Common Drug Review
Clinical Review Report

April 2017

Drug	budesonide (Cortiment MMX)
Indication	For the induction of remission in patients with active, mild to moderate ulcerative colitis
Reimbursement Request	As per indication
Dosage Form (s)	Delayed and extended release 9 mg tablets
NOC Date	June 20, 2016
Manufacturer	Ferring Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in gastroenterology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAI	Clinical Activity Index
CI	confidence interval
DB	double-blind
DD	double-dummy
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
IBD-QoL	Inflammatory Bowel Disease Quality of Life Questionnaire
ITT	intention-to-treat population
LOCF	last observation carried forward
MMX	Multi Matrix System
PC	placebo-controlled
PG	parallel-group
PP	per-protocol
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SD	standard deviation
UC	ulcerative colitis
UCDAI	Ulcerative Colitis Disease Activity Index
ULN	upper limit of normal
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) that is localized to the colon, and symptoms include diarrhea, pain, bloody stools, fatigue, and weight loss. If left untreated, inflammation may progress, leading to mucosal damage and potentially fatal complications such as perforation and sepsis. According to the Crohn's and Colitis Foundation of Canada in 2012, there are approximately 233,000 Canadians living with IBD, with 104,000 diagnosed with UC. More than 10,200 new cases of IBD are diagnosed every year (5,700 with Crohn's disease [CD] and 4,500 with UC), an incidence of 0.7%; 20% to 30% of people with IBD are diagnosed before the age of 20 years. Budesonide is a corticosteroid with anti-inflammatory properties, although the precise mechanism of action is not known. The oral and rectal formulations of budesonide have existing indications for the management of UC and CD. Budesonide MMX (Multi Matrix System) is a new formulation of budesonide that is available as 9 mg delayed- and extended-release tablets for oral administration. The Health Canada indication is for the induction of remission in patients with active, mild to moderate UC. The recommended dose is one tablet per day in the morning for up to 8 weeks.

Indication under review
For the induction of remission in patients with active, mild to moderate ulcerative colitis.
Reimbursement criteria requested by sponsor
As per indication

The objective of this review is to perform a systematic review of the beneficial and harmful effects of budesonide MMX for the induction of remission in patients with active, mild to moderate UC.

Results and interpretation

Included studies

Two manufacturer-sponsored, multi-centre, double-blind, placebo-controlled randomized controlled trials (RCTs) met the inclusion criteria for this systematic review. CORE I (N = 510) and CORE II (N = 512) evaluated the efficacy and safety of budesonide MMX 9 mg in adult patients with active mild to moderate UC. The CORE I study also included a mesalamine (Asacol 2,400 mg) treatment group, while the CORE II study included a budesonide (Entocort EC 9 mg) treatment group, although the studies were not powered to compare these drugs to placebo or budesonide MMX and were included as a reference arm. The primary end point in the CORE studies was clinical and endoscopic remission at week 8, which was defined as an Ulcerative Colitis Disease Activity Index (UCDAI) score ≤ 1 with subscores of 0 for rectal bleeding and stool frequency; a normal mucosa by endoscopy; and a ≥ 1-point reduction in endoscopy score from baseline. Secondary end points included clinical improvement as defined by a ≥ 3-point improvement in UCDAI score from baseline to week 8, and endoscopic improvement as defined by a ≥ 1-point improvement in the UCDAI mucosal appearance subscore from baseline to week 8. Health-related quality of life was evaluated by the Inflammatory Bowel Disease Quality of Life Questionnaire (IBD-QoL) as an exploratory outcome. Other exploratory outcomes included histological healing and symptom resolution at week 8.

The main limitations of the CORE studies included the high percentage of patients who discontinued treatment, the potential loss of randomization due to the exclusion of patients from the ITT population

after a protocol amendment, the placebo effects seen in both trials, the enrolment of a patient population with more advanced disease that may not be reflective of the population that would receive budesonide MMX, and the use of clinical and endoscopic end points that may not be reflective of clinical practice. CORE II may not have been appropriately powered due to the revised definition of the intention-to-treat (ITT) population, in which the number of patients did not meet the initial power calculations.

Efficacy

The primary end point in the CORE studies was clinical and endoscopic remission at week 8. In both CORE studies, the proportion of patients who achieved complete remission at week 8 was greater in the budesonide MMX group than in the placebo group (CORE I: 17.9% versus 7.4%; CORE II: 17.4% versus 4.5%). The mean difference in the proportion of patients achieving complete remission with budesonide MMX compared with placebo was statistically significant in both studies (CORE I: 10.4%; 95% confidence interval [CI], 2.2% to 18.7%; *P* = 0.0143; and CORE II: 12.9%; 95% CI, 4.6% to 21.3%; *P* = 0.0047). The proportion of patients who achieved complete remission in the budesonide MMX groups was lower than was seen in two eight-week, placebo-controlled mesalamine (5-aminosalicylic acid [5-ASA]) trials for mild to moderate UC, but this may be due to the enrolment of a more severe patient population in the CORE studies who had a median duration of disease of three to four years, and more than 50% who had prior experience with mesalazine.

In both CORE studies, the proportion of patients with clinical improvement at week 8 was greater in the budesonide MMX group compared with the placebo group (CORE I: 33.3% versus 24.8%; CORE II: 42.2% versus 33.7%). The mean difference in the proportion of patients achieving clinical improvement with budesonide MMX compared with placebo was not statistically significant in both studies (CORE I: 8.5%; 95% CI, –2.8% to 19.9%; *P* = 0.1420; and CORE II: 8.5%; 95% CI, –5.0% to 22.0%; *P* = 0.2215). In both CORE studies, the proportion of patients with endoscopic improvement at week 8 was greater in the budesonide MMX group than in the placebo group (CORE I: 41.5% versus 33.1%; CORE II: 42.2% versus 31.5%). Because statistical significance was not reached for clinical improvement in both studies, no statistical analyses were performed for the comparison of budesonide MMX versus placebo with regard to endoscopic improvement due to the hierarchical testing procedure.

Quality of life was cited as an important outcome from patient group input. Health-related quality of life as measured by the IBD-QoL questionnaire was an exploratory end point in the CORE studies, with higher scores (range 32 to 224) indicating better quality of life. In CORE I, the mean (standard deviation [SD]) IBD-QoL total score at baseline was [redacted] in the budesonide MMX group and [redacted] in the placebo group. In CORE II, the mean (SD) IBD-QoL total score at baseline was [redacted] in the budesonide MMX group and [redacted] in the placebo group. In CORE I, the mean (SD) change from baseline in IBD-QoL total score at week 8 was [redacted] in the budesonide MMX group and [redacted] in the placebo group. In CORE II, the mean (SD) change from baseline in IBD-QoL total score at week 8 was [redacted] in the budesonide MMX group and [redacted] in the placebo group. The difference in mean change from baseline in IBD-QoL score between budesonide MMX and placebo groups were not statistically significant in both studies. However, as this was an exploratory end point where there was no hierarchical testing procedure, these results should be interpreted with caution.

