

Balsalazide

A Review of its Therapeutic Use in Mild-to-Moderate Ulcerative Colitis

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Data Selection

Sources: Medical literature published in any language since 1980 on balsalazide, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'balsalazide' or 'BX661A'. EMBASE search terms were 'balsalazide'. AdisBase search terms were 'balsalazide' or 'balsalazide disodium' or 'BX661A'. Searches were last updated 5 Jun 2002.

Selection: Studies in patients with ulcerative colitis who received balsalazide. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: balsalazide, ulcerative colitis, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

The aminosalicylate balsalazide is a prodrug which is metabolised by bacterial azo reductases in the colon to release its therapeutically active moiety mesalazine [mesalamine (US) or 5-aminosalicylic acid] and an inert carrier molecule. The systemic absorption of balsalazide and its metabolites is not required for the therapeutic efficacy of the drug, and has been demonstrated to be limited.

Data from well designed trials with a duration of 8 to 12 weeks show that oral balsalazide 6.75 g/day is as effective as (two trials) or more effective than (one trial) oral delayed-release (pH-dependent) mesalazine 2.4 g/day and appears to be as effective as oral sulfasalazine 3 g/day in the treatment of active mild-to-moderate ulcerative colitis. In addition, balsalazide appears to have a faster onset of action than mesalazine.

Furthermore, balsalazide was as effective as delayed-release mesalazine (dosages used were 1.2 and 1.5 g/day, where 1.6 g/day is recommended) and oral sulfasalazine 2 g/day (recommended dosage) in the prevention of relapse in ulcerative colitis in remission after 6 to 12 months of treatment; the balsalazide dosage was 3 g/day versus mesalazine and 2 g/day versus sulfasalazine. Although not well established, additional benefits may be achieved with balsalazide dosages up to 6 g/day.

Data from well designed, 2- to 12-month trials show that balsalazide is well tolerated by patients with ulcerative colitis in both acute and maintenance indications, and is better tolerated than standard formulations of sulfasalazine at therapeutically relevant dosages.

Conclusion: Balsalazide is a well tolerated and effective first-line therapeutic option for patients with ulcerative colitis, both for the treatment of active mild-to-moderate disease and as maintenance therapy to prevent disease relapse.

Pharmacodynamic Profile

Metabolism of the aminosalicylate balsalazide by bacterial azo-reductases in the colon yields the active moiety mesalazine [mesalamine (US) or 5-aminosalicylic acid] and the inert carrier molecule 4-aminobenzoyl- β -alanine (4-ABA).

The mechanism by which mesalazine (and thus balsalazide) exerts its therapeutic effects in ulcerative colitis is unclear. Potential anti-inflammatory effects of mesalazine include modification of the mucosal prostaglandin profile, mucosal electrolyte transport and possibly alteration of the microflora in the colon.

In addition, mesalazine has been reported to inhibit the release and synthesis of proinflammatory mediators *in vitro* (e.g. nitric oxide, leukotrienes, thromboxanes and platelet-activating factor). Furthermore, the compound inhibits the function of natural killer cells, mast cells, neutrophils, mucosal lymphocytes and macrophages, and is a scavenger/inhibitor of reactive oxygen species.

For patients with ulcerative colitis, mesalazine has been shown to inhibit the activation of nuclear factor κ B, which is an important transcription factor involved in the regulation of the expression of a number of (proinflammatory) cytokines and which regulates the expression of cellular adhesion molecules involved in inflammatory-cell migration.

Pharmacokinetic Profile

Systemic absorption of balsalazide is not likely to be relevant to its therapeutic efficacy because its active moiety exerts its effects locally in the colon. Systemic absorption of balsalazide is low.

Median maximum plasma concentration (C_{\max}) and area under the plasma concentration-time curve (0 to 12 hours) were $0.324 \mu\text{mol/L}$ and $1.34 \mu\text{mol} \cdot \text{h/L}$, respectively, for balsalazide after long-term administration of 3 to 6 g/day (data normalised to a statim dose of 3 g/day) to 54 adult patients with ulcerative colitis. In patients with ulcerative colitis receiving balsalazide 3 g/day for over 1 year, the systemic exposure to balsalazide was approximately 57 times greater than in healthy volunteers, but was still low.

The median time to C_{\max} of balsalazide is about 2 hours. In contrast, C_{\max} values of mesalazine ($2.62 \mu\text{mol/L}$) and 4-ABA ($<0.096 \mu\text{mol/L}$) were achieved 9 and 10 hours after a single dose of balsalazide 2.25g. The systemic uptake of balsalazide and its metabolites appears to be slightly increased in fasting patients.

Balsalazide is mainly eliminated via the faeces. In total, up to 25% of its metabolites (mesalazine, *N*-acetyl-mesalazine, 4-ABA and *N*-acetyl-4-ABA) are systemically absorbed and appear in the urine after inactivation by colonic mucosa and the liver. The clearance of *N*-acetylated mesalazine and 4-ABA is high (12 to 18 L/h and 24 to 30 L/h). The clearance of balsalazide itself is about 4.5 L/h. The half-life of *N*-acetyl-mesalazine is about 6 to 9 hours and the half-life of mesalazine is about 1 hour.

Balsalazide drug interaction studies are not available. Administration of orally administered antibacterials, however, putatively interferes with the release of mesalazine in the colon although no data are available to confirm this potential interaction.

Therapeutic Use

Data from randomised, double-blind trials show that balsalazide is an effective treatment for active mild-to-moderate ulcerative colitis and for the prevention of relapse in ulcerative colitis in remission.

Active Ulcerative Colitis

The efficacy of oral balsalazide in the treatment of active mild-to-moderate ulcerative colitis has been compared with that of oral delayed-release (pH-dependent) mesalazine and oral sulfasalazine during five randomised, double-blind, 8- to 12-week trials.

Balsalazide 6.75 g/day was as effective as (two trials) or more effective than (one trial) delayed-release mesalazine 2.4 g/day (recommended dosage) in the treatment of active disease as shown by data from well designed trials (percentage of patients achieving remission, primary outcomes). Importantly, the onset of action appeared to be faster for balsalazide 6.75 g/day than for mesalazine 2.4 g/day during some trials. During one trial, significantly more patients receiving balsalazide 6.75 g/day than those receiving delayed-release mesalazine 2.4 g/day were in complete remission at 4 and 8 weeks, and also at the end of this 12-week trial (primary outcome, $p < 0.05$). Furthermore, significant differences in secondary outcomes favouring balsalazide were recorded during this trial [these included sigmoidoscopic improvement, number of days without symptoms and use of relief medication, night-time rescue corticosteroid use, median time to complete relief and patient satisfaction ($p < 0.05$ for all items)].

