comment that the efficacy of such agents may be more dependent on patient adherence than the delivery system.¹

Cost

The cost of Asacol MR, Mesren MR, Mezavant XL and Ipocol are shown in Figure 2.

Brand	Strength	Quantity	Cost (4.8g daily dose) BNF 58 (September 2009)	Maxium licensed daily dose
Asacol MR	400mg	120	£4.16	2.4g
Asacol MR	800mg	180	£4.16	4.8g
Ipocol (generic)	400mg	120	£4.16	2.4g
Mesren MR (generic)	400mg	120	£2.71	2.4g
Mezavant XL	1200mg	60	£4.16	4.8g

Figure 2: Cost comparisons of Asacol MR, Ipocol, Mesren MR and Mezavant XL

On the basis of 2008/09 prescribing figures for England, we estimate that a substitution of Mesren MR for Asacol MR in patients with stable UC, and for those newly started on 5-aminosalicylate therapy, has the potential to save £20m in primary care prescribing costs over the next five years.

Discussion

Mesren MR contains the same active ingredient and tablet coating as the current market leader Asacol MR. The thickness of the Eudragit-S coating between the two preparations does not appear to be significantly different; this is reflected in the near identical dissolution and pharmacokinetic profiles.

Although no head-to-head clinical data comparing Mesren with Asacol MR are available, it is reassuring that a non-inferiority study, using Ipocol, which has a known difference in dissolution and pharmacokinetics, failed to demonstrate any clinically significant difference compared with Asacol MR.¹⁴ Furthermore, a prospectively designed superiority study comparing Mezavant XL with Asacol MR failed to demonstrate superiority of Mezavant XL in maintaining remission of UC.

Although Mesren MR is a generic preparation, interestingly, it is manufactured by the original licence holders, and in the same plant, as Asacol MR that is distributed across Europe, excluding the UK (see Figure 3 for manufacturing chronology). We cannot find any significant disparity between Asacol MR and Mesren MR with regards to their clinical, pharmaceutical,

pharmacokinetic, and manufacturing profile.

Regarding clinical practice, it should be noted that the current guidelines for the management of UC (British Society of Gastroenterology) state that the efficacy of a given mesalazine preparation may depend more on adherence than the delivery system, and does not differentiate between the choices of brand when initiating prescribing of mesalazine.

Since mesalazine acts topically, the drug needs to be available at the site of inflammation to be effective. Although it is suggested that the standard regulatory assessment process for generic products, using systemic bioequivalence data, is insufficient for evaluating topically acting, oral, modified-release products, the data reviewed in this article suggests that there is little clinical difference between the available pH-dependent products (Asacol MR, Mesren MR, and Mezavant XL). However, Mesren MR costs almost half as much as Asacol MR and Mezavant XL.

Because compliance is an important factor in the maintenance of remission in UC, we suggest the following pragmatic approach in achieving a successful therapeutic rationalisation of these formulations:

- Mesren MR should be prescribed instead of Asacol MR for all new patients, and for patients who require a change to their drug regimen. Discretion should be applied in switching patients to Mesren MR who have mild and/or stable UC.

- Mezavant XL should only be considered for select patients experiencing difficulty with a high pill burden (i.e. >2.4g/daily), since it has a convenient once-daily dosing advantage. Since Mezavant XL is almost twice the cost of Mesren MR, at the point of maintenance dose prescribing (i.e. ≤2.4g/daily), Mesren MR should be substituted.

