

Ulcerative colitis: budesonide multimatrix (Cortiment)

Evidence summary

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[nice.org.uk/guidance/esnm58](https://www.nice.org.uk/guidance/esnm58)

Key points from the evidence

The content of this evidence summary was up-to-date in June 2015. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Budesonide multimatrix (MMX, Cortiment) is a corticosteroid that is taken orally but exerts its action topically in the colon.

In two 8-week studies, budesonide MMX statistically significantly increased rates of combined clinical and endoscopic remission in adults with mild to moderate ulcerative colitis compared with placebo. However the effect size was small and the clinical relevance of the improvements is unclear. There was no statistically significant difference between budesonide MMX and placebo for clinical improvement and endoscopic improvement at week 8 (secondary end points). It is not known how budesonide MMX compares to other treatments for ulcerative colitis. Adverse event rates were not substantially different for budesonide MMX and placebo.

Regulatory status: In October 2014, a marketing authorisation was granted for budesonide MMX for inducing remission in mild to moderate active ulcerative colitis in adults for whom aminosalicilate treatment is not sufficient.

<p>Effectiveness</p> <ul style="list-style-type: none"> • In 2 RCTs (n=510 and n=512), a statistically significantly higher clinical and endoscopic remission rate at week 8 was observed for budesonide MMX compared with placebo (p=0.0143 and p=0.0047). • There was no statistically significant difference between budesonide MMX and placebo for clinical improvement (secondary end point). • These studies only included people not currently taking any concomitant medication for their condition. • No evidence versus active comparators is published at this time. 	<p>Safety</p> <ul style="list-style-type: none"> • The summary of product characteristics states that the most common adverse effects of budesonide MMX are nausea, upper abdominal pain, headache, insomnia, altered mood, decreased blood cortisol, influenza and viral upper respiratory tract infection. • The proportions of adverse events, serious adverse events and glucocorticoid adverse events seen with budesonide MMX were not substantially different from placebo in the 2 RCTs.
<p>Patient factors</p> <ul style="list-style-type: none"> • Alternative treatments are available for use orally and rectally, in a number of different formulations. • Budesonide MMX is not licensed for maintenance of remission in ulcerative colitis. • Other budesonide preparations (Entocort and Budenofalk) are not licensed for ulcerative colitis. • It is not known how budesonide MMX compares with other treatments for ulcerative colitis, alone or in combination. 	<p>Resource implications</p> <ul style="list-style-type: none"> • Budesonide MMX costs £75.00 for 30 tablets, with an 8-week course costing £140. • The cost of an 8-week course of other commonly prescribed options ranges from around £10 to £150 for oral treatment or £30 to £500 for topical treatments (see cost table for details).

Introduction and current guidance

Ulcerative colitis is the most common type of inflammatory bowel disease, and usually affects the rectum and a variable extent of the colon proximal to the rectum.

The NICE guideline on [ulcerative colitis](#) recommends a stepped approach for inducing remission in people with mild to moderate ulcerative colitis, with choice of treatment guided by the site of inflammation. Topical or oral aminosalicylates are generally used first-line: oral beclometasone dipropionate is an option for some people. Topical corticosteroids and oral prednisolone are options for people who cannot take or decline aminosalicylates. Combinations of treatments or immunosuppressants may be used if response to earlier treatment steps is inadequate.

[Full text of introduction and current guidance.](#)

Product overview

[Cortiment](#) is formulated to release budesonide, an oral corticosteroid, at a controlled rate throughout the colon to minimise systemic absorption. The licensed dose is 9 mg in the morning, for up to 8 weeks.

Budesonide MMX was granted a marketing authorisation in October 2014 and is licensed for inducing remission in mild to moderate active ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient.

[Full text of product overview.](#)

Evidence review

- This evidence summary is based on two 8-week, randomised, placebo and active-controlled phase III trials of similar design (CORE I [n= 510] and CORE II [n= 512]) that compared budesonide MMX (9 mg and 6 mg) with placebo in adults with mild to moderate ulcerative colitis ([Sandborn et al. 2012](#) and [Travis et al. 2014](#)). Only the results for the 9 mg strength of budesonide are discussed in this evidence summary because the 6 mg dose is unlicensed.
- Mesalazine ([Asacol](#)) and a different formulation of budesonide, which releases the drug in the ileum and ascending colon ([Entocort](#): licensed for Crohn's disease but not ulcerative colitis), were included as active controls in CORE I and CORE II respectively. However, neither trial was designed or powered to compare the efficacy of budesonide MMX with the active treatments.