Data from two small randomised, double-blind trials (8 and 12 weeks) primarily designed to assess tolerability suggest that balsalazide 6.75 g/day is as effec-

tive as sulfasalazine 3 g/day in the treatment of active ulcerative colitis (percentage of patients achieving remission).

Maintenance of Remission in Ulcerative Colitis

Data from randomised, double-blind trials with a duration of 6 and 12 months show that balsalazide is an effective maintenance treatment for patients with ulcerative colitis in remission. Active comparators in these trials included oral delayed-release mesalazine and oral sulfasalazine. In addition, balsalazide dose-comparison trials have been performed.

The efficacy of oral balsalazide 3 g/day in the maintenance of remission in ulcerative colitis was similar to that of oral delayed-release mesalazine 1.2 g/day (the recommended oral delayed-release mesalazine dosage is 1.6 g/day) during a 12-month trial. Nonetheless, significant differences (secondary outcomes) in favour of balsalazide were recorded after 3 months of treatment [i.e. blood in stool, blood on toilet paper, mucus with stool, disturbed sleep, symptom interference with sleep, asymptomatic nights ($p < 0.05$ for all items)].

Oral balsalazide 6 g/day proved to be more effective than both oral delayed-release mesalazine 1.5 g/day and oral balsalazide 3 g/day during another trial in patients with ulcerative colitis in remission (percentage of patients still in remission after 6 months of treatment, primary outcome).

After 6 months, there was no significant difference in the percentage of patients with ulcerative colitis still in remission between oral balsalazide 2 g/day and oral sulfasalazine 2 g/day (primary outcome).

Although oral balsalazide 6 g/day was significantly more effective than oral balsalazide 3 g/day in maintaining remission after 6 months in one trial ($p = 0.001$), no significant differences in the efficacy of maintaining remission were recorded during a 12-month trial specifically designed to compare the efficacy of oral balsalazide 3 and 6 g/day. Balsalazide 4 g/day, however, was significantly more effective than balsalazide 2 g/day in maintaining remission during another dose-comparison trial ($p < 0.01$).

Tolerability

In general, oral balsalazide is well tolerated at therapeutically relevant dosages, both by patients with active disease and by patients with ulcerative colitis in remission. The tolerability of balsalazide is likely to be similar to that of mesalazine, and does not appear to be dose-related. The most frequently reported ($\geq 3\%$) adverse events in patients with ulcerative colitis receiving balsalazide 6.75 g/day in placebo-controlled trials include headache (8%), abdominal pain (6%) diarrhoea (5%), nausea (5%), vomiting (4%), respiratory infection (4%) and arthralgia (4%).

During two clinical trials primarily designed to assess tolerability in patients with active disease, the number of withdrawals because of adverse events was significantly greater in the sulfasalazine (3 g/day) than in the balsalazide (6.75 g/day) groups (38 vs 4%, $p = 0.004$ and 31 vs 7% patients, $p = 0.041$). In addition, troublesome adverse events (not specified) occurred significantly more often in sulfasalazine 2 g/day than in balsalazide 2 g/day recipients (26 vs 5%, $p = 0.017$) during one, 6-month maintenance trial.

The tolerability of balsalazide 2.25 to 6.75 g/day was generally similar to or better than that of delayed-release mesalazine 1.2 to 2.4 g/day in patients with ulcerative colitis during well designed clinical trials (both indications). During one trial in patients with active disease, however, a significant difference favour-

Dosage and Administration

ing balsalazide 6.75 g/day over delayed-release mesalazine 2.4 g/day in the number of patients reporting adverse events was recorded (48 vs 71%, $p = 0.024$).

Balsalazide is indicated for the treatment of adult patients with mild-to-moderate active ulcerative colitis in both the US and the UK. In addition, the drug is approved as maintenance therapy for ulcerative colitis in remission in the UK.

For the treatment of active ulcerative colitis, an oral dosage of 2.25g (three 750mg capsules) three times daily is recommended, until remission is achieved or for 8 (US) or 12 (UK) weeks maximum.

As approved in the UK, balsalazide may be given orally at a dosage of 1.5g twice daily as maintenance treatment for ulcerative colitis in remission. In this context, UK prescribing information mentions possible additional benefits with balsalazide dosages up to 6 g/day.

In both the US and the UK, balsalazide is contraindicated for patients with hypersensitivity to any balsalazide component or metabolites including mesalazine or patients with a history of hypersensitivity to salicylates. Balsalazide is not recommended for use in children, as the tolerability of the drug in these patients has not been established. In the UK, the administration of balsalazide to breastfeeding or pregnant women, patients with severe hepatic impairment and patients with moderate to severe renal impairment is contraindicated. US prescribing information recommends caution when administering balsalazide to these patients. No dosage adjustments are required when balsalazide is administered to elderly patients.

1. Introduction

Ulcerative colitis is a chronic inflammatory disease with an annual incidence of approximately 7.3 per 100 000 persons in the US.^[1] The disease is characterised by a diffuse inflammation of the mucosa which is restricted to the colon.^[2,3] The inflammation involves the rectum and can extend proximally to part or all of the large intestine.^[2,3]

The most obvious clinical symptom of this disease is bloody diarrhoea, which is frequently accompanied by stool urgency, tenesmus and abdominal discomfort or pain.^[2] The clinical course of the disorder is typically characterised by exacerbations and remissions. Ulcerative colitis can be classified as mild, moderate or severe, based on clinical findings (table I).^[2]

The aetiology of ulcerative colitis is not exactly clear at present.^[3,4] The current views on the pathogenesis of this disease have been extensively reviewed by Farrell and Peppercorn.^[3] In short, available evidence suggests that environmental

factors, as opposed to genetic factors, are predominant triggers of ulcerative colitis.^[3,5-7] Environmental factors putatively disrupt regulatory mechanisms of mucosal immune systems resulting in an enhanced inflammatory response to colonic bacteria in genetically susceptible patients.^[3,4,8]

The environmental factors that have been implicated in the pathogenesis of ulcerative colitis include psychological stress,^[3] NSAID exposure,^[9] a high number of childhood infections^[3] and lack of breast feeding during infancy.^[3] In addition, the

Table I. Classification of ulcerative colitis according to the American College of Gastroenterology practice guidelines (Kornbluth and Sachar)^[2]

Severity	No. of stools/day	Bloody stools	Signs of systemic toxicity ^a
Mild	<4	Possible	No
Moderate	>4	Possible	Minimal
Severe	>6	Yes	Yes

^a Fever, tachycardia, anaemia or elevated erythrocyte sedimentation rate.

