New Medicine Assessment

Budesonide multimatrix MMX 9mg prolonged release tablets
(Cortiment®▼)

For induction of remission in adults with mild to moderate active ulcerative colitis where 5-ASA (aminosalicylate) treatment is not sufficient

Recommendation: RED

Budesonide MMX 9mg (Cortiment®) is recommended as an alternative to oral/topical corticosteroids, where these treatments are judged to be unsuitable or will cause unacceptable side effects, for the induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA (aminosalicylate) treatment is not sufficient.

Summary of supporting evidence:

- Cortiment® 9mg is the first oral formulation of budesonide to be licensed for UC and exerts its action topically in the colon.
- The CORE I and CORE II studies demonstrated a significantly higher rate of combined clinical and endoscopic remission for budesonide MMX 9mg compared to placebo. [1] [2]
- The CONTRIBUTE study showed budesonide MMX 9mg was significantly better than placebo at increasing the rate of combined clinical and endoscopic remission in patients refractory to 5-ASA treatment. [3]
- Three phase III studies showed the safety profile of budesonide MMX 9mg to be favourable to oral systemic corticosteroids and similar to that observed in patients using placebo.
- Current treatments for UC are not sufficiently effective with response rates of 40-70% among patients with mild to moderate disease using mesalazine. [4]
- No studies directly compared budesonide MMX 9mg to systemic oral corticosteroids precluding comparisons of efficacy between these treatments.
- The cost of using budesonide in place of other corticosteroid treatments would be approximately £9,298 to £14,748 depending on the choice of treatment used.
## Details of Review

### Name of medicine (generic & brand name):
Budesonide multimatrix (MMX) 9mg prolonged release tablets (Cortiment®)

### Strength(s) and form(s):
9mg prolonged release tablets

### Dose and administration:
One tablet (9mg) in the morning for up to 8 weeks with or without food. The tablet should be swallowed with a glass of water and must not be broken, crushed or chewed.

### BNF therapeutic class / mode of action
Gastrointestinal system / Chronic bowel disorders / Corticosteroids

### Licensed indication(s):
Induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA (aminosalicylate) treatment is not sufficient. [5]

### Course and cost:
- 30 x Cortiment® 9mg tablets = £75
- 8-week course costs £140

Prices are based on Monthly Index of Medical specialities (MIMS) list price as of May 2017.

### Current standard of care/comparator therapies:
- Oral aminosalicylates
- Topical aminosalicylates
- Topical corticosteroids
- Oral corticosteroids (following failure of other treatments)

Choice of agents depends on the site of inflammation and patient preference.

### Relevant NICE guidance:
- NICE clinical guideline (CG 166) Ulcerative colitis: management.
- NICE evidence summary (ESNM58) Ulcerative colitis: budesonide multimatrix (Cortiment)
### Background and context

**Ulcerative colitis (UC)** is the most common type of inflammatory disease of the bowel. It has an incidence in the UK of approximately 10 per 100,000 people annually, and a prevalence of approximately 240 per 100,000. This amounts to around 146,000 people in the UK with a diagnosis of UC. The cause of UC is unknown. Symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defaecate and abdominal pain. UC is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled. Typically, it has a relapsing–remitting pattern.

UC 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 as proctosigmoiditis. Left-sided colitis refers to disease involving the colon distal to the splenic flexure. Extensive colitis affects the colon proximal to the splenic flexure, and includes pan-colitis, where the whole colon is involved. Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and thereafter to maintain remission. The long-term benefits of achieving mucosal healing remain unclear. The treatment chosen for active disease is likely to depend on clinical severity, extent of disease and the person's preference.

The National Institute for Health and Care Excellence (NICE) published clinical guideline 166: “Ulcerative colitis: management” in June 2013. For inducing a remission in patients with mild to moderate disease, this guideline recommends a stepped approach, guided by the site of inflammation. The first step for patients with proctitis or proctosigmoiditis is to offer:

- a topical 5-ASA or
- a topical 5-ASA with an oral 5-ASA or
- consider an oral 5-ASA alone

Clinicians should take patient’s preferences into account and explain that oral 5-ASA is not as effective as a topical 5-ASA alone or combination treatment.