There were no head-to-head trials comparing budesonide MMX with other active treatments for mild to moderate UC. Although an Asacol 2,400 mg group was included in CORE I and an Entocort EC 9 mg group was included in CORE II, neither trial was designed to compare these groups to budesonide MMX. The manufacturer submitted a network meta-analysis (NMA) to compare budesonide MMX 9 mg to

other drugs for the induction of complete clinical remission in patients with active, mild to moderate UC. Based on the induction NMA, budesonide MMX was associated with a statistically significant improvement for induction of complete clinical remission compared with placebo and high-dose mesalazine. Due to significant limitations with the analysis because of a small network informed mainly of single-study connections and the inclusion of studies with different end point definitions and study durations, the results of the NMA for induction of complete clinical remission and maintenance of clinical remission are uncertain.

Harms

Budesonide is a corticosteroid with low systemic bioavailability when administered orally or rectally, due to extensive first-pass hepatic metabolism, which may limit systemic adverse effects caused by conventional corticosteroids. In CORE I, the incidence of adverse events was similar between the budesonide MMX and placebo groups (57.5% versus 62.8%). In CORE II, the incidence of adverse events was higher in the budesonide MMX group than in the placebo group (55.5% versus 44.2%). The most common adverse events included worsening UC, headache, nausea, insomnia, and abdominal pain. The incidence of serious adverse events was similar between the budesonide MMX and placebo groups in the CORE studies (CORE I: 2.4% versus 2.3%; CORE II: 3.1% versus 3.9%). In CORE I, the incidence of withdrawals due to adverse events was higher in the placebo group than in the budesonide group (18.6% versus 11.8%). In CORE II, the proportion of patients with withdrawals due to adverse events was higher in the budesonide group than in the placebo group (18.8% versus 14.7%). There were no deaths in the CORE studies.

In CORE I, glucocorticoid adverse events were similar between the budesonide and placebo groups (11.8% versus 10.1%). In CORE II, glucocorticoid adverse events were higher in the placebo group than in the budesonide MMX group (10.1% versus 6.3%). Common glucocorticoid adverse events included mood changes, sleep changes, and insomnia. The long-term effects of budesonide MMX 9 mg are unknown. However, the recommended treatment regimen for budesonide MMX is up to eight weeks.

Place in therapy

This information in this section is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review (CDR) reviewers for the purpose of this review.

The current standard of care for first-line therapy for persons with UC with a mild to moderate disease activity are oral and/or rectal 5-ASAs. In patients who do not have an adequate response to maximal dose 5-ASA, systemic corticosteroids (most commonly prednisone) may be used in an attempt to induce remission, whereas other patients may simply choose to deal with bothersome symptoms. A medication like budesonide MMX may be a preferred substitute for prednisone in these patients, as it has some efficacy in mild to moderate colitis in promoting treatment response and remission in UC, and may have a favourable side effect profile when compared with systemic corticosteroids. Budesonide MMX may be used in place of systemic corticosteroids for patients who developed a disease flare of mild to moderate severity, yet had been maintained in remission on immunomodulators and/or biologics. There is also the possibility that clinicians may attempt to use longer courses of budesonide MMX to try to maintain remission in patients who had a clinical response to a budesonide MMX–based induction course.

It seems unlikely that budesonide MMX will supplant the use of 5-ASAs as first-line therapy for most patients, yet it may have a role for patients with moderate levels of disease activity in combination with a 5-ASA, particularly in patients in whom initial induction therapy with systemic corticosteroids is being considered.

If budesonide MMX is used in clinical practice, it is unlikely that there will be any major changes in the use of diagnostic tests or strategies, and over the short term, it is unlikely that patients will need close monitoring for signs of toxicity.

Conclusions

Two eight-week, manufacturer-sponsored, multi-centre, double-blind, placebo-controlled RCTs met the inclusion criteria for this systematic review. CORE I and CORE II evaluated the efficacy and safety of budesonide MMX 9 mg in adult patients with active, mild to moderate UC. Results from the CORE studies demonstrated that a greater proportion of patients achieved complete clinical and endoscopic remission with budesonide MMX 9 mg than with placebo. The proportion of patients achieving remission was lower than has been seen in studies of 5-ASAs for mild to moderate UC, although this may be due to the enrolment of a more severe and difficult-to-treat population in the CORE studies. Although cited as an important outcome from patient input, no differences in quality of life according to the IBD-QoL were observed after eight weeks. As there were no head-to-head trials designed to compare budesonide MMX with active treatment, an indirect treatment comparison was provided, but significant limitations with the analysis made the results of the indirect comparison uncertain. Safety results from the CORE studies revealed no increased occurrences of corticosteroid-related adverse events with budesonide MMX compared with placebo, although the study duration was short.

TABLE 1: SUMMARY OF RESULTS

	CORE I			CORE II		
	Budesonide MMX 9 mg	Placebo	Asacol 2,400 mg	Budesonide MMX 9 mg	Placebo	Entocort EC 9 mg
N (ITT)	123	121	124	109	89	103
Clinical remission — primary end point						
Patients with remission at week 8, n (%)	22 (17.9)	9 (7.4)	15 (12.1)	19 (17.4)	4 (4.5)	13 (12.6)
Remission, % (95% CI)	17.9 (11.1 to 24.7)	7.4 (2.8 to 12.1)	12.1 (6.4 to 17.8)	17.4 (10.3 to 24.6)	4.5 (0.2 to 8.8)	12.6 (6.2 to 19.0)
Mean difference versus placebo, % (95% CI), *P* value[a]	10.4 (2.2 to 18.7), 0.0143	-	4.7 (–2.7 to 12.1), 0.2200[b]	12.9 (4.6 to 21.3), 0.0047	-	8.1 (0.4 to 15.9), 0.0481[b]
Clinical improvement (≥ 3-point improvement in UCDAI) — secondary end point						
Patients with improvement at week 8, n (%)	41 (33.3)	30 (24.8)	42 (33.9)	46 (42.2)	30 (33.7)	34 (33.0)
Improvement, % (95% CI)	33.3 (25.0 to 41.7)	24.8 (17.1 to 32.5)	33.9 (25.5 to 42.2)	42.2 (32.9 to 51.5)	33.7 (23.9 to 43.5)	33.0 (23.9 to 42.1)
Mean difference versus placebo, % (95% CI), *P* value[a]	8.5 (–2.8 to 19.9), 0.1420	-	9.1 (–2.3 to 20.4), 0.1189[b]	8.5 (–5.0 to 22.0), 0.2215	-	–0.7 (–14.1 to 12.7), 0.9185[b]
Endoscopic improvement (≥ 1-point improvement in UCDAI mucosal appearance subscore) — secondary end point						
Patients with improvement at week 8, n (%)	51 (41.5)	40 (33.1)	41 (33.1)	46 (42.2)	28 (31.5)	38 (36.9)
Improvement, % (95% CI)	41.5 (32.8 to 50.2)	33.1 (24.7 to 41.4)	33.1 (24.8 to 41.3)	42.2 (32.9 to 51.5)	31.5 (21.8 to 41.1)	36.9 (27.6 to 46.2)
Mean difference versus placebo, % (95% CI), *P* value[a]	8.4[c]	-	0 (–11.8 to 11.8), 0.9991[b]	10.7[c]	-	5.4 (–8.0 to 18.8), 0.4293[b]
IBD-QoL total score — exploratory end point						
Baseline, mean (SD)	146.6 (34.4)	141.1 (39.0)	138.6 (34.1)	140.2 (33.9)	147.7 (34.7)	139.3 (34.4)
Change from baseline at week 8, mean (SD)	19.1 (41.4)	23.2 (42.3)	30.5 (34.7)	21.4 (34.3)	23.7 (39.4)	21.9 (39.5)
Difference versus placebo (95% CI), *P* value[d]	(–10.7 to 8.7), 0.4768	-	(–3.6 to 15.7). 0.2564[b]	(–15.0 to 3.6), 0.5990	-	(–15.1 to 3.6), 0.9117[b]
Harms, n (%)						
N (safety)	**127**	**129**	**127**	**128**	**129**	**126**
Patients with > 0 AEs, n (%)	73 (57.5)	81 (62.8)	80 (63.0)	71 (55.5)	57 (44.2)	69 (54.8)
Patients with > 0 SAEs, n (%)	3 (2.4)	3 (2.3)	4 (3.1)	4 (3.1)	5 (3.9)	1 (0.8)
Patients with > 0 WDAEs, n (%)	15 (11.8)	24 (18.6)	14 (11.0)	24 (18.8)	19 (14.7)	22 (17.5)