specific make-up of the colonic microflora (i.e. the species of bacteria present) appears to be of importance in this disease.^[3,4,7] Interestingly, it is well established that smoking is a protective factor in ulcerative colitis but is detrimental in Crohn's disease.^[3]

Aminosalicylates are the mainstay of treatment of mild-to-moderate active ulcerative colitis and for maintenance of remission.^[3,10-13] Sulfasalazine, the prototype of this drug class, releases mesalazine (also known as mesalamine in the US or 5-aminosalicylic acid) and sulfapyridine after azo-bond cleavage by colonic bacterial azo reductases.^[13,14] Mesalazine is now recognised as the clinically active moiety of sulfasalazine, and its carrier molecule sulfapyridine has been implicated in most of the adverse events occurring in patients receiving sulfasalazine.^[10-16] This knowledge has led to the development of mesalazine as a pure therapeutic entity (requiring delayed-release formulations to facilitate drug delivery to the colon) and of prodrugs such as balsalazide in which the sulfapyridine moiety of sulfasalazine has been replaced [in the case of balsalazide with the inert carrier molecule 4-aminobenzoyl- β -alanine (4-ABA, figure 1)].^[11,12,14,16,17] On a molecular basis, the commonly used dosage of balsalazide 6.75 g/day is equivalent to mesalazine 2.4 g/day.^[18]

A brief overview of the clinical and pharmacological properties of balsalazide in the treatment of

patients with ulcerative colitis has previously been published in *Drugs*.^[17] This article provides a comprehensive review of the clinical data available for balsalazide in the treatment of mild-to-moderate ulcerative colitis and summarises the key pharmacodynamic and pharmacokinetic properties of the drug.

2. Pharmacodynamic Profile

The pharmacodynamic profile of mesalazine, the therapeutically active moiety of the prodrug balsalazide, has been extensively reviewed in *Drugs*^[11,12] and elsewhere.^[14,19] This section therefore provides only a brief overview of the mechanism of action of mesalazine.

Like the aetiology of the aspecific inflammation characteristic of ulcerative colitis (section 1), the mechanism by which mesalazine (and thus balsalazide) exerts its therapeutic effects is not completely clear at present. Potentially beneficial (i.e. anti-inflammatory) effects of mesalazine include modification of the mucosal prostaglandin profile, mucosal electrolyte transport and possibly alteration of the microflora in the colon.^[12,17,19] In addition, mesalazine has been reported to inhibit the release and synthesis of proinflammatory mediators including nitric oxide, leukotrienes, thromboxanes and platelet-activating factor. Furthermore, the compound inhibits the function of

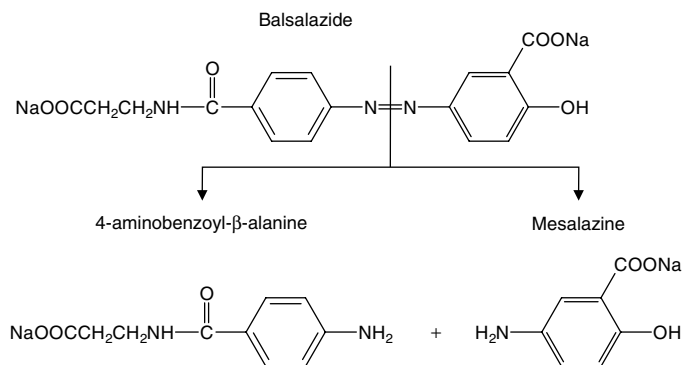


Fig. 1. Chemical structures of the prodrug balsalazide and its metabolites (after azo reduction by colonic bacteria), mesalazine (clinically active component) and 4-aminobenzoyl- β -alanine (inert carrier molecule).^[14,19]

Table II. Overview of the *in vitro* effects of mesalazine (the active metabolite of the prodrug balsalazide) on human colon biopsy specimens and peripheral blood cells^[11,12,21,22]

Effects on lipid mediator release

Inhibits the release or synthesis of LTB₄, LTC₄ and PAF from colon biopsy specimens from patients with ulcerative colitis
Inhibits the synthesis of 5-, 11-, 12- and 15-HETE from polymorphonuclear leucocytes
Inhibits the release of PGD₂ from human mast cells

Effects on cytokine release

Inhibits the release or synthesis of IL-1, IL-2 and IL-6 from human monocytes
Inhibits the release of IL-1 from colon biopsy specimens from patients with ulcerative colitis

Effects on reactive oxygen metabolites

Scavenger/inhibitor of superoxide and hypochlorous acid released from human polymorphonuclear leucocytes

Miscellaneous effects

Inhibits nuclear factor κB activation in mucosal biopsy specimens from patients with ulcerative colitis
Inhibits IFNγ-induced HLA-DR expression by intestinal epithelial cell lines
Inhibits IFNγ binding to a colonic carcinoma cell line
Inhibits human platelet activation

HETE = hydroxyeicosatetraenoic acid; **HLA** = human lymphocyte antigen; **IFN** = interferon; **IL** = interleukin; **LT** = leukotriene; **PAF** = platelet activating factor; **PG** = prostaglandin.

natural killer cells, mast cells, neutrophils, mucosal lymphocytes and macrophages.^[12,17,19] Lastly, mesalazine is a scavenger/inhibitor of reactive oxygen species.^[20] The *in vitro* effects of mesalazine observed in human cells and tissues are summarised in table II.

Interestingly, administration of mesalazine to patients with ulcerative colitis has recently been shown to inhibit the activation of nuclear factor κB (NF-κB) in mucosal biopsy specimens (table II).^[21] NF-κB is an important transcription factor involved in the regulation of the expression of a number of (proinflammatory) cytokines such as tumour necrosis factor, interleukin (IL)-1, IL-2, IL-6 and IL-8. In addition, NF-κB regulates the expression of cellular adhesion molecules including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin and mucosal addressin cell adhesion molecule-1 which, in turn, are involved in inflammatory-cell migration.^[21]

3. Pharmacokinetic Profile

The pharmacokinetic profile of balsalazide has been reviewed previously in *Drugs*.^[17] This section provides a brief overview of the key pharmacokinetic properties of the drug, drawn largely from the manufacturer's prescribing information^[18,23] in the absence of other data.