For patients with left-sided or extensive UC: offer a high induction dose of an oral 5-ASA, consider adding a topical 5-ASA or oral beclometasone dipropionate taking patient’s preferences into account.

Oral prednisolone should be considered to induce remission in patients with a mild to moderate first presentation or inflammatory exacerbation of UC who cannot tolerate or who decline aminosalicylates, or in whom aminosalicylates are contraindicated.

The second step for all patients with mild to moderate UC is to consider adding oral prednisolone to 5-ASA therapy if there is no improvement within four weeks of starting or if symptoms worsen. Oral tacrolimus can be considered for addition to oral prednisolone if there is an inadequate response after two to four weeks.

The use of oral corticosteroids is associated with a significant risk of treatment emergent adverse events. The adverse events are dose-related, where patients receiving long-term oral corticosteroids (more than 3 weeks duration) or those needing frequent courses (3 or 4 per year) are at greater risk. Osteoporosis, diabetes mellitus, hypertension and adrenal insufficiency are potential systemic adverse events attributable to long-term or repeated courses of oral corticosteroids.

Cortiment® 9mg oral prolonged release tablets are a formulation of micronised budesonide in a
multi-matrix (MMX) structure designed to exert the action of budesonide in the colon. Cortiment® is licensed for induction of remission in patients with mild to moderate active UC where 5-ASA treatment is not sufficient. [5] The role in therapy for budesonide MMX may be to induce remission of UC before systemic corticosteroids are commenced; to reduce the risk of corticosteroid associated adverse events.

Summary of evidence

Summary of efficacy data in proposed use:

**Pivotal studies**

Two pivotal randomised, 8 week, double-blind, placebo-controlled, phase III studies **CORE I** [1] and **CORE II** [2] have been undertaken. Both studied adult patients (18 to 75 years) with active mild to moderate UC for at least six months defined by a UC Disease Activity Index (UCDAI) score of ≥4 to ≤10 (a composite score of stool frequency, rectal bleeding, mucosal appearance and physician’s ratings). Both studies included treatment arms for budesonide MMX 9mg daily and 6mg daily; an active control group (using 2.4g of mesalazine daily [Asacol®] in **CORE I** and budesonide EC 9mg daily [Entocort®] in **CORE II**); and a placebo group. Patients receiving 5-ASA at screening underwent a washout before randomisation and concomitant use of 5-ASA was not permitted during the study periods.

Patients were excluded from both studies if they had a presumed or verified pregnancy or ongoing lactation; severe UC or limited proctitis; evidence/hist of toxic megacolon; presence of infection; blood disorders (anaemia, leucopenia or agranulocytopenia); renal or hepatic disease or insufficiency; type 1 diabetes mellitus; glaucoma; previous use of oral or rectal corticosteroids within 4 weeks of screening, immunosuppressive agents within 8 weeks of screening or anti-TNF agents within 3 months of screening.

The primary efficacy endpoint for both studies was combined clinical and endoscopic remission at week 8 strictly defined as a total UCDAI score of ≤1 and a ≥1 point reduction in the baseline endoscopic score. Secondary efficacy endpoints included clinical improvement, endoscopic improvement, symptom resolution and histologic healing.

**CORE I study**

The **CORE I** study found that the primary outcome of combined clinical and endoscopic remission was achieved by significantly more budesonide MMX 9mg than placebo patients (17.9% vs 7.4% [CI95% 2.2; 18.7, p=0.0143]) with an odds ratio (OR) of 2.71 [CI95% 1.19; 6.16]). The active control group (using mesalazine 2.4g) and the budesonide MMX 6mg group achieved numerical but not significant improvements in combined and endoscopic remission.