	CORE I			CORE II		
	Budesonide MMX 9 mg	Placebo	Asacol 2,400 mg	Budesonide MMX 9 mg	Placebo	Entocort EC 9 mg
N (ITT)	123	121	124	109	89	103
Number of deaths	0	0	0	0	0	0
Notable harms, n (%)						
Glucocorticoid effect	15 (11.8)	13 (10.1)	10 (7.9)	8 (6.3)	13 (10.1)	14 (11.1)
Moon face	0	0	1 (0.8)	2 (1.6)	4 (3.1)	1 (0.8)
Striae rubrae	0	2 (1.6)	0	0	0	0
Flushing	0	1 (0.8)	2 (1.6)	0	1 (0.8)	1 (0.8)
Fluid retention	2 (1.6)	1 (0.8)	1 (0.8)	0	2 (1.6)	0
Mood changes	5 (4.0)	3 (2.3)	2 (1.6)	2 (1.6)	7 (5.4)	6 (4.8)
Sleep changes	4 (3.2)	7 (5.4)	1 (0.8)	3 (2.3)	4 (3.1)	7 (5.6)
Insomnia	5 (4.0)	6 (4.7)	2 (1.6)	1 (0.8)	2 (1.6)	3 (2.4)
Acne	3 (2.4)	3 (2.3)	4 (3.1)	1 (0.8)	2 (1.6)	3 (2.4)
Hirsutism	0	0	1 (0.8)	0	0	1 (0.8)

AE = adverse event; CI = confidence interval; IBD-QoL = Inflammatory Bowel Disease Quality of Life Questionnaire; ITT = intention-to-treat; MMX = Multi Matrix System; SAE = serious adverse event; SD = standard deviation; UCDAI = Ulcerative Colitis Disease Activity Index; WDAE = withdrawal due to adverse event.

[a] *P* values were calculated using the chi-square test, with a significance level of 0.025 for comparisons of budesonide MMX versus placebo and 0.05 for comparison of Asacol or Entocort EC versus placebo. Results are presented for the worst-case scenario for missing data.

[b] The study was not powered to detect a difference between Asacol (CORE I) or Entocort EC (CORE II) and placebo.

[c] Statistical comparison of endoscopic improvement of budesonide MMX 9 mg versus placebo was not conducted as this end point fell below a non-statistically significant parameter in the testing hierarchy.

[d] *P* values were calculated using the Wilcoxon rank-sum test, with all tests conducted at a significance level of 0.05. Missing data were imputed using the last observation carried forward method.

Source: Clinical Study Reports.[1,2]

1. INTRODUCTION

1.1 Disease prevalence and incidence

Ulcerative colitis (UC) and Crohn's disease (CD) are both forms of inflammatory bowel disease (IBD), although the two are considered distinct from each other. UC is found in the colon, and the inflammation leads to diarrhea, pain, and bloody stools. Patients also experience extra-intestinal symptoms such as fatigue and weight loss. If left untreated, inflammation may progress, leading to mucosal damage and potentially fatal complications such as perforation and sepsis. Chronic inflammation is a recognized risk factor for malignancy, and patients with UC are at increased risk of developing colon cancer.

According to the Crohn's and Colitis Foundation of Canada in 2012, there were approximately 233,000 Canadians living with IBD, with 104,000 diagnosed with UC.[3] More than 10,200 new cases of IBD are diagnosed every year (5,700 with CD and 4,500 with UC), an incidence of 0.7%; 20% to 30% of people with IBD are diagnosed before the age of 20 years.[3] Canada has one of the highest incidences and prevalences of IBD in the world.[3]

1.2 Standards of therapy

As there is no cure for UC, the goal of therapy is the induction and maintenance of systemic steroid-free remission. According to the *Canadian Clinical Practice Guidelines for Ulcerative Colitis* (2015), the recommended first-line treatment for patients with mild to moderate UC for induction and maintenance of remission is 5-aminosalicylic acid (5-ASA) therapy, which include sulfasalazine, olsalazine, and mesalamine/mesalazine in various oral and rectal formulations.[4] For patients with mild to moderate UC who are unable to obtain complete remission with 5-ASA therapy, oral or rectal corticosteroids are recommended for induction of remission.[4] Corticosteroids are not recommended for maintaining complete remission, as their prolonged use is associated with adverse effects.[4] The use of immunosuppressants such as thiopurines is not recommended for the induction of remission, but may be used to maintain corticosteroid-free remission.[4] Methotrexate is not recommended for the induction or maintenance of remission.[4] Biologics such as anti-tumour necrosis alpha agents are recommended for patients with moderate to severe UC who have failed on other therapies.[4] Non-pharmacological measures include dietary and lifestyle changes, and surgery, which is the ultimate outcome in a number of patients.

1.3 Drug

Budesonide is a corticosteroid with anti-inflammatory properties, although the precise mechanism of action is not known. Budesonide has extensive first-pass hepatic metabolism, which decreases systemic bioavailability, and has been available in oral and rectal formulations for the management of UC and CD. Budesonide MMX is an oral formulation of budesonide that uses Multi Matrix colonic delivery technology to permit the release of budesonide at a controlled rate throughout the colon.[5] Budesonide MMX is available as 9 mg delayed- and extended-release tablets for oral administration. The Health Canada indication is for the induction of remission in patients with active, mild to moderate UC. The recommended dose is one tablet per day in the morning for up to eight weeks.