3.1 Absorption

Because balsalazide exerts its therapeutic effects via the local release of mesalazine in the colon,^[17,23] systemic absorption of the prodrug is not likely to be relevant to its therapeutic efficacy. Systemic absorption of balsalazide is less than 1%.^[23] Protein binding of mesalazine is about 40%.^[23]

The median pharmacokinetic values for balsalazide after long-term administration of 3 to 6 g/day (data normalised to a statim dose of 3 g/day) to 54 adult patients with ulcerative colitis were as follows: maximum plasma concentration (C_{max}) 0.324 μmol/L, trough plasma concentration (C_{min}) 0.035 μmol/L and area under the plasma concentration-time curve (0 to 12 hours) 1.34 μmol • h/L.^[17] Systemic exposure to balsalazide (measured by mean AUC values) is approximately 56 times higher in patients with ulcerative colitis than in healthy volunteers receiving balsalazide 3 g/day for over 1 year (450 vs 8 μg • h/L).^[18]

Median C_{max} of balsalazide was reached within 2 hours of administration.^[17] Following administration of a single oral dose of balsalazide 2.25g, C_{max} values of mesalazine (2.62 μmol/L) and 4-ABA (<0.096 μmol/L) were achieved after 9 and 10 hours.^[17]

Interestingly, plasma parent prodrug C_{max} values were markedly greater after a single oral dose of sulfasalazine (2.0g) compared with balsalazide (2.25g) during a crossover study in 24 healthy volunteers (45.7 vs 0.065 μmol/L).^[24]

3.2 Metabolism and Elimination

Most of an orally administered balsalazide dose is eliminated via the faeces.^[23] In total, about 25% of its metabolites (mesalazine, *N*-acetyl-mesalaz-

ine, 4-ABA and *N*-acetyl-4-ABA) are systemically absorbed after inactivation by the colonic mucosa and the liver.^[23] Systemic absorption of 4-ABA accounts for only 10 to 15% of the total absorption of balsalazide metabolites.^[23]

Median C_{\max} values for mesalazine and *N*-acetyl-mesalazine in plasma (3.95 and 4.80 $\mu\text{mol/L}$) were higher than for balsalazide in patients with ulcerative colitis who received balsalazide 3 to 6 g/day.^[17] Plasma concentrations of 4-ABA remained below the limit of detection at all times.^[17]

Only *N*-acetylated mesalazine and 4-ABA are recovered in the urine to any measurable extent, and their clearance is high (12 to 18 L/h and 24 to 30 L/h).^[23] The clearance of balsalazide itself is about 4.5 L/h.^[17] The elimination half-life of *N*-acetyl-mesalazine is about 6 to 9 hours, whereas that of mesalazine is only about 1 hour.^[23]

3.3 Special Patient Groups

The pharmacokinetics of balsalazide and its metabolites do not appear to be influenced by age^[17,23] or genetic polymorphism.^[23] C_{\max} values, however, were greater in female than in male patients^[17] and fasting appears to slightly increase the systemic uptake of balsalazide and its metabolites, although no dosage adjustments are required.^[23]

Patients with mild renal impairment [creatinine clearance of <4.8 L/h (80 ml/min)] receiving balsalazide (dosage not stated) had higher C_{\min} values (0.06 vs 0.02 $\mu\text{mol/L}$) than patients with normal renal function.^[17] In addition, balsalazide clearance was slightly lower in patients with mild renal dysfunction (4.03 vs 4.88 L/h).^[17] Renal impairment, however, did not markedly affect AUC values (1.17 vs 1.37 $\mu\text{mol/L}$, respectively).^[17]

3.4 Drug Interactions

Administration of orally administered antibacterials may interfere with the release of mesalazine in the colon, although this has not been confirmed by clinical data.^[18] In addition, balsalazide administration may increase plasma concentrations of drugs that are actively secreted by the kidneys (e.g. methotrexate).^[23]

Mesalazine and mesalazine-containing products have been reported to reversibly inhibit thiopurine methyltransferase, which is responsible for the conversion of 6-mercaptopurine to 6-methylmercaptopurine.^[25] This inhibition may lead to increased exposure to 6-mercaptopurine or azathioprine when mesalazine-containing agents are coadministered with these immunosuppressants. This, in turn, may lead to an increased risk of myelosuppression and leucopenia.^[25]

During a small 8-week trial in patients with Crohn's disease receiving azathioprine (2.0 to 2.1 mg/kg/day) or 6-mercaptopurine (1.1 to 1.2 mg/kg/day), the frequency of total leucocyte counts of $\leq 3.5 \times 10^9/\text{L}$ was 5 of 10 patients also receiving mesalazine 4 g/day, 6 of 11 patients additionally receiving sulfasalazine 4 g/day and 2 out of 10 patients in the balsalazide 6.75 g/day group.^[25]

4. Therapeutic Use

The efficacy of oral balsalazide has been investigated in several well designed trials in both patients with active ulcerative colitis^[26-30] and in those whose disease was in remission (maintenance therapy).^[31-35] Inclusion and exclusion criteria for these trials are summarised in table III, and the key findings are presented in table IV (active disease) and table V (maintenance therapy). Two of the trials in patients with active ulcerative colitis were primarily designed to assess tolerability.^[27,28]

The efficacy of oral balsalazide was compared with that of oral mesalazine and sulfasalazine in both indications. During all trials where mesalazine was the comparator drug, a delayed-release (pH-dependent) mesalazine formulation was administered.^[26,29,30,34,35] The delayed-release system consisted of mesalazine tablets coated with an acrylic-based resin (Eudragit®-S¹), which prevents the release of mesalazine from the tablet until pH is >7.0. Sulfasalazine, like balsalazide, is cleaved in the colon to release mesalazine (section 1). Both prodrugs were administered as capsules. Generally,

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

Table III. Inclusion and exclusion criteria for the trials reviewed in tables IV and V assessing the efficacy of balsalazide in adult patients with ulcerative colitis

Inclusion	Exclusion
Trials in active disease	
Active ulcerative colitis confirmed by sigmoidoscopy ^[26-30]	Crohn's disease ^[26,28,29]
Disease >12cm beyond anal margin ^[26,30]	Use of other mesalazine agents, ^[26-29] oral/rectal corticosteroids, ^[26,27] antibacterials ^[29] or immunosuppressive drugs ^[29]
	Stool pathogens, parasites or toxins ^[26-29]
	Sulfasalazine intolerance ^[27-29]
	Hepatic or renal disease ^[27-29] or malignancies ^[29]
	Pregnancy ^[27-29]
	Exclusion criteria not stated ^[30]
Trials in maintenance of remission	
Ulcerative colitis in remission ^[31-35]	Use of oral or topical corticosteroids, ^[31,32,34,35] azathioprine, ^[31,32] antibacterials ^[35] or immunosuppressants ^[34,35]
Disease >15cm beyond the anal margin ^[31,33] or at least involving the sigmoid colon ^[35]	Crohn's disease ^[32,34]
Remission lasting <1 year ^[34,35]	Hepatic or renal disease ^[31,32]
	Pregnancy ^[31,32]
	Exclusion criteria not stated ^[33]

dummy tablets/capsules were used during the trials to assure blinding.