For the secondary outcome efficacy points budesonide MMX 9mg demonstrated numerical but not significant improvements in clinical and endoscopic improvements compared to placebo. Improvements in symptom resolution were significant for budesonide MMX 9mg versus placebo, however the percentage of patients with histological healing were not significantly different between any active treatment groups. [1]

**CORE II study**

In the **CORE II** study, the rate of combined clinical and endoscopic remission with budesonide MMX 9mg was significantly higher than with placebo (17.4% vs 4.5%; OR 4.49 [CI95% 1.47; 13.75, p=0.0047]). For the active control group (using Entocort®) improvement in the rate of
combined and endoscopic remission achieved borderline significance compared to placebo, while patients using budesonide MMX 6mg improved numerically relative to placebo.

For the secondary outcome efficacy points budesonide MMX 9 mg increased clinical improvement and endoscopic improvement rates compared with placebo, but these differences did not reach statistical significance. Nevertheless, histological healing and symptom resolution were statistically superior in the budesonide MMX 9 mg group compared with the placebo group. [2]

Other efficacy data:

An additional phase III, double-blind, randomised study (CONTRIBUTE [3]) compared budesonide MMX 9mg with placebo in patients with mild to moderate UC not adequately controlled with oral 5-ASA treatment. Eligible patients had a UCDAI score of ≥4 to ≤10 and an inadequate response to an oral 5-ASA for ≥six weeks before randomisation. They were randomised to receive budesonide MMX 9mg orally daily (n=230) or placebo (n=228) for eight weeks and previous 5-ASA treatment was continued. The primary outcome was combined clinical and endoscopic remission at eight weeks (defined as UCDAI score ≤1, with a rectal bleeding score of 0, stool frequency score of 0 and mucosal appearance score of 0) which was achieved by significantly more budesonide MMX than placebo patients: 13% versus 7.5% respectively, p=0.0488. In terms of secondary outcomes, clinical remission did not differ significantly between treatments but endoscopic remission and histologic healing were significantly better with budesonide MMX. [8]

Summary of safety data:

In the completed studies, budesonide MMX 9mg was administered at any dose (single or multiple) to approximately 500 patients for up to 8 weeks. The public assessment report deems this to be an acceptable safety database given the well-known safety profile of orally administered budesonide 9mg in inflammatory bowel disease. [4] In a pooled analysis of the CORE I and II studies adverse events were reported in 56.5% of budesonide MMX 9mg and 53.5% of placebo patients. [9] The CONTRIBUTE study reported adverse events in 31.8% and 27.1% of budesonide MMX 9mg and placebo patients respectively. [3] Across all studies the rate of serious adverse events was low (<8%) and glucocorticoid–related effects were slightly raised compared to placebo occurring in less than 9% of patients. The authors of the CORE I and II pooled analysis concluded that the incidence of glucocorticoid-related effects with budesonide MMX 9mg was not substantially different from that observed with placebo. [9]

The most frequently reported adverse events were exacerbations of UC, headache, nausea, abdominal pain and nasopharyngitis. The summary of product characteristics (SPC) for budesonide MMX 9mg (Cortiment®) lists the following adverse events [5]:

Table 1: SPC list of adverse events

<table>
<thead>
<tr>
<th>MedDRA System Organ Classification</th>
<th>Preferred Term of Adverse Event</th>
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<tbody>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
</tr>
<tr>
<td>Nervous System disorders</td>
<td>Headache</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Drug ineffective</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
</tr>
<tr>
<td>Investigations</td>
<td>Blood cortisol decrease</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Cushingoid syndrome</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Influenza</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

Budesonide MMX 9mg is contraindicated in patients with hypersensitivity to the active substance, soya oil, peanut oil or any other excipient contained in Cortiment® and should not be used by patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Budesonide MMX 9mg should be used with caution in patients with infections, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts or with any other condition where the use of glucocorticoid therapy may have unwanted effects. Concomitant administration of potent CYP3A4 inhibitors/inducers should be avoided (e.g. ketoconazole, carbamazepine etc.). As with other drugs primarily being metabolised through CYP3A4, regular ingestion of grapefruit or grapefruit juice simultaneously with budesonide administration should be avoided. Corticosteroid interactions that may present a significant hazard to selected patients are those with heart glycosides (increased effect due to reduced potassium levels) and diuretics (increased elimination of potassium). Administration of antacids or cholestyramine should be at least 2 hours after taking budesonide MMX 9mg to prevent reduced absorption.