Indication under review
For the induction of remission in patients with active, mild to moderate ulcerative colitis.
Reimbursement criteria requested by sponsor
As per indication

Table 2: Key Characteristics of Drugs for the Induction of Remission in Mild to Moderate Ulcerative Colitis

	Budesonide MMX	5-ASAs	Systemic Corticosteroids
Mechanism of Action	Anti-inflammatory corticosteroid with targeted release to the colon — exact mechanism of action unknown.	Reduces synthesis of inflammatory mediators (e.g., cytokines, prostaglandins), immunosuppressants, and bacteriostatic.	Anti-inflammatory actions — exact mechanism of action unknown.
Indication[a]	For the induction of remission in patients with active, mild to moderate UC. The safety and efficacy in children aged ≤ 18 years have not been established.	For the treatment of mild to moderate active UC and the maintenance of remission of mild to moderate UC. The safety and efficacy in children have not been established.	To tide the patient over in a critical period of the disease in UC.
Route of Administration	Oral	Oral or rectal	Oral or rectal
Recommended Dose[b]	9 mg once daily	Mesalamine/mesalazine (Asacol, 400 mg slow-release [pH >7] tablets): 800 mg to 3,200 mg daily taken orally in divided doses. Mesalamine/mesalazine MMX (Mezavant, 1.2 g delayed- and extended-release tablets): 2.4 g to 4.8 g taken orally once daily. Mesalamine/mesalazine rectal (Salofalk, 500 mg and 1,000 mg suppositories): 1,000 mg to 1,500 mg per day. Mesalamine/mesalazine rectal (Pentasa, 1 g and 4 g enema, or 1 g suppositories): 1 g to 4 g enema once daily, or 1 g suppository once daily. Olsalazine (Dipentum, 250 mg capsules): 500 mg to 3,000 mg daily taken orally	Betamethasone sodium phosphate (Betnesol, 5 mg/100 mL enema): one enema nightly for 2 to 4 weeks. Hydrocortisone: individualized dosage according to severity of disease and patient's response. Prednisone: individualized dosage according to severity of disease and patient's response.

	Budesonide MMX	5-ASAs	Systemic Corticosteroids
		in divided doses (each dose not to exceed 1 g). Sulfasalazine (Salazopyrin, 500 mg tablets): 2 tablets taken orally 3 to 4 times daily.	
Serious Side Effects / Safety Issues	Corticosteroid-related short- and long-term adverse effects (e.g., weight gain, blurred vision, suppressed growth)	Bone marrow suppression, heart problems, hepatic failure, nephrotoxicity	Corticosteroid-related short- and long-term adverse effects (e.g., weight gain, blurred vision, suppressed growth)

5-ASA = 5-aminosalicylic acid; MMX = Multi Matrix System; UC = ulcerative colitis.
[a] Health Canada indication.
[b] Recommended dosing in adult patients.
Source: Health Canada product monographs: Cortiment,[6] Asacol,[7] Mezavant,[8] Salofalk,[9] Pentasa,[10] Dipentum,[11] Salapyrin,[12] Betneso.[13]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of oral budesonide Multi Matrix System for the induction of remission in patients with active, mild to moderate ulcerative colitis.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with active, mild to moderate ulcerative colitis Subgroups of interest: • Severity of disease (mild/moderate) • Extent of disease (proctosigmoiditis/left-sided/extensive) • Prior 5-ASA use (yes/no) • Prior corticosteroid use (yes/no) • Duration of disease • Age
Intervention	Oral budesonide Multi Matrix System 9 mg
Comparators	• 5-ASAs (e.g., mesalamine, olsalazine, sulfasalazine) • Corticosteroids (e.g., prednisone, hydrocortisone, betamethasone, rectal budesonide) • Immunomodulators (e.g., thiopurines, methotrexate) • Biologics (e.g., adalimumab, golimumab, infliximab, vedolizumab) • Placebo
Outcomes	**Key efficacy outcomes:** Clinical and endoscopic remission Clinical and endoscopic response HRQoL as measured by a validated scale[a] Outcomes measuring function and disability **Other efficacy outcomes:** Mucosal healing determined by histology **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms: corticosteroid-related AEs
Study Design	Published and unpublished phase III RCTs

5-ASA = 5-aminosalicylic acid; AE = adverse event; DB = double-blind; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] In the input received by CADTH from patient groups, these outcomes were identified as being of particular importance to patients.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were budesonide/Cortiment^{MMX} and delayed-release formulation.

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on June 21, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on October 19, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4: Details of Included Studies and described in section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