4.1 Active Ulcerative Colitis

As summarised in table IV, the efficacy of oral balsalazide in the treatment of active ulcerative colitis has been compared with that of oral sulfasalazine^[27,28] and oral delayed-release (pH-dependent) mesalazine^[26,29,30] during randomised, double-blind, multicentre trials. In two trials,^[28,30] randomisation was stratified based on disease severity. Generally, both patients with disease relapse and newly diagnosed patients were included. Patients with severe active ulcerative colitis (requiring oral corticosteroids with or without topical corticosteroids) were only included in one trial.^[28] Efficacy

was assessed by the occurrence of symptoms and sigmoidoscopic appearance (table IV).

4.1.1 Versus Delayed-Release Mesalazine

Balsalazide 6.75 g/day is as effective as or more effective than delayed-release mesalazine 2.4 g/day (recommended dosage^[36]) in the treatment of active mild-to-moderate ulcerative colitis over 8 to 12 weeks (table IV).^[26,29,30] During one trial, complete remission was achieved in significantly more patients receiving balsalazide 6.75 g/day at 4, 8 and 12 weeks than in those receiving delayed-release mesalazine 2.4 g/day (99 of 101 randomised patients were included in the primary outcome analysis, $p < 0.05$) [table IV].^[26] No significant differences in primary outcomes were recorded during two 8-week trials comparing balsalazide 6.75 g/day with delayed-release mesalazine 2.4 g/day (43 vs 41% of patients achieving remission^[30] and 55 vs 45% of patients with improvement in rectal bleeding,^[29] table IV).

During the trial by Levine et al.^[29] significantly more patients in the balsalazide 6.75 g/day than in the delayed-release mesalazine 2.4 g/day group showed sigmoidoscopic improvement after 2 ($p = 0.006$) and 8 ($p = 0.03$) weeks of treatment (figure 2, secondary outcome, intent-to-treat analysis). In addition, during the trial by Green et al.,^[26] significantly more patients treated with balsalazide 6.75 g/day (32%) than those treated with delayed-release mesalazine 2.4 g/day (20%) were symptom free after 12 weeks of treatment (secondary outcome, $p < 0.003$). Further significant secondary outcome differences in favour of balsalazide 6.75 g/day compared with delayed-release mesalazine 2.4 g/day were recorded for the number of days without symptoms and use of relief medication (24 vs 14%, $p = 0.0084$), night-time rescue rectal corticosteroid use (0.06 vs 0.21 times/night, $p = 0.044$) and patient satisfaction ($p = 0.0038$) in the first 4 weeks of treatment.^[26]

Importantly, remission appears to be achieved sooner when patients are treated with balsalazide 6.75 g/day than with mesalazine 2.4 g/day. In one trial, the median time to complete relief was significantly shorter in the balsalazide group than in

Table IV. Summary of randomised, double-blind, multicentre trials assessing the efficacy of balsalazide (BAL) in the treatment of patients with active ulcerative colitis

Reference	Duration (wk)	Treatment and dosage (g/day)	No. of evaluable pts	Main efficacy parameter ^a	% of pts
Compared with delayed-release mesalazine (MES)					
Green et al. ^{b[26]}	12	BAL 6.75	50	Complete remission ^c	62*
		MES 2.4 ^d	49		37
Levine et al. ^{e[29]}	8	BAL 6.75	53	Improvement in rectal bleeding ^f	55 [†]
		BAL 2.25	50		35
Pruitt et al. ^[30]	8	MES 2.4 ^d	51	Symptomatic remission ^h	45
		BAL 6.75	84		43 ^g
		MES 2.4 ^d	89		41 ^g
Compared with sulfasalazine (SUL)					
Green et al. ^{e,i,j[28]}	12	BAL 6.75	28	Remission ^k	75
		SUL 3	29		59
Mansfield et al. ^{e,j[27]}	8	BAL 6.75	26	Clinical and sigmoidoscopic remission ^l	50
		SUL 3	24		38

a Primary clinical outcome except for trials by Green et al.^[28] and Mansfield et al.^[27]

b All-patients-treated analysis.

c No/mild symptoms, sigmoidoscopy grade 0/1, no rectal corticosteroid use within 4 days.

d Delayed-release formulation (resin-coated tablets).

e Intent-to-treat analysis.

f Improvement by at least one category in a disease activity scale comprising four categories (i.e. normal, mild, moderate or severe).

g Estimated from graph.

h Functional assessment of 'normal' or 'mild' and absence of rectal bleeding.

i 28% of patients included in this trial had severe ulcerative colitis (defined as requiring oral corticosteroids with or without topical corticosteroids).

j Primarily designed to assess tolerability.

k Return of stool frequency (with or without pain) to that present before relapse, without the presence of blood, and remission confirmed by biopsy.

l Stool frequency ≤ 2 /day without blood and a sigmoidoscopic appearance of normal rectal mucosa or minimal erythema.

pts = patients; * $p < 0.05$ vs MES (all-patients-treated analysis); [†] $p = 0.045$ vs BAL 2.25 g/day.

the mesalazine group (10 vs 25 days, $p = 0.003$).^[26] In addition, there was a trend towards a faster response with balsalazide in another trial (median time to remission of 25 days compared with 37 days for mesalazine; $p = 0.194$).^[30] Lastly, significant differences in sigmoidoscopic score improvement in favour of balsalazide were recorded as early as 2 weeks after initiation of treatment (figure 2, $p < 0.006$).^[29]

4.1.2 Versus Sulfasalazine

Despite a trend towards greater efficacy with balsalazide, there were no significant differences (intent-to-treat analysis) between the efficacy of balsalazide 6.75 g/day and that of sulfasalazine 3

g/day (recommended dosage is 3 to 4 g/day^[37]) in the treatment of active ulcerative colitis during an 8-week^[27] and a 12-week trial^[28] primarily designed to assess tolerability (table IV). Trials were generally small (<30 patients per treatment group). Of the 57 patients included in the trial by Green et al.,^[28] 42 concomitantly received oral and/or topical corticosteroids.