Due to the potential of glucocorticoids to reduce immune response particular care may be necessary to avoid exposure to chicken pox and measles. Responses to vaccines may also be reduced when administered concomitantly with budesonide. The use of budesonide MMX 9mg results in lower systemic steroid levels than conventional oral glucocorticoid therapy, therefore...
transfer from other systemic oral corticosteroid therapies to budesonide may result in corticosteroid withdrawal symptoms. The SPC states that when budesonide MMX treatment is discontinued, it may be useful to gradually reduce the dose at the discretion of the treating physician. However budesonide MMX is only available as a 9mg tablet which must be swallowed whole to ensure the prolonged release. Therefore the options for gradually reducing the dose would be limited to increasing the dosing interval. [5]

Strengths and limitations of the evidence:

Strengths:

- Cortiment® 9mg is the first oral formulation of budesonide to be licensed for UC and exerts its action topically in the colon.
- The public assessment report concluded that treatment with budesonide MMX 9mg can be beneficial for some patients and, given the limitations of the currently available treatments (systemic oral corticosteroids), budesonide MMX 9mg presents clinicians with an additional therapeutic option. [4]
- Current treatment for UC is not sufficiently effective with response rates of 40-70% among patients with mild to moderate disease using mesalazine. [4]
- The CORE I and CORE II studies demonstrated a significantly higher rate of combined clinical and endoscopic remission for budesonide MMX 9mg compared to placebo. [1] [2]
- The CONTRIBUTE study showed that budesonide MMX 9mg was significantly better than placebo at increasing the rate of combined clinical and endoscopic remission in patients refractory to 5-ASA treatment. [3]
- Three phase III studies showed the safety profile of budesonide MMX 9mg to be favourable to oral systemic corticosteroids and similar to that observed in patients using placebo. [1] [2] [3]
- The public assessment report states that although the treatment effect was small, experts considered the results of the phase III studies to be of clinical relevance due to the strict study criteria for patient inclusion and the strict criteria of clinical remission including endoscopy. [4]

Limitations:

- Although active controls (mesalazine and budesonide EC) were included in the CORE I and II studies, neither study was powered to compare the efficacy of budesonide MMX with these treatments.
- The power of the studies was reduced by exclusion of randomised patients from the intention to treat analysis based on histological evidence of active disease which came to light after randomisation.
- Oral prednisolone would have been a more appropriate comparator than budesonide EC (Entocort®) because NICE recommends prednisolone in patients unable to use 5-ASA and following 5-ASA treatment failure.
- The use of lower dose mesalazine (2.4mg) as an active control may not have been appropriate for all study participants. This may have led to results showing no significant difference between mesalazine and placebo in the rate of combined clinical and endoscopic remission despite mesalazine being a well-established and effective treatment for UC.
- In a post-hoc analysis of CORE I and II results, placebo rates of remission appeared somewhat lower in patients who did not use 5-ASA before study entry. This may have
potentially altered the study results. The public assessment report stated that this anomaly may have been caused by a carry-over effect of prior 5-ASA use as the washout period for 5-ASA was only two days.

- The baseline demographics of participants were variable in terms of duration of disease and disease extent in the CORE I and II studies which may have affected study outcomes.
- Due to the strict definition of remission used in the CORE I and II study design leading to lower treatment effect, it is not possible to compare the results of the CORE I and II studies to study results of other comparator treatments showing comparatively larger treatment effects.

**SMC cost effectiveness evidence:**

In October 2015 the SMC considered budesonide MMX for the induction of remission in adult patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient (the licensed indication). The SMC assessment concluded that budesonide MMX is not recommended for use within NHS Scotland, as similar cost effectiveness with the reference product (rectal budesonide) was not demonstrated. [10]

Following resubmission in October 2016, budesonide MMX was accepted for restricted use in NHS Scotland for use in patients with UC who present with active left-sided disease and/or proctosigmoiditis who are not suitable for oral prednisolone, as an alternative to budesonide rectal formulations or off-label oral budesonide.