- For the primary end point of combined clinical and endoscopic remission at week 8, budesonide MMX was statistically significantly more effective than placebo in both randomised controlled trials (RCTs). In CORE I, 17.9% of people taking budesonide MMX were in clinical and endoscopic remission at week 8, compared with 7.4% of people taking placebo (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.19 to 6.16, $p=0.0143$). Similar results were seen in CORE II, with 17.4% of people taking budesonide MMX in clinical and endoscopic remission at week 8, compared with 4.5% of people taking placebo (OR 4.49, 95% CI 1.47 to 13.72, $p=0.0047$). The [public assessment report](#) for budesonide MMX notes that the [clinical importance](#) of the 10–13% improvement over placebo is questionable, although, it also notes that rather strict remission criteria were used in the studies.
- There was no statistically significant difference in clinical improvement (secondary end point) between budesonide MMX and placebo in either trial. Because a [hierarchical testing model](#) was used and the difference between the groups in clinical improvement was not statistically significant, statistical comparisons between budesonide MMX and placebo for endoscopic improvement and other outcomes are considered exploratory only.
- Pooled data from CORE I and CORE II showed 56.5% of people treated with budesonide MMX reported an adverse event, compared with 53.5% in the placebo group. The most common adverse events reported for budesonide MMX across CORE I and CORE II were relapse or worsening of ulcerative colitis (13.3% compared with 14.0% for placebo); headache (11.4% compared with 10.5% for placebo); nausea (5.1% compared with 4.3% for placebo); and abdominal pain (3.5% compared with 5.8% for placebo). The most common potential glucocorticoid-related effects for budesonide MMX were mood changes (2.7% compared with 3.9% for placebo), sleep changes (2.7% compared with 4.3% for placebo), insomnia (2.4% compared with 3.1% for placebo) and acne (1.6% compared with 1.9% for placebo) ([Sandborn et al. 2015](#)).
- A high number of people were recruited to the studies and subsequently excluded from efficacy analyses, particularly in CORE II, primarily because of normal histology results. This may have affected the [statistical power](#) of the studies to detect differences between the groups.
- The studies were undertaken in people who were not currently taking any concomitant medication for their condition. Therefore, it is not known how well budesonide MMX works in combination with an aminosalicylate (topical or oral). It is also unclear how well budesonide MMX works in people who do not respond to aminosalicylates. A further study comparing budesonide MMX with placebo as add-on therapy to oral aminosalicylates in people with ulcerative colitis has been undertaken but has not been fully published (the [Contribute trial](#)). Budesonide MMX has not been compared with topical corticosteroids or oral prednisolone,

which are recommended second-line options in the NICE guideline on [ulcerative colitis](#). The studies did not report on speed of onset of budesonide MMX or the active controls.

[Full text of evidence review.](#)

Context

The 28-day cost (excluding VAT) of Budesonide MMX 9 mg tablets is £70. The 28-day cost (excluding VAT) of other commonly prescribed treatments for ulcerative colitis ranges from:

- £5.16 to £52.79 for oral corticosteroids
- £24.66 to £79.33 for oral aminosalicylates
- £14.00 to £272.00 for topical corticosteroids and
- £40.01 to £53.44 for topical aminosalicylates.

[Full text of context.](#)

Estimated impact for the NHS

Localities will need to take safety, efficacy, cost and patient factors into account when considering the place in therapy of budesonide MMX.

Budesonide MMX is licensed for inducing remission in mild to moderate active ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient. The [public assessment report](#) concluded that treatment with budesonide MMX can be beneficial for some people and, given the limitations of the currently available treatments, presents clinicians with an additional therapeutic option. The report suggests that the role for budesonide MMX may be to induce remission of ulcerative colitis before systemic corticosteroids are tried, which are associated with more severe adverse effects. Whether budesonide MMX should be used as first- or second-line therapy, after use of an aminosalicylate or in combination with an aminosalicylate (topical or oral) cannot be determined based on the available published evidence.

[Full text of estimated impact for the NHS.](#)

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Ulcerative colitis is the most common type of inflammatory bowel disease. There are around 146,000 people in the UK with a diagnosis of ulcerative colitis. It is a lifelong disease that usually has a relapsing-remitting pattern. The cause of ulcerative colitis is unknown.

Ulcerative colitis usually affects the rectum and a variable extent of the colon proximal to the rectum. The inflammation is continuous in extent. Inflammation of the rectum is referred to as proctitis and inflammation of the rectum and sigmoid colon as proctosigmoiditis. Left-sided colitis refers to disease involving the colon distal to the splenic flexure (a sharp bend between the transverse and the descending colon). Extensive colitis affects the colon proximal to the splenic flexure, and includes pancolitis, where the whole colon is involved.