During the trial by Mansfield et al.,^[27] significant improvements from baseline in bowel frequency score were recorded after 2 ($p = 0.011$), 4 ($p = 0.011$) and 8 ($p < 0.001$) weeks of treatment in the balsalazide group. In the sulfasalazine group, the improvement in bowel frequency score was

Table V. Summary of randomised, double-blind trials assessing the efficacy of balsalazide (BAL) in the maintenance of remission in patients with ulcerative colitis^a

Reference	Duration (mo)	Treatment and dosage (g/day)	No. of pts	% of pts in remission at end of trial ^b
Compared with delayed-release mesalazine (MES)				
Green et al. ^[34]	12	BAL 3	49 ^c	58 ^d (79) ^e
		MES 1.2 ^f	46 ^c	58 ^d (65) ^e
Kruis et al. ^[35]	6	BAL 3	48	44 ^g
		BAL 6	40	78 ^{g**†}
		MES 1.5 ^f	44	57 ^g
Compared with sulfasalazine (SUL)				
McIntyre et al. ^[32]	6	BAL 2	41	51 ^h
		SUL 2	38	63 ^h
Balsalazide dosage comparison				
Giaffer et al. ^[31]	12	BAL 2	65	45 ^h
		BAL 4	68	64 ^{h*}
Green et al. ^[33]	12	BAL 3	54	77 ⁱ
		BAL 6	54	68 ⁱ

- a All but one^[32] were multicentre trials.
- b Primary outcomes and intent-to-treat analysis, unless stated otherwise.
- c Four patients in the delayed-release MES group were lost to follow-up immediately after randomisation; statistical analysis included only treated patients.
- d No recurrence of moderate or severe symptoms.
- e Three-month results.
- f Delayed-release formulation (1.6 g/day recommended).^[36]
- g Clinical as well as endoscopic remission.
- h No recurrence of previous symptoms.
- i No recurrence of clinical symptoms and sigmoidoscopic or histological abnormalities.

pts = patients; * p < 0.01 vs balsalazide 2 g/day; ** p = 0.045 vs delayed-release mesalazine 1.5 g/day; † p = 0.001 vs balsalazide 3 g/day.

only significantly different from baseline at week 4 and 8 (p = 0.03). No significant differences between treatments groups were observed.^[27]

4.1.3 Balsalazide Dosage Comparison

During the trial by Levine et al.,^[29] balsalazide 6.75 g/day proved to be significantly (p = 0.045) more effective than balsalazide 2.25 g/day (percentage of patients with improvement in rectal bleeding by at least one severity category, primary outcome) according to intent-to-treat analysis (table IV). In addition, secondary outcomes (intent-to-treat analysis) revealed significant differences in favour of high-dose balsalazide for the number of patients with sigmoidoscopic score improvement (74 vs 52%, p = 0.031) and stool frequency improvement (49 vs 25%, p = 0.013).^[29]

4.2 Maintenance of Remission in Ulcerative Colitis

Oral balsalazide is an effective maintenance treatment for the prevention of disease relapse in patients with ulcerative colitis in remission as demonstrated by five randomised, double-blind trials with a duration of 6^[32,35] and 12^[31,33,34] months (table V). All but one^[32] were multicentre trials. The comparators were oral delayed-release (pH-dependent) mesalazine (section 4.2.1) and oral sulfasalazine (section 4.2.2). In addition, balsalazide dose-comparison trials have been performed in these patients (section 4.2.3). The primary endpoint of these trials was the percentage of patients still in remission at the end of the study period. Remission was generally defined as no recurrence of clinical symptoms (see table V for details).

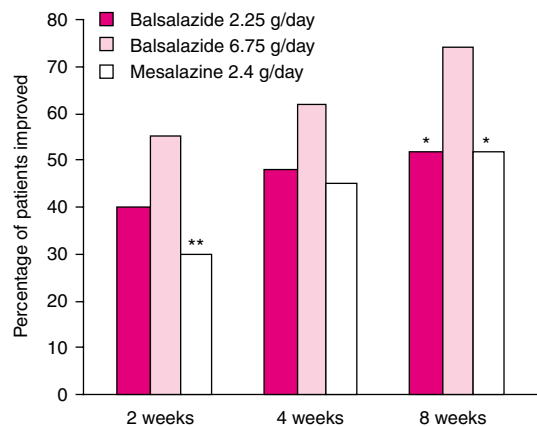


Fig. 2. Percentage of patients with mild-to-moderate active ulcerative colitis showing sigmoidoscopic score improvement after 2, 4 and 8 weeks of treatment with oral balsalazide 2.25 g/day ($n = 49$), balsalazide 6.75 g/day ($n = 49$) and delayed-release mesalazine 2.4 g/day ($n = 49$) during a randomised, double-blind trial (secondary outcomes, intent-to-treat analysis).^[29] * $p = 0.03$, ** $p = 0.006$ vs balsalazide 6.75 g/day.

4.2.1 Versus Delayed-Release Mesalazine

The efficacy of oral balsalazide 3 g/day in the maintenance of remission in ulcerative colitis was similar to that of oral delayed-release mesalazine 1.2 g/day (recommended oral delayed-release mesalazine dosage is 1.6 g/day^[36]) during a 12-month trial (table V).^[34] After 12 months of treatment, the percentage of patients still in remission (no recurrence of moderate or severe clinical symptoms) was 58% for both treatment arms (primary outcome, $n = 95$ treated patients, all-patients-treated analysis). After 3 months, these values were slightly higher (79% for patients receiving balsalazide 3 g/day and 65% for delayed-release mesalazine 1.2 g/day recipients), but the difference was not significant ($p = 0.10$).^[34] Nonetheless, significant differences (secondary outcomes) in favour of balsalazide were recorded on patients' diary card assessments after 3 months of treatment (i.e. blood on stool, blood on toilet paper, mucus with stool, disturbed sleep, symptom interference with sleep, asymptomatic nights; $p < 0.05$).^[34]

Oral balsalazide at the higher dosage of 6 g/day proved to be more effective in maintaining remis-

sion than both oral delayed-release mesalazine 1.5 g/day and oral balsalazide 3 g/day during a 6-month trial in patients with ulcerative colitis (intent-to-treat analysis, table V).^[35] After 6 months, 78% of patients receiving balsalazide 6 g/day maintained remission (clinical as well as endoscopic, primary outcome); these percentages were significantly lower for delayed-release mesalazine 1.5 g/day (57%; $p = 0.045$) and balsalazide 3 g/day (44%; $p = 0.001$), which had similar efficacy.^[35]

4.2.2 Versus Sulfasalazine

After 6 months, there was no significant difference in the percentage of patients with ulcerative colitis still in remission (no recurrence of previous symptoms) between oral balsalazide 2 g/day and oral sulfasalazine 2 g/day [recommended dosage] (primary outcome, intent-to-treat analysis, table V).^[32]

4.2.3 Balsalazide Dosage Comparison

Although oral balsalazide 6 g/day was significantly more effective than oral balsalazide 3 g/day in maintaining remission after 6 months in the trial by Kruis et al.^[35] (section 4.2.1), no significant differences were recorded during a 12-month trial specifically designed to compare the efficacy of oral balsalazide 3 and 6 g/day (table V).^[33] Balsalazide 4 g/day, however, was significantly more effective than balsalazide 2 g/day in maintaining remission (no recurrence of previous symptoms) during another dose-comparison trial (intent-to-treat analysis, table V).^[31]