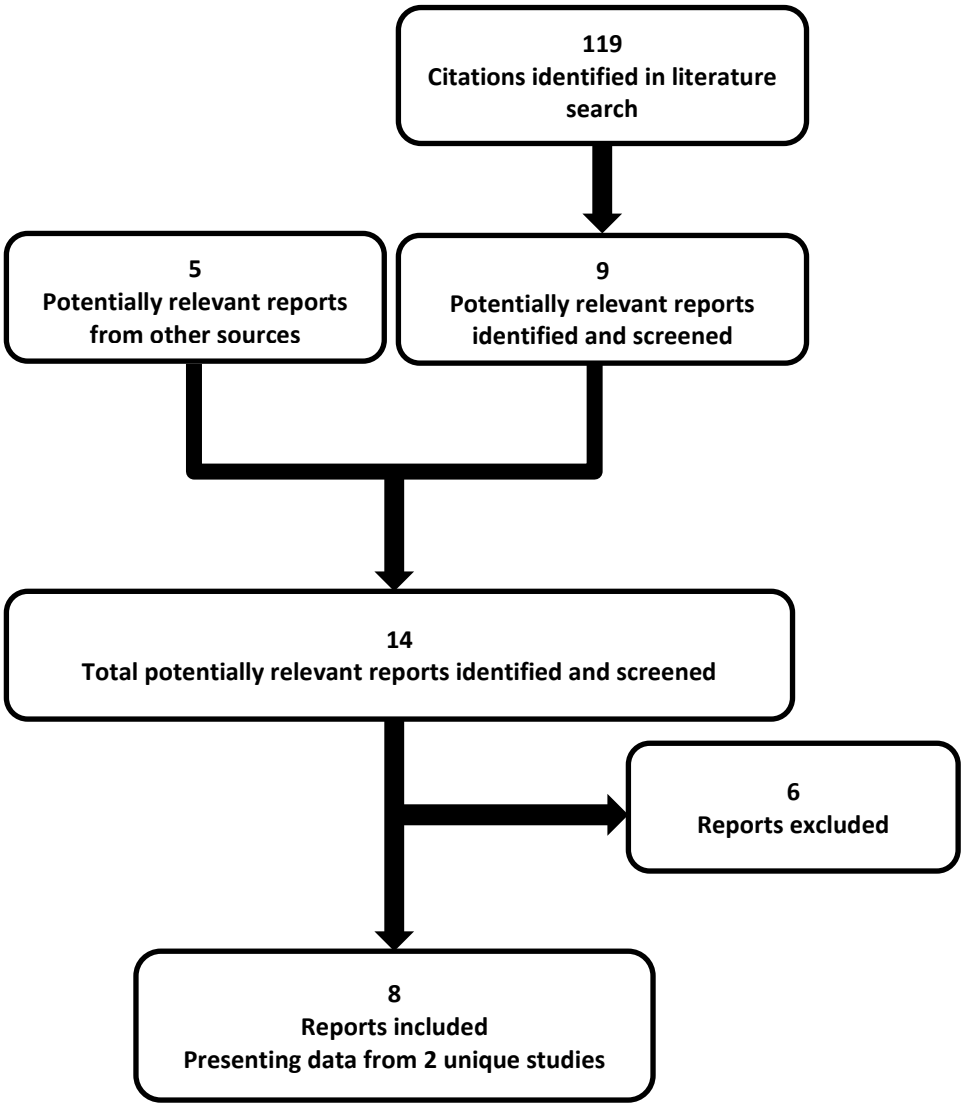


TABLE 4: DETAILS OF INCLUDED STUDIES

		CORE I	CORE II
DESIGNS & POPULATIONS	**Study Design**	DB DD PG RCT	
	Locations	108 centres in 4 countries: Canada, US, Mexico, India	69 centres in 15 countries: Europe, Russia, Israel, Australia
	Randomized (N)	510	512
	Inclusion Criteria	Patients aged 18 to 75 years with active mild to moderate UC (UCDAI score 4 to 10) for at least 6 months	
	Exclusion Criteria	• Diagnosis of severe UC (UCDAI > 10) • Presence of limited distal proctitis (from anal verge up to 15 cm above the pectineal line), infectious colitis, or a history of toxic megacolon • Presence of severe anemia, leucopenia, or granulocytopenia • Use of the following drugs: oral or rectal steroids in last 4 weeks; immunosuppressive drugs in last 8 weeks; use of anti-TNF alpha drugs in last 3 months • Presence of liver cirrhosis, renal disease or insufficiency, and/or impairment of biohumoral parameters (2 × ULN of ALT, AST, GGT, or creatinine) • Diagnosis of type 1 diabetes, glaucoma, hepatitis B, hepatitis C, or HIV • Concomitant use of any rectal preparations, antibiotics, or cytochrome P450 3A4 inducers or inhibitors • Presence of complications requiring therapy with corticosteroids and/or immunosuppressive agents	
DRUGS	**Intervention**	Budesonide MMX 9 mg orally once daily Budesonide MMX 6 mg orally once daily[a]	
	Comparator(s)	Placebo Mesalamine (Asacol, 400 mg tablets) 2,400 mg orally over 3 doses (2 tablets per dose) daily	Placebo Budesonide (Entocort EC, 3 mg slow-release capsules) 9 mg (3 capsules) once daily
DURATION	**Phase**		
	Washout	2 days	
	DB	8 weeks	
	Follow-up	2 weeks (safety)	
OUTCOMES	**Primary End Point**	Clinical remission at week 8, defined by the following: UCDAI score ≤ 1 with subscores of 0 for rectal bleeding and stool frequency; normal mucosa by endoscopy; a ≥ 1-point reduction in endoscopy score from baseline.	
	Other End Points	**Secondary** • Clinical improvement (≥ 3-point improvement in UCDAI from baseline at week 8 • Endoscopic improvement (≥ 1-point improvement in mucosal appearance subscore from baseline to week 8) **Other** • Symptom resolution (UCDAI stool frequency and rectal bleeding subscores of 0) • Histological healing (total histological score ≤ 1 for all biopsy specimens) • IBD-QoL scores • CAI score ≤ 4 • Treatment failure (worsening of UC) after 8 weeks	

		CORE I	CORE II
NOTES	**Publications**	Sandborn et al., 2012[14]	Travis et al., 2013[15]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAI = Clinical Activity Index; DB = double-blind; DD = double-dummy; GGT = gamma-glutamyl transferase; IBD-QoL = Inflammatory Bowel Disease Quality of Life Questionnaire; MMX = Multi Matrix System; NR = not reported; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; TNF = tumour necrosis factor; UC = ulcerative colitis; UCDAI = Ulcerative Colitis Disease Activity Index; ULN = upper limit of normal.
Note: Four additional reports were included (CADTH Common Drug Review submission,[16] FDA Medical Review,[17] FDA Statistical Review,[18] European Medicines Agency Public Assessment Report[19]).
[a] The 6 mg dose does not have a Health Canada indication for UC.
Source: Clinical Study Reports.[1,2]

3.2 Included studies

3.2.1 Description of studies

CORE I (N = 510) and CORE II (N = 512) were multi-centre, double-blind, double-dummy, randomized controlled trials that evaluated the efficacy and safety of budesonide MMX 9 mg and 6 mg compared with placebo in adult patients with active, mild to moderate UC. The CORE I study also included a mesalamine (Asacol) group, while the CORE II study included a budesonide (Entocort EC) group. Only the results for the budesonide MMX 9 mg group will be presented, as this is the dose of interest for this review (the 6 mg dose does not have a Health Canada–approved indication for UC).

The CONTRIBUTE study was a double-blind, placebo-controlled randomized controlled trial (RCT) conducted in the US that evaluated the efficacy and safety of budesonide MMX 9 mg compared with placebo in adult patients with active, mild to moderate UC who were inadequately controlled with oral 5-ASAs.The CONTRIBUTE study was submitted by the manufacturer in abstract format. As there are currently no publications or clinical study reports for this study, results are not presented here.

3.2.2 Populations

a) Inclusion and exclusion criteria

In the CORE studies, patients aged between 18 and 75 years with active, mild to moderate UC for at least six months, as determined by a UCDAI score between 4 and 10, were eligible for inclusion. Patients were excluded if they had a diagnosis of severe UC (UCDAI > 10), or the presence of limited distal proctitis, infectious colitis, or toxic megacolon. Patents with blood disorders (anemia, leucopenia, granulocytopenia), liver cirrhosis, or renal disease were also excluded. Patients were excluded if they had used the following drugs within a period of time prior to enrolment: oral or rectal steroids in the last four weeks; immunosuppressive drugs in the last eight weeks; anti-tumour necrosis factor alpha (TNF alpha) drugs in the last three months.

b) Baseline characteristics

The mean age of patients ranged from 41 to 45 years across the treatment groups in the CORE studies, and the proportion of males ranged from 53% to 63%. In the CORE I study, approximately 50% of patients were white and 34% of patients were Asian, while in the CORE II study, almost all patients were white. The median time since diagnosis of UC was 3.3 years in CORE I and 3.9 years in CORE II. In both studies, the majority of patients had had a diagnosis of UC for more than one year. The proportion of patients with proctosigmoiditis, left-sided colitis, or extensive/pancolitis was generally evenly distributed between groups in both studies. The median number of flares in the last two years was two, and ranged from zero to 90 flares in CORE I and zero to 15 flares in CORE II. Approximately 56.1% of