The NICE guideline on [ulcerative colitis](#) recommends a stepped approach for inducing remission in people with mild to moderate ulcerative colitis, with choice of treatment guided by site of inflammation. The recommendations for treating adults are as follows:

Step 1 to induce remission in mild to moderate ulcerative colitis

Proctitis and proctosigmoiditis

- Offer a topical aminosalicylate alone (suppository or enema, taking into account the person's preferences) or
- Consider adding an oral aminosalicylate to a topical aminosalicylate or
- Consider an oral aminosalicylate alone, taking into account the person's preferences and explaining that this is not as effective as a topical aminosalicylate alone or combined treatment.

In people who cannot take or decline aminosalicylates, offer a topical corticosteroid or oral prednisolone, taking into account the person's preferences. Oral prednisolone may also be considered for people with subacute proctitis or proctosigmoiditis.

Left-sided and extensive ulcerative colitis

- Offer an oral aminosalicylate (at a high induction dose in adults).
- Consider adding a topical aminosalicylate or oral beclometasone dipropionate, taking into account the person's preferences.

To induce remission in people who cannot take or decline aminosalicylates, or who have subacute ulcerative colitis, offer oral prednisolone.

Step 2 to induce remission in mild to moderate ulcerative colitis

All extents of disease

- Consider adding oral prednisolone to aminosalicylate therapy if there is no improvement within 4 weeks of starting step 1 aminosalicylate therapy or if symptoms worsen despite treatment. Stop beclometasone dipropionate if adding oral prednisolone.
- Consider adding oral tacrolimus to oral prednisolone if there is an inadequate response to oral prednisolone after 2–4 weeks.

Management of severe ulcerative colitis is also covered by the NICE guideline on [ulcerative colitis](#) but is outside the scope of this evidence summary. See the [NICE pathway](#) and [NICE clinical knowledge summary on ulcerative colitis](#) for more information on the condition.

Product overview

Drug action

According to the [summary of product characteristics](#) budesonide multimatrix (MMX, Cortiment) is an oral corticosteroid that acts topically in the colon. The tablets have a gastro-resistant coating that dissolves in lower intestinal fluids with a pH of more than 7 and, subsequently, the MMX system releases budesonide at a controlled rate throughout the colon and minimises systemic absorption.

Licensed therapeutic indication

Budesonide MMX was granted a marketing authorisation in October 2014. It was launched in the UK in April 2015.

[Cortiment](#) is licensed for inducing remission in mild to moderate active ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient.

Course and cost

According to the [summary of product characteristics](#), the licensed dose is 9 mg in the morning, for up to 8 weeks. When treatment is discontinued, it may be useful to gradually reduce the dose (at the discretion of the treating physician).

Budesonide MMX costs £75.00 for 30 tablets, with an 8-week course costing £140 ([MIMS](#), May 2015).

Evidence review

This evidence summary is based on 2 randomised, placebo and active-controlled, phase III trials of budesonide MMX tablets ([Sandborn et al. 2012](#) and [Travis et al. 2014](#)), supplemented with pooled data from the 2 trials ([Sandborn et al. 2015](#)) and information from the [public assessment report](#) for budesonide MMX. A further study comparing budesonide MMX with placebo as add-on therapy to oral aminosalicylates in people with ulcerative colitis has been undertaken but has not been fully published and is not discussed in this evidence summary (the [Contribute trial](#)).

[CORE I](#) ([Sandborn et al. 2012](#)) and [CORE II](#) ([Travis et al. 2014](#))

- Design: both phase III trials were 8-week, multicentre, randomised, double-blind, double-dummy, parallel-group, placebo and active-controlled trials.
- Population: CORE I was conducted in the USA and India, and CORE II was predominately conducted in Europe (including centres in the UK). In CORE I, 510 participants were randomised and in CORE II, 512 participants were randomised. Both trials recruited adults aged 18 to 75 years (median age 42 years in CORE I and mean age 38 years in CORE II) with diagnosis of ulcerative colitis for at least 6 months, which was confirmed from a biopsy taken at baseline colonoscopy. Participants had an Ulcerative Colitis Disease Activity Index (UCDAI) score of 4 to 10 points (average 7 points in both studies). The UCDAI is a composite score of 4 clinical and endoscopic parameters (stool frequency, rectal bleeding, mucosal appearance and

physician's rating of disease activity), with a score of 4 to 5 indicating mild disease, 6 to 10 indicating moderate disease and more than 10 indicating severe disease. Across the 2 studies, approximately two-thirds of participants had moderate ulcerative colitis and 20% to 40% had extensive disease (pancolitis) (see [public assessment report](#)). Concurrent treatments for ulcerative colitis were not permitted: people receiving oral aminosalicylates at screening were required to stop their medication at least 2 days before randomisation. People who had received the following treatments were excluded from the trial: oral or rectal corticosteroids within 4 weeks of screening; immunosuppressive agents within 8 weeks of screening; and tumour necrosis factor alpha (TNF α) inhibitors within 3 months of screening. The [public assessment report](#) states that the trial population seemed to be in accordance with the population that might be treated with steroids. In general, baseline characteristics were similar between treatment groups in each study and between the studies.