5. Tolerability

In general, oral balsalazide is well tolerated at therapeutically relevant dosages by patients with ulcerative colitis. The tolerability of balsalazide is likely to be similar to that of mesalazine.^[23] According to US prescribing information, the most frequently reported ($\geq 3\%$) adverse events in patients with ulcerative colitis receiving balsalazide 6.75 g/day ($n = 259$) in placebo-controlled trials include headache (8%), abdominal pain (6%) diarrhoea (5%), nausea (5%), vomiting (4%), respiratory infection (4%) and arthralgia (4%).^[18]

During two clinical trials primarily designed to assess tolerability in patients with active disease, the number of withdrawals because of adverse events was significantly greater in the sulfasalazine (3 g/day) than in the balsalazide (6.75 g/day) groups (38 vs 4%, $p = 0.004$ ^[27] and 31 vs 7% patients, $p = 0.041$ ^[28]) [see section 4 for study design details].

In addition, headache (54 vs 19%, $p = 0.018$), nausea (33 vs 8%, $p = 0.035$) and vomiting (16 vs 0%, $p = 0.030$) occurred significantly more often in patients receiving sulfasalazine than in balsalazide 6.75 g/day recipients during one of these tolerability trials.^[27] The occurrence of other GI events, including dyspepsia and abdominal pain, was evenly balanced between treatment groups in this trial.^[27] Minor adverse events were common in both balsalazide 6.75 g/day (96%) and sulfasalazine 3 g/day (93%) recipients.^[28]

During these trials, sulfasalazine was administered in gelatin capsules. The tolerability of balsalazide, however, has not been compared with that of delayed-release sulfasalazine formulations. Delayed-release formulations putatively prevent irritation of the gastric mucosa by sulfasalazine.^[37]

Interestingly, 70% of 43 sulfasalazine-intolerant patients with ulcerative colitis or Crohn's disease did tolerate balsalazide (2 g/day) and olsalazine (1 g/day) during a randomised, crossover trial (30 days for each drug).^[38] This percentage was 63% for delayed-release mesalazine (1.2 g/day). Only four patients were intolerant to all three drugs. Patients included in this tolerability trial were intolerant to even small dosages (1 g/day) of both standard and enteric-coated sulfasalazine preparations.^[38]

The tolerability of balsalazide 6.75 and 2.25 g/day was generally similar to or better than that of delayed-release (pH-dependent) mesalazine 2.4 g/day in patients with active ulcerative colitis during three well designed clinical trials (see section 4 for study design details).^[26,29,30] During one trial there was a significant difference favouring balsalazide over delayed-release mesalazine in the number of patients reporting adverse events (48 vs

71%; $p = 0.024$).^[26] The incidence of adverse events in patients receiving balsalazide 2.25 g/day did not differ significantly from that in patients receiving the 6.75 g/day dosage, suggesting that the incidence of adverse events in balsalazide recipients is not dose related.^[29]

Long-term administration of balsalazide 2 to 6 g/day to patients with ulcerative colitis in remission was generally well tolerated during well designed, 6- to 12-month trials (see section 4 for study design details).^[31-35] Troublesome adverse events (not specified) occurred significantly more often in sulfasalazine 2 g/day than in balsalazide 2 g/day recipients (26 vs 5%, $p = 0.017$) during one 6-month trial.^[32] The tolerability profiles of balsalazide 3 g/day, 6 g/day and mesalazine 1.5 g/day were similar during a well designed, 6-month trial.^[35] After 12 months there were no significant differences in the incidence of adverse events in another maintenance trial comparing balsalazide 3 g/day with mesalazine 1.2 g/day.^[34] Adverse events occurred in 61 and 65% of patients respectively.^[34] Headaches, GI symptoms, respiratory infections, laboratory-test abnormalities related to ulcerative colitis, pain and flu-like disorders were the most commonly reported adverse events during this trial.^[34]

Adverse events occurring during balsalazide long-term maintenance trials do not appear to be dose related. During a 12-month trial comparing balsalazide 2 g/day to 4 g/day, 8% of patients withdrew due to adverse events (six in the 4 g/day group and four in the 2 g/day group).^[31] Furthermore, there were no significant differences in the occurrence of adverse events in balsalazide recipients when the 3 g/day dosage was compared to the 6 g/day dosage.^[35]

Generally, there were no changes in haematological, biochemical or urine chemistry tests in balsalazide recipients during both maintenance and active-disease trials.^[27,28,31,34] During one trial, however, ALT decreased by an average of 2.29 IU/L in balsalazide 3 g/day recipients compared with an increase of 1.83 IU/L in mesalazine 1.5 g/day recipients, although this difference was

considered unlikely to be of clinical significance.^[34] Urinalysis data suggest that no renal impairment occurred in patients with ulcerative colitis in remission receiving balsalazide 3 g/day over 12 months.^[34]

6. Dosage and Administration

Balsalazide is indicated for the treatment of adult patients with mild-to-moderate active ulcerative colitis in both the US^[18] and the UK.^[23] In addition, the drug is approved as maintenance therapy for ulcerative colitis in remission in the UK.^[23]

For the treatment of active ulcerative colitis, an oral dosage of 2.25g (three 750mg capsules) three times daily (i.e. 6.75 g/day) is recommended, until remission is achieved or for 8 (US)^[18] or 12 (UK)^[23] weeks maximum.

As approved in the UK, balsalazide may be given orally at a dosage of 1.5g twice daily as maintenance treatment for ulcerative colitis in remission.^[23] In this context, UK prescribing information mentions possible additional benefits with balsalazide dosages up to 6 g/day.^[23]

No dosage adjustments are required for elderly patients in both therapeutic modalities.^[18,23]

In both the US and the UK, balsalazide is contraindicated for patients with hypersensitivity to any balsalazide component or metabolites including mesalazine or patients with a history of hypersensitivity to salicylates.^[18,23] Balsalazide is not recommended for use in children, as the tolerability of the drug in these patients has not been established.^[18,23] In the UK, the administration of balsalazide to breast-feeding or pregnant women, patients with severe hepatic impairment and patients with moderate-to-severe renal impairment is contraindicated.^[23] US prescribing information recommends caution when administering balsalazide to these patients.^[18] In both the US and the UK, caution is recommended when balsalazide is administered to patients with mild renal impairment.^[18,23]

Mesalazine-containing compounds in general have been associated with chronic tubulo-interstitial nephritis.^[39,40] Although there have been no re-

ports of renal impairment in patients receiving balsalazide, caution should be exercised when balsalazide is administered to patients with known renal dysfunction or a history of renal disease.^[18]