The published SMC advice from the resubmission of budesonide MMX makes reference to a company submitted cost-minimisation analysis of budesonide MMX for UC patients who have left sided disease and/or proctosigmoiditis who are not suitable for oral prednisolone and who would otherwise receive budesonide rectal foam or off-label oral budesonide. [8]

The assumption of comparable efficacy was based on the indirect comparisons of budesonide MMX and budesonide rectal foam. A one-year time horizon was used and it was assumed that 70% of patients would require 1 course of treatment lasting 8 weeks and 30% would require 2 courses. The analysis included only the medicine acquisition costs of budesonide MMX, rectal foam and off-label oral formulations of budesonide. Medicines wastage was included for budesonide rectal foam and budesonide MMX where the number of packs required was rounded up. No wastage was included for the other treatments. There was no specific administration or monitoring costs associated with budesonide MMX or comparators.

The results of the analysis showed that budesonide MMX is cost-minimising versus a weighted average comparator of other budesonide treatments, with estimated savings of £57. The total cost for budesonide MMX was estimated to be £195 and for the weighted average comparator the total cost was £252. The results were also presented comparing the cost of budesonide MMX with each comparator (table 2).

<table>
<thead>
<tr>
<th>Table 2: Results comparing budesonide MMX with individual comparators</th>
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<tbody>
<tr>
<td><strong>Budesonide MMX (Cortiment®)</strong></td>
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<tr>
<td>Off-label oral budesonide (Budenofalk®)</td>
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<tr>
<td>Off-label oral budesonide (Entocort®)</td>
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<tr>
<td>Budesonide rectal foam (Budenofalk®)</td>
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</table>
Prescribing and risk management issues:

Cortiment® tablets should be swallowed whole with a glass of water and must not be broken, crushed or chewed as the film coating is intended to ensure a prolonged release. [5]

Confusion between the other oral budesonide brands is possible as the licensed indications, dosage forms and dosing schedules are different e.g. Budenofalk and Entocort 3mg prescribed as 3 capsules daily whereas Cortiment® dosing is one 9mg tablet daily. Careful counselling and advice is necessary for patients to ensure that they are aware of the dosing schedule of their medication. This is particularly important for patients previously prescribed a budesonide product (off-license) for which the number of capsules/tablets taken was different. [11]

Commissioning considerations:

Table 3, comparative unit costs:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EXAMPLE REGIMEN</th>
<th>PACK COST</th>
<th>COST PER PATIENT PER COURSE/PER YEAR (EX VAT)</th>
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<tbody>
<tr>
<td>Oral corticosteroids</td>
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<tr>
<td>Budesonide MMX 9 mg prolonged release tablets (Cortiment)</td>
<td>9mg daily</td>
<td>£70.00</td>
<td>£140 (8 week course)</td>
</tr>
<tr>
<td>Beclometasone dipropionate 5 mg sustained release tablets (Clipper)</td>
<td>5mg daily</td>
<td>£56.56</td>
<td>£56.56 (4 week course)</td>
</tr>
<tr>
<td>Prednisolone 5 mg tablets</td>
<td>20mg to 40mg daily</td>
<td>£0.86</td>
<td>£7.65 (Based on an 8 week reducing regimen)</td>
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<tr>
<td>Oral aminosalicylates</td>
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<tr>
<td>Mesalazine 400 mg modified release tablets (Asacol MR)</td>
<td>2.4g daily in divided doses (doubled to 4.8 daily in acute attack)</td>
<td>£54.90 (for pack of 168)</td>
<td>£109.80 (additional cost if dose doubled for 8 weeks to treat acute attack)</td>
</tr>
<tr>
<td>Sulfasalazine 500 mg gastroresistant tablets</td>
<td>1-2g four times daily</td>
<td>£7.64</td>
<td>£30.56 to £61.12 (8 week course)</td>
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<tr>
<td>Topical aminosalicylates</td>
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<tr>
<td>Mesalazine 1 g suppositories (Pentasa)</td>
<td>0.5-1g twice daily</td>
<td>£4.82 (for pack of 10)</td>
<td>£26.99 to £53.98 (4 week course)</td>
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<tr>
<td>Topical corticosteroids</td>
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<tr>
<td>Hydrocortisone 10% foam (Colifoam)</td>
<td>1–2 times a day for 2–3 weeks, then reduced to once daily on alternate days</td>
<td>£9.33</td>
<td>£14.00 to £30.66 (4 week course)</td>
</tr>
</tbody>
</table>