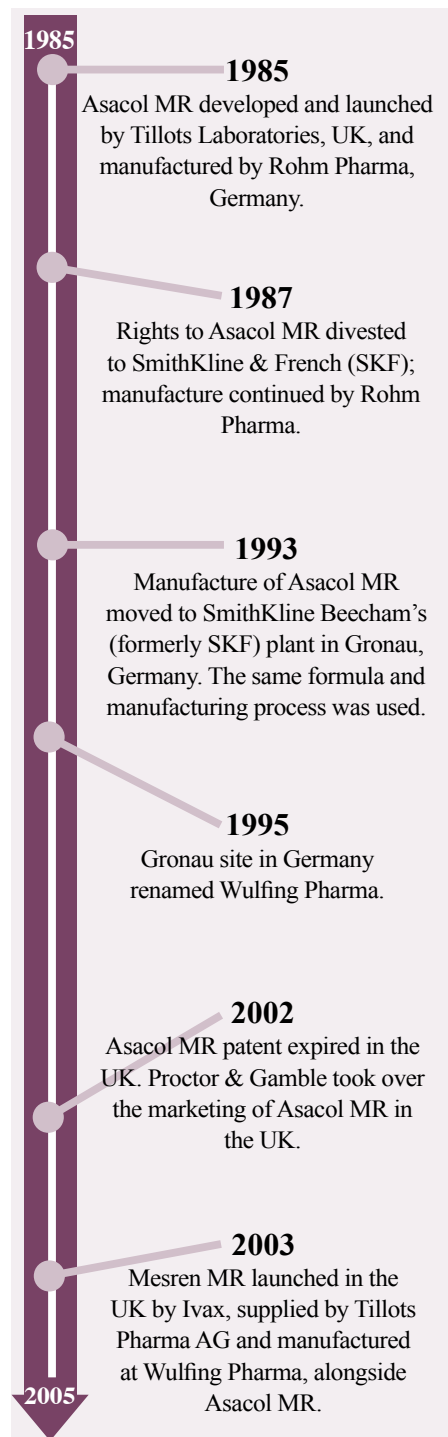


Figure 3: The chronology of Asacol MR and Mesren MR manufacturing¹⁸

Written by Anthony Grosso, principal pharmacist, Pritesh Bodalia, senior pharmacist, and Miren Shah, pharmacist, all at University College London Hospitals NHS Foundation Trust.

Conflicts of interest: none declared.



References

1. Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;53:v1-v16.
2. Travis S, Stange E, Lémann M, Øresland T, Bemelman W, Chowers Y et al. European evidence-based consensus on the management of ulcerative colitis: current management. *J Crohn's Colitis* 2008;2: 24-62.
3. Sutherland LR, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD000544. DOI: 10.1002/14651858.CD000544.pub2.
4. Loftus EV. A practical perspective on ulcerative colitis: patients needs from aminosalicylate therapies. *Inflamm Bowel Dis* 2006;12:1107-13.
5. Kane S, Huo D, Aikens J, Hanauer S. Medication non-adherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med* 2003;114:39-43.
6. The European Parliament and the Council of the European Union. Directive 2001/83/EC. The community code relating to medicinal products for human use. Article 10.
7. Committee for Medicinal Products for Human use. Guideline on the investigation of bioequivalence (draft). London: European Medicines agency;2008.
8. Kamm MA, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T, et al. Once-daily high concentration MMX mesalazine in active ulcerative colitis. *Gastroenterology* 2007;132:66-75
9. Lichtenstein GR, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T, et al. Effect of once or twice-daily MMX mesalazine (SPD476) for the induction of remission of mild to moderate active ulcerative colitis. *Clin Gastroenterol Hepatol* 2007;5:95-102.
10. Sandborn WJ, Kamm MA, Lichtenstein GR, Lyne A, Butler T and Joseph RE. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild to moderate ulcerative colitis: a combined analysis of two randomised, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther* 2007;26:205-15.
11. Kamm MA, Lichtenstein GR, Sandborn WJ, Schreiber S, Lees K, Barrett K and Joseph RE. Randomized trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008;57: 893-902.
12. Prantera C, Kohn A, Campieri M, Caprilli R, Cottone M, Pallone F, et al. Clinical trial: ulcerative colitis maintenance treatment with 5-ASA: a 1-year, randomised multicentre study comparing MMX with Asacol. *Aliment Pharmacol Ther* 2009;30:908-18.
13. Forbes A, Al-Damluji A, Ashworth S, Bramble M, Herbert K, Ho J, et al. Multicentre randomized-controlled clinical trial of Ipcol, a new enteric-coated form of mesalazine, in comparison with Asacol in the treatment of ulcerative colitis. *Alim Pharmacol Ther* 2005;21:1099-1104.
14. Fadda HM, Basit AW. Dissolution of pH responsive formulations in media resembling intestinal fluids: bicarbonate versus phosphate buffers. *J Drug Del Sci Tech* 2005;15:273-9.
15. Sandborn WJ, Hanauer SB. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003;17:29-42.
16. National Prescribing Centre. Modified-release preparations. *MeReC Bulletin* 2000;11:13-16.
17. British National Formulary. Chapter 1.5.1: Chronic bowel disorders; Inflammatory bowel disease; Aminosalicylates. *BMJ Group and RPS Publishing* 2009;58:54-5.
18. TEVA UK Limited. Asacol and Mesren (mesalazine MR 400mg) chronology fact sheet. March 2007. Data on file.

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