7. Place of Balsalazide in the Management of Mild-to-Moderate Ulcerative Colitis

In accordance with the unknown aetiology of ulcerative colitis, the aim of therapy is to reduce symptoms and to prevent/postpone relapse in patients whose disease is in remission.^[2] At present, aminosalicylates are the mainstay of treatment of mild-to-moderate ulcerative colitis, both in active disease and in relapse prevention.^[2,7,41-47] The prototype of this drug class is the prodrug sulfasalazine, which releases its active moiety mesalazine and its carrier molecule sulfapyridine after cleavage by bacterial azo-reductases in the colon (section 1). The identification of mesalazine as the clinically active metabolite and sulfapyridine as the main cause of the poor tolerability of sulfasalazine has led to the development of alternatives for the delivery of mesalazine to the colon. Examples are delayed-release mesalazine formulations (in order to prevent absorption of the drug in the GI tract before reaching its therapeutic target) and the prodrug balsalazide, in which the sulfapyridine group has been replaced by the inert carrier molecule 4-ABA (section 1).

American College of Gastroenterology practice guidelines state that extensive active mild-to-moderate ulcerative colitis should initially be treated with oral salicylates. In the case of distal disease, rectal mesalazine or corticosteroids can also be considered, based on patient preference.^[2] In general, oral corticosteroids are administered only to patients who failed to respond to oral aminosalicylates, with or without rectal (corticosteroid) therapy.^[2]

As reviewed in section 4.1, data from well designed, 8- to 12-week trials show that oral balsalazide is an effective treatment for mild-to-moderate active ulcerative colitis. Oral balsalazide 6.75 g/day was as effective as (two trials) or more effec-

tive than (one trial) oral delayed-release (pH-dependent) mesalazine 2.4 g/day (clinically relevant dosage) [see section 4.1]. In addition, data from well designed trials suggests that the onset of action for balsalazide 6.75 g/day is faster than for mesalazine 2.4 g/day recipients. Lastly, secondary endpoints from two trials primarily designed to assess tolerability suggest that balsalazide 6.75 g/day is as effective as sulfasalazine 3 g/day (section 4.1).

The chronic and relapsing nature of ulcerative colitis requires maintenance therapy to prolong the period of remission and delay the onset of acute exacerbations. The previously mentioned guidelines recommend oral salicylates as maintenance therapy for ulcerative colitis in remission.^[2] In the case of distal disease, rectal aminosalicylates can also be administered. Rectal corticosteroids, however, are not recommended as maintenance therapy by these guidelines.^[2]

Unlike in the UK, balsalazide is not approved by the US Food and Drug Administration as maintenance therapy in ulcerative colitis in remission (section 6). Nonetheless, well designed 6- to 12-month trials consistently show that balsalazide is an effective therapy for the prevention of relapses in this chronic disease (section 4.2). The drug at a dosage of 3 g/day proved to be as effective as oral delayed-release (pH-dependent) mesalazine 1.2 or 1.5 g/day and the 2 g/day dosage was as effective as oral sulfasalazine 2 g/day during 6- to 12-month trials (US prescribing information for delayed-release mesalazine recommends a dosage of 1.6 g/day for maintenance treatment^[36] and a dosage of 2 g/day is recommended for sulfasalazine^[37]). Interestingly, balsalazide 6 g/day was significantly more effective than delayed-release mesalazine 1.5 g/day and balsalazide 3 g/day in maintaining remission during one well designed trial. Another trial directly comparing balsalazide 3 and 6 g/day, however, showed no significant difference (section 4.2). Consistent with these findings, UK prescribing information recommends balsalazide to be administered at a dosage of 3 g/day as maintenance

therapy, and mentions possible additional beneficial effects of the 6 g/day dosage (section 6).

As the sulfapyridine moiety of sulfasalazine has been implicated in most of the adverse events associated with this drug, both balsalazide and (delayed-release) mesalazine are theoretically better tolerated (section 1). Indeed, balsalazide up to dosages of 6.75 g/day is well tolerated by patients with ulcerative colitis and is better tolerated than oral sulfasalazine at therapeutically relevant dosages, both as maintenance therapy and as a treatment for patients with active ulcerative colitis (see section 5). Seventy percent of patients with known intolerance to sulfasalazine tolerated balsalazide during a small, well designed tolerability trial (see section 5).

Although balsalazide has been shown to be an effective treatment in mild-to-moderate ulcerative colitis, the use of aminosalicylates in general as therapy for severe (oral corticosteroid-requiring) disease remains a matter of uncertainty.^[2,48] Patients with severe ulcerative colitis requiring oral corticosteroids were included in one balsalazide trial only, and this trial was primarily designed to assess tolerability. Further trials are therefore required to elucidate the appropriateness of (high-dose) balsalazide treatment in severe active ulcerative colitis, both as monotherapy and in combination with, for example, oral or topical corticosteroids. In addition, trials primarily designed to assess therapeutic efficacy are required to confirm the observation that balsalazide is as effective as sulfasalazine in the treatment of active ulcerative colitis. Further clinical trials are also required to investigate whether higher dosages of balsalazide (6 g/day) indeed have an additive value over balsalazide 3 g/day in the maintenance treatment of ulcerative colitis in remission. Moreover, the efficacy of oral balsalazide has not been compared with that of topical mesalazine in patients with distal ulcerative colitis. Lastly, trials comparing the efficacy of balsalazide with that of placebo as maintenance therapy or as treatment for active disease are lacking.

In conclusion, data from well designed trials show that oral balsalazide is an effective treatment for mild-to-moderate ulcerative colitis, both in active disease and in maintenance of remission. Balsalazide is as effective as or more effective than oral delayed-release mesalazine and appears to be as effective as oral sulfasalazine in the treatment of active mild-to-moderate ulcerative colitis. Importantly, balsalazide 6.75 g/day appears to have a faster onset of action than mesalazine 2.4 g/day. Furthermore, balsalazide 3 g/day has been shown to be as effective as delayed-release mesalazine (dosages used were 1.2 and 1.5 g/day, where 1.6 g/day is recommended) and balsalazide 2 g/day was as effective as oral sulfasalazine 2 g/day (recommended dosage) in the prevention of relapse in ulcerative colitis in remission. Although not well established, additional benefits may be achieved with balsalazide dosages up to 6 g/day in patients whose disease is in remission. Lastly, balsalazide is better tolerated than standard preparations of sulfasalazine at therapeutically relevant dosages in both indications. Balsalazide is therefore a first-line treatment option, both for patients with active disease and for patients with ulcerative colitis in remission.

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