- Intervention and comparison: in both trials, participants were randomised at a 1:1:1:1 ratio to budesonide MMX 9 mg daily, budesonide MMX 6 mg daily, placebo and an active control arm. The active control used in CORE I was mesalazine 2.4 g ([Asacol](#): 2 x 400 mg tablets 3 times daily) and in CORE II was another budesonide prolonged release formulation ([Entocort](#): 3 x 3 mg capsules daily), which is licensed for Crohn's disease and not ulcerative colitis, and releases budesonide in the ileum and ascending colon, rather than throughout the colon like budesonide MMX. The active control arms were included for internal reference and validation; neither trial was designed or [statistically powered](#) to compare the efficacy of budesonide MMX with other active treatments for ulcerative colitis. The 6 mg dose of budesonide MMX was included to establish the lowest effective dose. It is not licensed in the UK; therefore, the results for this dose are not discussed in the evidence summary. The method of randomisation used suggests [allocation was concealed](#).
- Efficacy outcomes: the primary efficacy end point in both studies was combined clinical and endoscopic remission at week 8. Remission was defined as a total UCDAI score of 1 or less (with individual rectal bleeding, stool frequency and mucosal appearance scores of 0) and a reduction of 1 or more in baseline endoscopic index score at week 8. Secondary end points were clinical improvement (defined as a 3 point or more improvement in UCDAI from baseline to week 8) and endoscopic improvement (defined as a 1 point or more improvement in the mucosal appearance parameter of the UCDAI score from baseline to week 8).
- Safety outcomes: participants were monitored for adverse events and for potential glucocorticoid-related effects. Morning plasma cortisol levels were assessed at baseline and at week 8.
- Analysis: Efficacy analyses were performed in the modified [intention to treat](#) (mITT) population, which included all randomised participants who received at least 1 dose of the

study drug, had histologically confirmed active ulcerative colitis at baseline and no violations of entry criteria (absence of infective colitis) or good clinical practice guidelines. The mITT population in CORE I included 489 participants and in CORE II included 410 participants.

Table 1 Summary of CORE I: Sandborn et al. (2012)

	Budesonide MMX 9 mg daily	Mesalazine tablets (Asacol) 2.4 g daily	Placebo	Analysis
Randomised	n=127	n=127	n=128	
Efficacy ^a	n=123	n=124	n=121	
Primary outcome: clinical and endoscopic remission at 8 weeks, percentage of participants (95% CI) ^b	17.9% (11.1% to 24.7%)	12.1% (6.4% to 17.8%)	7.4% (2.8% to 12.1%)	Budesonide MMX compared with placebo: OR 2.71 (95% CI 1.19 to 6.16) p=0.0143 Mesalazine compared with placebo: p=0.2200 Not statistically significant
Selected secondary outcomes:				
Clinical improvement at 8 weeks, percentage of participants (95% CI) ^c	33.3% (25.0% to 41.7%)	33.9% (25.5% to 42.2%)	24.8% (17.1% to 32.5%)	Budesonide MMX compared with placebo: p=0.1420 Not statistically significant

Endoscopic improvement at 8 weeks, percentage of participants (95% CI) ^d	41.5% (32.8% to 50.2%)	33.1% (24.8% to 41.3%)	33.1% (24.7% to 41.4%)	Budesonide MMX compared with placebo: p=0.1746 Not statistically significant Nominal p value only ^e
Safety^f	n=127	n=127	n=129	
Participants reporting any adverse events	57.5% (73/127)	63.0% (80/127)	62.8% (81/129)	Statistical analyses not reported
Participants reporting treatment-related adverse events	28.3% (36/127)	24.4% (31/127)	26.4% (34/129)	Statistical analyses not reported
Participants reporting serious adverse events	2.4% (3/127)	3.1% (4/127)	2.3% (3/129)	Statistical analyses not reported
Adverse events leading to discontinuation	11.8% (15/127)	11.0% (14/127)	18.6% (24/129)	Statistical analyses not reported

Abbreviations: CI, [confidence interval](#); g, gram; MMX, multimatrix; OR, odds ratio; p, [p value](#)

^a Efficacy population: randomised participants who received at least 1 dose of study drug, excluding participants with major good clinical practice or entry criteria violations and those with normal histology at baseline. Exclusions were primarily due to normal histology at study entry.

^b Clinical and endoscopic remission defined as a Ulcerative Colitis Disease Activity Index (UCDAI) score ≤ 1 , with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in the endoscopic index score. Exclusions were primarily due to normal histology at study entry.