patients in the CORE I study and 57.8% of patients in the CORE II study had previously used mesalazine/mesalamine for UC. Approximately 5.1% of patients in the CORE I study and 23.1% of patients in the CORE II study had previously used sulfasalazine.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2,400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (ITT)	**123**	**121**	**124**	**109**	**89**	**103**
Demographics						
Age, mean years (SD)	41.5 (12.4)	41.0 (13.4)	43.8 (12.3)	42.8 (13.9)	44.8 (13.0)	43.4 (14.0)
Age, median years (range)	42 (19 to 68)	39 (18 to 77)	45 (18 to 72)	44 (20 to 69)	42 (19 to 74)	445 (19 to 75)
Male, n (%)	77 (63)	68 (56)	69 (56)	64 (59)	57 (64)	55 (53)
White, n (%)	60 (49)	64 (53)	61 (49)	107 (98)	89 (100)	103 (100)
Asian, n (%)	44 (36)	39 (32)	43 (35)	1 (1)	0	0
Disease history						
Age at diagnosis, median years (range)	34 (13 to 66)	33 (16 to 73)	35 (5 to 68)	35 (13 to 66)	35 (14 to 68)	37 (12 to 67)
Duration of disease, median years (range)	3.2 (0 to 40)	2.8 (0 to 38)	4.8 (0 to 49)	3.2 (0 to 38)	4.0 (0 to 49)	4.6 (0 to 31)
≤ 1 year, n (%)	34 (28)	35 (29)	23 (19)	22 (20)	15 (17)	19 (18)
>1 to ≤ 5 years, n (%)	43 (35)	44 (36)	42 (34)	49 (45)	36 (40)	39 (38)
> 5 years, n (%)	46 (37)	42 (35)	59 (48)	38 (35)	38 (43)	45 (44)
Disease extent, n (%)						
Proctosigmoiditis	34 (28)	41 (34)	37 (30)	[redacted]	[redacted]	[redacted]
Left-sided colitis	32 (26)	34 (28)	35 (28)	[redacted]	[redacted]	[redacted]
Extensive/pancolitis	56 (46)	40 (33)	52 (42)	[redacted]	[redacted]	[redacted]
Number of flares in last 2 years, median (range)	2 (0 to 90)	2 (0 to 24)	2 (0 to 80)	3 (0 to 8)	2 (0 to 15)	2 (0 to 15)
Severity of last flare, n (%)						
Mild	31 (25)	30 (25)	25 (20)	[redacted]	[redacted]	[redacted]
Moderate	82 (67)	79 (65)	81 (65)	[redacted]	[redacted]	[redacted]
Baseline UCDAI score, median (range)	7 (2 to 10)	7 (1 to 11)	7 (2 to 11)	7 (3 to 10)	7 (2 to 10)	7 (2 to 11)
Baseline Endoscopic Index Score, median (range)	7 (3 to 12)	7 (0 to 12)	8 (1 to 12)	7 (3 to 12)	7 (3 to 12)	7 (3 to 12)
Treatment history						
N (safety)	**127**	**129**	**127**	**128**	**129**	**126**
Any prior medication, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mesalamine/mesalazine	[redacted]	[redacted]	[redacted]	66 (52)	75 (58)	70 (56)
Sulfasalazine	[redacted]	[redacted]	[redacted]	33 (26)	28 (22)	30 (24)
Folic acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2,400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (ITT)	**123**	**121**	**124**	**109**	**89**	**103**
Bisacodyl	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multivitamin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hydrocortisone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITT = intention-to-treat; MMX = Multi Matrix System; SD = standard deviation; UCDAI = Ulcerative Colitis Disease Activity Index.
Source: Clinical Study Reports.[1,2]

3.2.3 Interventions

In the CORE studies, patients were administered treatment regimens in a double-dummy design (Table 6 and Table 7). Budesonide MMX 9 mg was administered once daily after breakfast. In CORE I, Asacol was administered over three doses of two 400 mg tablets each daily. In CORE II, Entocort EC was administered over one dose of three 3 mg tablets after breakfast.

TABLE 6: TREATMENT REGIMENS IN CORE I

Time of Day	Budesonide MMX 9 mg	Placebo	Asacol
After breakfast	• One budesonide MMX 9 mg tablet • Two Asacol-matching placebo tablets	• One budesonide MMX–matching placebo tablet • Two Asacol-matching placebo tablets	• One budesonide MMX–matching placebo tablet • Two Asacol 400 mg tablets
After midday meal	• Two Asacol-matching placebo tablets	• Two Asacol-matching placebo tablets	• Two Asacol 400 mg tablets
After evening meal	• Two Asacol-matching placebo tablets	• Two Asacol-matching placebo tablets	• Two Asacol 400 mg tablets

MMX = Multi Matrix System.
Source: Clinical Study Report.[1]

TABLE 7: TREATMENT REGIMENS IN CORE II

Time of day	Budesonide MMX 9 mg	Placebo	Entocort EC
After breakfast	• One budesonide MMX 9 mg tablet • Three Entocort EC–matching placebo capsules	• One budesonide MMX–matching placebo tablet • Three Entocort EC–matching placebo capsules	• One budesonide MMX–matching placebo tablet • Three Entocort EC 3 mg capsules

MMX = Multi Matrix System.
Source: Clinical Study Report.[2]

In CORE I and II, patients underwent a two-day washout period prior to double-blind treatment, during which they were not to use drugs for the treatment of UC. Concomitant medications for the treatment of UC were not permitted during the study. In addition, the use of antibiotics, pro-kinetic and anti-motility agents, and CYP3A4, 5 and 7 inhibitors and inducers were prohibited during the study.

Treatment compliance was determined by comparing the amount of drug dispensed with the amount of drug returned, and patients who had taken 80% to 120% of their study drug were regarded as compliant.

3.2.4 Outcomes

a) Clinical and endoscopic remission and response

The primary end point in the CORE studies was clinical and endoscopic remission at week 8. To be considered in remission, patients had to meet the following criteria: UCDAI score ≤ 1 with subscores of 0 for rectal bleeding and stool frequency; a normal mucosa by endoscopy; a ≥ 1-point reduction in Endoscopic Index Score from baseline.

The UCDAI was assessed at screening and day 56 (week 8). The UCDAI comprises four components: stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity. Each component is scored from 0 (normal or none) to 3 (stool frequency, > 4 stools/day; rectal bleeding, mostly blood; mucosal appearance, exudation and spontaneous bleeding; physician's rating, severe). The total UCDAI score is the sum of the score of the four component subscores, and scores can range from 0 to 12, with higher scores indicating more severe disease. No minimal clinically important difference (MCID) for the total UCDAI score was identified (see 0).

Clinical improvement was a secondary end point and defined as a ≥ 3-point improvement in UCDAI score from baseline to week 8. Endoscopic improvement was a secondary end point and defined as a ≥ 1-point improvement in the UCDAI mucosal appearance subscore from baseline to week 8. Symptom resolution was an exploratory end point and was defined as having UCDAI stool frequency and rectal bleeding subscores of 0.

The Endoscopic Index (EI) Score is based on endoscopic data of four macroscopic criteria: vascular pattern of mucosa (0 = normal, 1 = faded/disturbed, or 2 = completely absent), granulation scattering reflection of light (0 = no, 2 = yes), mucosal damage (0 = none, 2 = slight [< 10 ulcers per 10 cm mucosa], or 4 = pronounced [≥ 10 ulcers per 10 cm mucosa]), and vulnerability of the mucosa (0 = none, 2 = slightly increased [contact bleeding], or 4 = greatly increased [spontaneous bleeding]).[20] The total score is obtained by summing all of the individual criteria scores, and endoscopic remission is defined as an EI < 4.[20] No MCID for the EI score was identified (see 0).

b) Clinical Activity Index

The Clinical Activity Index (CAI) is a tool that assesses disease activity in patients with UC. Seven clinical features are evaluated,[20] with the total index score ranging from 0 to 25: 0 to 4 inactive (remission); 5 to 10 mild activity; 11 to 17 moderate activity; and ≥ 18 high activity.[21] It combines objective and subjective measures, for which individual scores are assigned. The objective measures include extra-intestinal UC manifestations (0 = none, 3 = iritis, 3 = erythema nodosum, or 3 = arthritis), number of stools per week (0 = < 18, 1 = 18 to 35, 2 = 36 to 60, or 3 = > 60), sublingual temperature (0 = ≤ 38°C or 3 = > 38°C), and laboratory findings (0 = erythrocyte sedimentation rate [ESR] after one hour of ≤ 50 mm and hemoglobin [Hb] ≥ 10 g/dL; 1 = ESR after one hour of > 50 and ≤ 100 mm; 2 = ESR after one hour > 100 mm; or 4 = Hb < 10 g/dL).[20] The three subjective measures include general well-being during the previous week (0 = good, 1 = average, 2 = poor, 3 = very poor), blood in stool in the previous week (0 = none or once, 2 = a little [≤ 30%], 4 = a lot [> 30]), and a sum of abdominal pain and/or cramps incidences in the previous week (0 = none, 1 = mild, 2 = moderate, 3 = severe).[20] Clinical remission for the CAI is defined as CAI ≤ 4.[20] No MCID for the CAI score was identified (see 0).