Costs based on MIMS or drug tariff list prices from May 2017. This table does not imply therapeutic equivalence of drugs or doses.
Associated additional costs or available discounts:

None

Productivity, service delivery, implementation:

It is expected that patients with mild to moderate UC who are refractory to oral 5-ASA treatment, would be initiated on further treatment to induce remission by a specialist gastroenterologist.

Anticipated patient numbers and net budget impact:

NICE clinical guideline Ulcerative colitis: management states that UC has a prevalence of approximately 240 per 100,000 equating to 3,600 patients across the Lancashire health economy. Estimations provided by the gastroenterologist requesting a New Medicine Review of budesonide MMX 9mg tablets suggest that 20 patients would receive this treatment within the clinician's provider trust. Extrapolating this estimation across all provider trusts across the Lancashire footprint would give a total of 80 patients receiving budesonide MMX 9mg.

Using assumptions made in the SMC health economic evidence, 70% of patients would require 1 course of budesonide MMX 9mg tablets lasting 8 weeks and 30% would require 2 courses annually. Therefore, the average annual treatment cost per patient for budesonide MMX 9mg tablets would be £195.

The total annual spend for 80 patients using budesonide MMX 9mg would be £15,600.

Cortiment 9mg tablets are licensed for induction of remission in patients with mild to moderate active ulcerative colitis (UC) where 5-ASA treatment is not sufficient. The most appropriate comparator treatments for the induction of remission where 5-ASA treatment is not sufficient are topical and oral systemic corticosteroids. Using the above assumptions, the annual cost of treating 80 patients with these comparators is as follows:

- Prednisolone 5mg tablets- £852
- Beclometasone dipropionate 5mg tablets- £6,302
- Hydrocortisone 10% foam- £1,560 to £3,416.

Therefore the additional cost of treating patients with budesonide MMX 9mg is £14,748 to £9,298 depending on the choice of treatment used.

Innovation, need, equity:

Current treatments to induce remission in patients with mild to moderate UC have limited and variable efficacy while alternative treatment options following 5-ASA failure (including oral systemic corticosteroids and immunosuppressive agents) have the potential to cause frequent and severe adverse events. The safety profile of budesonide MMX 9mg is favourable compared to the current alternative treatment options.
References


<table>
<thead>
<tr>
<th>Levels</th>
<th>Criteria</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Level 1</td>
<td>Patient-oriented evidence from:</td>
<td>High quality individual RCT = allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)</td>
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<tr>
<td></td>
<td>• high quality randomised controlled trials (RCTs) with low risk of bias</td>
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<td></td>
<td>• systematic reviews or meta-analyses of RCTs with consistent findings</td>
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<tr>
<td>Level 2</td>
<td>Patient-oriented evidence from:</td>
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<td>• clinical trials at moderate or high risk of bias</td>
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<td>• systematic reviews or meta-analyses of such clinical trials or</td>
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<td>• with inconsistent findings</td>
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<td>• cohort studies</td>
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<td>• case-control studies</td>
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<tr>
<td>Level 3</td>
<td>Disease-oriented evidence, or evidence from:</td>
<td>Any trial with disease-oriented evidence is Level 3, irrespective of quality</td>
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<td>• consensus guidelines</td>
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<td></td>
<td>• expert opinion</td>
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</tr>
<tr>
<td></td>
<td>• case series</td>
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