^c Clinical improvement, defined as a ≥ 3 point improvement in UCDAI from baseline to the end of week 8. Data for 95% CI taken from the [public assessment report](#).

^d Endoscopic improvement defined as a ≥ 1 point improvement in the mucosal appearance sub-score of the UCDAI. Data for 95% CI taken from the [public assessment report](#).

^e As per the [hierarchical testing procedure](#) for secondary end points, because clinical improvement was not statistically significant, formal statistical comparisons for endoscopic improvement should be considered to be exploratory only.

^f Safety population: Participants who received at least 1 dose of study drug.

Table 2 Summary of CORE II: [Travis et al. \(2014\)](#)

	Budesonide MMX 9 mg daily	Budesonide (Entocort) 9 mg daily	Placebo	Analysis
Randomised	n=127	n=126	n=128	
Efficacy ^a	n=109	n=103	n=89	

Primary outcome: Clinical and endoscopic remission at 8 weeks, percentage of participants (95% CI) ^b	17.4% (10.3% to 24.7%)	12.6% (6.2% to 19.0%)	4.5% (0.2% to 8.8%)	Budesonide MMX compared with placebo: OR 4.49 (95% CI 1.47 to 13.72) p=0.0047 Budesonide (Entocort) compared with placebo: p=0.0481
Secondary outcomes:				
Clinical improvement at 8 weeks, percentage of participants (95% CI) ^c	42.2% (32.9% to 51.5%)	33.0% (23.9% to 42.1%)	33.7% (23.9% to 43.5%)	Budesonide MMX compared with placebo: p=0.2215 ^d Not statistically significant
Endoscopic improvement at 8 weeks, percentage of participants (95% CI) ^e	42.2% (32.9% to 51.5%)	36.9% (27.6% to 46.2%)	31.5% (21.8% to 41.1%)	Budesonide MMX compared with placebo: Not statistically significant Nominal analysis only ^f
Safety^g	n=128	n=126	n=129	
Participants reporting adverse events	55.5% (71/128)	54.8% (69/126)	44.2% (57/129)	Statistical analyses not reported
Participants reporting treatment-related adverse events	25.8% (33/128)	23.0% (29/126)	24.0% (31/129)	Statistical analyses not reported

Participants reporting any serious adverse events	3.1% (4/128)	0.8% (1/126)	3.9% (5/129)	Statistical analyses not reported
Adverse events leading to discontinuation	18.8% (24/128)	17.5% (22/126)	14.7% (19/129)	Statistical analyses not reported

Abbreviations: Abbreviations: CI, confidence interval; g, gram; MMX, multimatrix; OR, odds ratio; p, p value

^a Efficacy population: randomised participants who received at least 1 dose of study drug, excluding participants with major good clinical practice or entry criteria violations and those with normal histology at baseline. In this study, a large number of exclusions occurred due to normal histology at study entry.

^b Clinical and endoscopic remission defined as a Ulcerative Colitis Disease Activity Index (UCDAI) score ≤ 1 , with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in the endoscopic index score. Data for 95% CI taken from the [public assessment report](#).

^c Clinical improvement, defined as a ≥ 3 point improvement in UCDAI from baseline to the end of Week 8. Data for 95% CI taken from the [public assessment report](#).

^d Additional trial results taken from [clinicaltrials.gov NCT00679380](https://clinicaltrials.gov/NCT00679380).

^d Endoscopic improvement defined as a ≥ 1 point improvement in the mucosal appearance sub-score of the UCDAI. Data for 95% CI taken from the [public assessment report](#).

^e As per the hierarchical testing procedure for secondary end points, because clinical improvement was not statistically significant, formal statistical comparisons for endoscopic improvement should be considered to be exploratory only.

^f Safety population: Participants who received at least 1 dose of study drug.

Clinical effectiveness

Primary end point: clinical and endoscopic remission at week 8

Budesonide MMX 9 mg was statistically significantly more effective than placebo at inducing clinical and endoscopic remission at week 8 in both randomised controlled trials (RCTs). In [CORE I](#), 17.9% of people taking budesonide MMX 9 mg were in clinical and endoscopic remission at week 8, compared with 7.4% of people taking placebo (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.19 to 6.16, $p=0.0143$). Similar results were seen in [CORE II](#), with 17.4% of people taking budesonide MMX 9 mg in clinical and endoscopic remission at week 8, compared with 4.5% of people taking placebo (OR 4.49, 95% CI 1.47 to 13.72, $p=0.0047$).

In [CORE I](#), mesalazine 2.4 g daily (Asacol) was not statistically significantly more effective than placebo at inducing clinical and endoscopic remission at week 8 (12.1% compared with 7.4%, $p=0.2200$). In contrast, [CORE II](#) found budesonide (Entocort) 9 mg daily achieved a statistically significantly higher remission rate at week 8 compared with placebo (12.6% compared with 4.5%, $p=0.0481$). Neither trial was designed or powered to compare the efficacy of budesonide MMX with the other active treatment (mesalazine and budesonide [Entocort]).