The CAI score was assessed at screening, day 14, day 28, and day 56. Investigators used the highest score for blood in stool, abdominal pain and/or cramps, and temperature due to colitis that occurred in the seven days prior to the visit excluding the colonoscopy day. The proportion of patients achieving a CAI score ≤ 4 was an exploratory end point in the CORE studies.

c) Inflammatory Bowel Disease Quality of Life Questionnaire

The Inflammatory Bowel Disease Quality of Life Questionnaire (IBD-QoL), a 32-item questionnaire, is a disease-specific (CD and UC) instrument that captures how the participant felt during the two weeks before the measurement time point. Questions are related to symptoms the patient might have had as a result of UC, how the patient felt in general, how the patient's mood was, and social or work problems the patient might have had resulting from UC. The total IBD-QoL score ranges between 32 and 224, with higher scores representing better quality of life. The scores of patients in remission usually range from 170 to 190. The MCID for the IBD-QoL is considered to be between 16 and 32 points for CD; no MCID was found for UC (see 0).

d) Mucosal healing

A colonoscopy was performed at screening and day 56 (week 8), during which three biopsies were taken from the colonic lesions considered to be most severe. Each specimen was examined by a central histopathologist who was blinded to treatment allocation. The histological activity grade was determined using criteria developed by Saverymuttu et al., 1986.[22] The Saverymuttu histological assessment assigns scores within four categories from 0 (normal) to 3: enterocytes (3 = frank ulceration), crypts (3 = crypt abscesses), mononuclear cells (3 = marked increase), and neutrophils (3 = marked increase). Histologic healing was an exploratory end point and defined as having a total histologic score of ≤ 1 for all biopsy specimens.

e) Harms

Adverse events (AEs) were defined as any untoward medical occurrence during the course of the study, whether or not thought to be related to the study drug. All AEs were recorded from the time the patient signed the informed consent form until 14 days following the last study drug administration. Treatment-emergent AEs were defined as AEs that occurred after administration of study drug or, if present before treatment, which increased in intensity following commencement of treatment. Serious adverse events (SAEs) included any unexpected medical occurrence that resulted in death, was considered life-threatening, or resulted in disability or hospitalization.

Glucocorticoid-related AEs were followed until stabilization of the event or until 28 days after the last study drug administration. Glucocorticoid-related AEs included moon face, striae rubrae, flushing, fluid retention, sleep changes, insomnia, acne, hirsutism, and mood changes. Morning plasma cortisol concentrations were taken at each visit.

3.2.5 Statistical analysis

a) Sample size calculation

In the CORE studies, assuming remission rates of 27% for placebo (based on two previous studies of Entocort EC in CD) and 47% for budesonide MMX (based on a phase II study of budesonide MMX 9 mg in UC), 110 patients per group provided 80% power to detect a statistically significant difference between budesonide MMX and placebo at the two-sided significance level of 0.025. Assuming a dropout rate of 10%, 123 patients per group were planned for budesonide MMX and placebo. Although the study was not powered to detect a difference between budesonide MMX and Asacol (CORE I) or Entocort EC (CORE II), 123 patients were also planned to be randomized to the Asacol and Entocort EC groups.

b) Primary end point

The chi-square test at a significance level of 0.025 was used to compare the proportion of patients with clinical remission at week 8 in the budesonide MMX group versus the placebo group.

c) Secondary end points

A testing hierarchy was employed for the secondary end points in the following order if at least one primary end point comparison was statistically significant: clinical improvement or endoscopic improvement. A significance level of 0.025 was used for the comparison of each budesonide MMX group and placebo.

d) Other end points

Statistical analyses for other end points were conducted if at least one primary end point comparison between budesonide MMX and placebo was statistically significant.

e) Missing data

If the UCDAI could not be calculated for a patient because of missing data, the patient was excluded from the analysis (observed case). For clinical improvement, endoscopic improvement, symptom resolution, histological healing, and CAI end points, missing data that resulted in the inability to calculate the end point resulted in either exclusion of the patient from the analysis (observed case) or the assumption that the patient did not meet the end point (worst case). For IBD-QoL, last observation carried forward (LOCF) was used for missing data in which the previous calculation of the IBD-QoL was carried forward — baseline values were not carried forward.

f) Analysis populations

Intention-to-treat (ITT) analysis population: All patients who received at least one dose of study drug, had no major entry criteria or Good Clinical Practice (GCP) violations, and had no histologic evidence of active disease at baseline. The ITT population was used for the analysis of all efficacy end points and patients were analyzed according to their randomized treatment assignment. The definition of the ITT population was modified after a protocol amendment prior to unblinding of the study from an original definition of all randomized patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment.

Per-protocol (PP) population: All patients in the ITT population who completed the study or were treated with the randomized study drug for at least 14 days before withdrawal due to treatment failure and did not have major protocol violations.

Safety analysis population: All patients who received at least one dose of study drug. Patients were analyzed according to the actual treatment received.

3.3 Patient disposition

In the CORE I study, 35% of patients in the placebo group discontinued treatment during the study, compared with 27% in the budesonide MMX group and 23% in the Asacol group (Table 8). Discontinuations between groups were generally similar in the CORE II study, and ranged from 22% in the placebo group to 28% in the Entocort EC group. The most common reasons for discontinuation were treatment failure and withdrawal of consent.