Secondary end points: clinical improvement and endoscopic improvement

[CORE I](#) and [CORE II](#) each found no statistically difference between budesonide MMX 9 mg and placebo for clinical improvement ($p=0.1420$ and $p=0.2215$ respectively). Because a [hierarchical testing model](#) was used and the difference between the groups in clinical improvement was not statistically significant, statistical comparisons for endoscopic improvement between budesonide MMX and placebo are considered exploratory only.

There were no statistically significant differences in either secondary end point for the active controls (mesalazine 2.4 g and budesonide [Entocort] 9 mg) compared with placebo.

When the results of [CORE I](#) and [CORE II](#) were pooled, the difference between budesonide MMX 9 mg and placebo in clinical improvement remained not statistically significant (37.5% compared with 28.6%, $p=0.0572$). The pooled results for endoscopic improvement showed a statistically significant difference compared with placebo (41.8% compared with 32.4%, $p=0.0410$) ([Sandborn et al. 2015](#)), although clinical improvements were not statistically significant.

Subgroup analyses

The [public assessment report](#) for budesonide MMX reports that post-hoc analyses showed that remission rates were lower for patients with extensive disease and moderate disease severity. Further post-hoc analysis did not provide compelling and consistent differences in remission rates for budesonide MMX in people with or without prior aminosalicylate use. More than 50% of participants had received an aminosalicylate before screening.

Safety and tolerability

CORE I and CORE II

Pooled data from [CORE I](#) and [CORE II](#) showed 56.5% of people (144 out of 255) treated with budesonide MMX 9 mg reported an adverse event, compared with 53.5% in the placebo group (138 out of 258) ([Sandborn et al. 2015](#)). In [CORE I](#), 63.0% (80 out of 127) of people taking mesalazine

reported an adverse effect. In CORE II, adverse events were reported by 54.8% of people (69 out of 126) taking budesonide (Entocort).

The most common adverse events reported for budesonide MMX 9 mg across [CORE I](#) and [CORE II](#) were relapse or worsening of ulcerative colitis (13.3% compared with 14.0% in the placebo group); headache (11.4% compared with 10.5% for placebo); nausea (5.1% compared with 4.3% for placebo); and abdominal pain (3.5% compared with 5.8% for placebo) ([Sandborn et al. 2015](#)).

Across [CORE I](#) and [CORE II](#), the most common potential glucocorticoid-related effects for budesonide MMX 9 mg were mood changes (2.7% compared with 3.9% for placebo), sleep changes (2.7% compared with 4.3% for placebo), insomnia (2.4% compared with 3.1% for placebo) and acne (1.6% compared with 1.9% for placebo). The authors concluded that the incidence observed for budesonide MMX 9 mg was not substantially different from that observed for placebo ([Sandborn et al. 2015](#)).

A decrease in mean morning plasma cortisol level from baseline to week 8 was observed for budesonide MMX 9 mg in both RCTs (a change of -17.9% in [CORE I](#) and -28.9% in [CORE II](#)). Plasma cortisol levels remained within the reference range (5 to 25 micrograms/decilitre) throughout the study period and the decrease in plasma levels does not appear to have been translated into an increase in clinical glucocorticoid effects.

Public assessment report

The [public assessment report](#) for budesonide MMX states that approximately 300 people have used the drug at its licensed dose (9 mg daily) and that this is an acceptable number given the well-known safety for oral budesonide in inflammatory bowel disease. The maximum treatment duration of 8 weeks and lack of long-term data was considered acceptable because budesonide MMX is licensed only for induction of remission and not maintenance of remission.

Summary of product characteristics

According to the [summary of product characteristics](#), the most common adverse effects for budesonide MMX 9 mg are nausea, upper abdominal pain, headache, insomnia, altered mood, decreased blood cortisol, influenza and viral upper respiratory tract infection (incidence between 1 in 10 and 1 in 100).

Evidence strengths and limitations

Both of the RCTs included active controls (mesalazine and budesonide [Entocort]), but neither study was designed or powered to compare the efficacy of budesonide MMX with these other treatments. The [public assessment report](#) for budesonide MMX states that mesalazine was a suitable comparator, although it is generally used in a different population (first-line in treatment-naïve patients). However, budesonide (Entocort) might not be the most appropriate comparator because, unlike budesonide MMX, the drug is not released throughout the colon. It is also not licensed to treat ulcerative colitis. The [public assessment report](#) states that systemic oral corticosteroids may have been a more appropriate comparator than budesonide (Entocort) because they are recommended for people who have not responded to initial aminosalicylate therapy. The [public assessment report](#) goes on to state that the US Food and Drug Administration (FDA) considered treating people with oral prednisolone for 8 weeks may result in excessive steroid exposure.

CORE I found mesalazine 2.4 g to be no more effective than placebo at inducing clinical and endoscopic remission, although concerns have been raised that the dose of mesalazine used in the study was too low to demonstrate efficacy ([Criscuoli et al. 2013](#)). Also, according to the [public assessment report](#), the active comparator arm was included in CORE I (and CORE II) for validation purposes and that the lack of a statistically significant efficacy of mesalazine over placebo, therefore, raises questions about the validity of the data for the target population.

Statistically significantly more people taking budesonide MMX achieved remission at week 8 compared with placebo. However, the [public assessment report](#) notes that the [clinical importance](#) of the 10–13% improvement over placebo is questionable and not supported by statistically significant effects on the secondary end points.

CORE I and CORE II both used strict definitions for clinical and endoscopic remission, which the authors of CORE II state were partially chosen to minimise the placebo response. Of note, endoscopic remission was defined via full colonoscopy results, rather than less comprehensive flexible sigmoidoscopy values. The [public assessment report](#) states that the primary end point of clinical and endoscopic remission was acceptable, although the inclusion of an endoscopic score and no mucosal friability may have resulted in a rather strict remission criterion. [Sandborn et al. \(2015\)](#) note that the response rate in their pooled analysis of CORE I and CORE II was lower than response rates seen with other treatments for ulcerative colitis at week 8 (17.7% compared with 29.2% to 59.5%), and state that this was because of the strict definitions of remission.

A high number of people were recruited to the studies and subsequently excluded from efficacy analyses, particularly in CORE II. This was primarily because histology was undertaken centrally to confirm active inflammation was present and results took a long time to obtain. Also, violations of good clinical practice occurred in some centres. This may have affected the power of the studies to detect differences between the groups.

The studies were undertaken in people with active, mild to moderate ulcerative colitis (confirmed by histology) who were not currently taking any concomitant medication for their condition. Therefore, it is not known how well budesonide MMX works in combination with an aminosalicylate (topical or oral). Although over half of patients were previously taking mesalazine or sulfasalazine, it is unclear how well budesonide MMX works in people who do not respond to aminosalicylates. Budesonide MMX has not been compared with topical corticosteroids or oral prednisolone, which are recommended second-line options in the NICE guidance on [ulcerative colitis](#). It is also not known whether budesonide MMX is effective to maintain remission in ulcerative colitis and this is outside of the licensed indication. The studies did not report on speed of onset of budesonide MMX or the active controls.

Context

Alternative treatments

The NICE guideline on [ulcerative colitis](#) recommends that the choice of treatment to induce remission in people with a mild to moderate first presentation or inflammatory exacerbation of ulcerative colitis should be guided by site, severity and stage in therapy. Recommended treatments include:

- Oral aminosalicylates.
- Topical rectal aminosalicylates.
- Topical rectal corticosteroids.
- Oral prednisolone.
- Oral beclometasone dipropionate.
- Oral tacrolimus.

NICE recommendations for treating ulcerative colitis are outlined in more detail in the [introduction](#) to this evidence summary.

Budesonide MMX is licensed for inducing remission in mild to moderate active ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient. Table 2 shows costs for treatments that may be considered at a similar stage in the treatment pathway to budesonide MMX. A number of different strengths and formulations are available for each drug: the products included in table 2 are the most commonly prescribed individual drugs and formulations (oral and topical) based on the NHS prescription cost analysis for England 2013.

Other oral budesonide preparations licensed for use in Crohn's disease (Entocort CR and Budenofalk) release the drug in the distal ileum and right colon, do not deliver budesonide to the left colon and, therefore, are not optimally designed for the treatment of patients with ulcerative colitis. Neither of these products is licensed for use in people with ulcerative colitis: therefore, they are not included in table 3.

Table 3: Costs of alternative treatments

Drug	Usual adult dose ^a	28-day cost excluding VAT
Oral corticosteroids and aminosalicylates		
Budesonide MMX 9 mg prolonged release tablets (<u>Cortiment</u>)	9 mg daily	£70.00 ^b
Beclometasone dipropionate 5 mg sustained release tablets (<u>Clipper</u>)	5 mg daily	£52.79 ^b
Prednisolone 5 mg tablets	20 mg to 40 mg daily	£5.16 to £10.32 ^c
Balsalazide 750 mg capsules (<u>Colazide</u>)	2.25 g three times daily	£58.97 ^c
Mesalazine 400 mg modified release tablets (<u>Asacol MR</u>)	2.4 g daily in divided doses	£54.90 ^c
Olsalazine 500 mg tablets (<u>Dipentum</u>)	1 g daily in divided doses	£79.33 ^c
Sulfasalazine 500 mg gastroresistant tablets	1 g to 2 g four times daily	£24.66 to £49.32 ^c
Topical corticosteroids and aminosalicylates		

Budesonide rectal foam 2 mg per dose (Budenofalk)	2 mg daily	£114.22 ^b
Hydrocortisone 10% foam (Colifoam)	1 dose once or twice daily for 2 to 3 weeks, then once daily on alternative days	£14.00 to £30.66 ^b
Prednisolone rectal foam 20 mg per dose	20 mg once or twice daily ^d	£136.00 to £272.00 ^c
Mesalazine foam enema 1 g per dose (Asacol)	1 g daily	£53.44 ^b
Mesalazine 1 g suppositories (Pentasa)	1 g daily	£40.01 ^c
<p>^a Doses shown do not represent the full range that can be used and do not imply therapeutic equivalence. Taken from the relevant summaries of product characteristics unless stated otherwise.</p> <p>^b Costs based on MIMS, May 2015; excluding VAT.</p> <p>^c Costs based on the Drug Tariff, May 2015; excluding VAT.</p> <p>^d Dose taken from the British National Formulary.</p>		

Estimated impact for the NHS

Likely place in therapy

Localities will need to take safety, efficacy, cost and patient factors into account when considering the place in therapy of budesonide MMX.

Budesonide MMX has been shown to statistically significantly induce clinical remission at 8 weeks in people with mild to moderate active ulcerative colitis compared with placebo. However, the effect size was small (10–13%) and its clinical relevance was questioned in the [public assessment report](#). No difference was seen between budesonide MMX and placebo for the secondary outcomes, clinical improvement and endoscopic improvement. The study was not designed to compare budesonide MMX directly with active comparators and it is not known how it compares with other treatments for ulcerative colitis, alone or in combination.

Budesonide MMX appears to be well-tolerated. The proportions of adverse events, serious adverse events and glucocorticoid adverse events seen with the product were not substantially different from placebo.

Budesonide MMX is licensed for inducing remission in mild to moderate active ulcerative colitis in adults for whom aminosalicylate treatment is not sufficient. The [public assessment report](#) concluded that treatment with budesonide MMX can be beneficial for some people and, given the limitations of the currently available treatments, presents clinicians with an additional therapeutic option. The report suggests that the role for budesonide MMX may be to induce remission of ulcerative colitis before systemic corticosteroids are tried, which are associated with more severe adverse effects. Specialists involved in the production of this evidence summary agreed that this was its likely place in therapy. According to the [public assessment report](#), whether budesonide MMX should be used as first- or second-line therapy, after use of an aminosalicylate or in combination with an aminosalicylate (topical or oral) cannot be determined based on the available data and should be determined by the prescriber. The [Contribute study](#) compared budesonide MMX with placebo as add-on therapy to oral aminosalicylates in people with ulcerative colitis and may provide more information when the results are fully published.

Considering other drugs for ulcerative colitis that may be used in combination with or instead of aminosalicylates, budesonide MMX is more expensive than oral corticosteroids. The cost of rectal corticosteroid and rectal mesalazine preparations is dependent on the drug and dosage: budesonide MMX is less expensive than some preparations but more expensive than others. Some people may prefer to take budesonide MMX than an oral corticosteroid because it is expected to have less adverse effects. People may also differ in their preference between a rectal and oral preparations.

Estimated usage

It is not possible to provide estimated usage based on the available data.

The [costing template](#) supporting the NICE guideline on [ulcerative colitis](#) estimates that at step 2 therapy, 42% of people will be taking step 1 aminosalicylate therapy, 39% of people will be taking oral prednisolone and 1% of people will be taking oral tacrolimus.

Relevance to NICE guidance programmes

Budesonide MMX was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

In 2013, NICE published a guideline on [ulcerative colitis](#) (NICE guideline CG166), which has been incorporated into a [NICE pathway](#).

NICE has also published a guideline on [colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas](#) (NICE guideline CG118).

NICE has published 2 technology appraisals relating to ulcerative colitis:

- [Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy \(including a review of TA140 and TA262\)](#), NICE technology appraisal guidance 329.
- [Infliximab for acute exacerbations of ulcerative colitis](#), NICE technology appraisal guidance 163.

The following NICE technology appraisal relating to ulcerative colitis is in development:

- [Ulcerative colitis \(moderate to severely active\) – vedolizumab](#), expected date of publication June 2015.

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Hamilton has no relevant interests to declare.

Dr Nightingale has been sponsored to attend an educational event by Calea.

Dr Murray has received honoraria for work on advisory boards or as a speaker, chair from AbbVie, Almirall, Merck Sharp & Dohme and Shire.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

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