TABLE 8: PATIENT DISPOSITION

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
Screened, N	803[a]			613[a]		
Randomized, N (%)	510[a]			512[a]		
	127 (100)	128 (100)[b]	127 (100)	128 (100)	129 (100)	126 (100)
Discontinued, n (%)	34 (27)	45 (35)	29 (23)	33 (26)	28 (22)	35 (28)
Adverse event	6 (5)	10 (8)	7 (6)	2 (2)	1 (1)	3 (2)
Loss to follow-up	5 (4)	4 (3)	2 (2)	1 (1)	1 (1)	0
Investigator decision	2 (2)	2 (2)	2 (2)	2 (2)	1 (1)	2 (2)
Protocol violation	1 (1)	2 (2)	1 (1)	0	0	0
Treatment failure	9 (7)	14 (11)	8 (6)	21 (16)	17 (13)	21 (17)
Withdrew consent	11 (9)	10 (8)	9 (7)	6 (5)	7 (5)	7 (6)
Other	0	3 (4)	0	1 (1)	1 (1)	1 (1)
Excluded from ITT, n (%)	4 (3)	8 (6)	3 (2)	17 (13)	40 (31)	23 (18)
Infectious colitis at entry	1 (1)	1 (1)	0	0	0	0
Normal histology at entry	3 (2)	6 (5)	3 (2)	12 (9)	33 (26)	16 (13)
GCP violation	0	0	0	9 (7)	20 (16)	12 (10)
Treated but not randomized	0	0	0	1 (1)	1 (1)	0
Major entry criteria violation	0	0	0	1 (1)	0	0
ITT, N (%)	123 (97)	121 (95)	124 (98)	109 (85)	89 (69)	103 (82)
PP, N (%)	69 (54)	61 (48)	73 (57)	84 (66)	67 (52)	72 (57)
Safety, N (%)	127 (100)	129[b]	127 (100)	128 (100)	129 (100)	126 (100)

GCP = Good Clinical Practice; ITT = intention-to-treat; MMX = Multi Matrix System.
[a] Includes patients randomized to the budesonide MMX 6 mg group (not presented).
[b] One patient randomized to the budesonide MMX 6 mg group (not presented) received placebo instead.
Source: Clinical Study Reports.[1,2]

3.4 Exposure to study treatments

Treatment compliance was determined by comparing amount of drug dispensed with the amount of drug returned, and was presented for tablets (budesonide MMX) and capsules (Asacol or Entocort EC). More than 80% of patients were considered to be compliant with tablets and capsules (80% to 120% of drug taken). The median exposure across treatment groups was 56 days (8 weeks).

TABLE 9: TREATMENT COMPLIANCE AND EXPOSURE; SAFETY POPULATION

	CORE I			CORE II		
	Budesonide MMX 9 mg	Placebo	Asacol 2,400 mg	Budesonide MMX 9 mg	Placebo	Entocort EC 9 mg
N (safety)	**127**	**129**	**126**	**128**	**129**	**126**
Tablet compliance (budesonide MMX), n (%)						
< 80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80% to 120%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 120%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Capsule compliance (Asacol or Entocort EC), n (%)						
< 80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80% to 120%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 120%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Duration of treatment (days)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MMX = Multi Matrix System; SD = standard deviation.
Source: Clinical Study Reports.[1,2]

3.5 Critical appraisal

3.5.1 Internal validity

The definition of the ITT population was modified after a protocol amendment prior to unblinding of the CORE studies. The updated definition excluded patients (CORE I: 6% versus 3%; CORE II: 31% versus 13%, placebo versus budesonide MMX, respectively) who had major entry criteria or GCP violations or histologic evidence of active disease at baseline. Although this may be clinically appropriate, the number of patients included in the updated ITT in CORE II (109 in the budesonide MMX group; 89 in the placebo group) may not have been sufficient to meet original power calculations (110 patients per group). Because of the exclusion of patients from the original ITT population after the protocol amendment, it is unclear whether randomization would have been appropriately maintained across treatment groups. Regardless, it is unclear whether this would have biased the results in favour of the budesonide MMX treatment group or the placebo group. There was a high incidence of discontinuations across groups in both CORE trials (22% to 35%), with the most common reasons being treatment failure and withdrawal of consent.

A double-dummy design was used to maintain blinding across the three treatment groups in each study. However, corticosteroid-related AEs are associated with treatments like budesonide, and may have potentially resulted in participants knowing if they were on treatment with budesonide MMX. However, AE data suggested that the incidence of corticosteroid-related AE was similar across treatment groups, and therefore this is less of a concern.

The placebo group demonstrated that a proportion of patients achieved complete remission, clinical remission, and endoscopic remission, as determined by UCDAI and CAI scores and subscores. This suggests that there was a large placebo effect in the CORE studies, which may have made it increasingly difficult to ascertain differences between active treatment versus placebo.

Missing data were imputed using different methods for different outcomes — worst case and observed case. However, only the worst-case analysis was presented in this review, as it is the more conservative method.

3.5.2 External validity

The clinical expert consulted for this review noted that an eight-week study duration would be sufficient to detect a clinical response, but not necessarily complete remission as defined in the trial, which also included an endoscopic component. In clinical practice, remission is commonly defined according to clinical symptoms rather than endoscopic parameters as in the trial, and access to endoscopy would vary across providers, which may limit generalizability of the results. The clinical expert also noted that the patient population enrolled may have more advanced disease (median three to four years since diagnosis) and be less responsive to medications because of failure to other therapies. The majority of patients had prior experience with 5-ASAs, although few patients had prior experience with systemic corticosteroids or biologics.

The washout period used prior to treatment in the CORE studies was two days. According to the clinical expert, this is likely a sufficient amount of time to wash out 5-ASA from systemic circulation, but not necessarily enough time to wash out the effect of 5-ASA at a cellular level. As the majority of patients were previously on 5-ASA therapy, there may have been residual 5-ASA activity that contributed to the clinical effectiveness seen across treatment groups, including placebo.

According to the clinical expert, the use of the specific scoring systems like the UCDAI and IBD-QoL applied in the clinical trials are not necessarily used in clinical practice, where definitions of clinical response and remission may be more qualitative than quantitative.

The current first-line therapy for patients with UC is 5-ASAs. The next available treatment option for patients with UC are systemic corticosteroids such as prednisone, or no additional treatment, as some patients may choose to deal with the symptoms. The clinical expert consulted for the review indicated that budesonide MMX would likely be considered for use if patients are inadequately controlled on 5-ASAs. Therefore, budesonide MMX would be considered an alternative treatment to systemic corticosteroids or as an alternative to no additional treatment after 5-ASAs in patients who choose not to take systemic corticosteroids. The CORE studies compared budesonide MMX to placebo, and therefore do not provide evidence for a more relevant comparator such as prednisone. Although Asacol (5-ASA) was used as a reference arm in CORE I, budesonide MMX is likely to be used after an inadequate response with 5-ASA therapy.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (section 2.2, Table 3). See 0 for detailed efficacy data.

3.6.1 Clinical and endoscopic remission

In both CORE studies, the proportion of patients who achieved complete remission at week 8 was greater in the budesonide MMX group compared with the placebo group (CORE I: 17.9% versus 7.4%; CORE II: 17.4% versus 4.5%). The mean difference in proportion of patients achieving remission with budesonide MMX compared with placebo was statistically significant in both studies (CORE I: 10.4%; 95% confidence interval [CI] 2.2% to 18.7%; *P* = 0.0143; and CORE II: 12.9%; 95% CI, 4.6% to 21.3%, *P* = 0.0047). Clinical remission in the PP populations was similar to those observed in the ITT populations.

a) Subgroup analyses

Subgroup analyses by age were performed for the primary end point in the individual CORE studies (Table 12). The analyses were performed using mean age of the population as a cut-off (42 years in CORE I, 43.5 years in CORE II). In CORE I, the mean difference in the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 1.3% (95% CI, –9.2% to 11.7%) in patients aged 42 years or younger and 21.0% (95% CI, 8.8% to 33.2%) in patients older than 42 years. In CORE II, the mean difference in the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 15.9% (95% CI, 3.6% to 28.2%) in patients aged 43.5 years or younger and 10.0% (95% CI, –1.2% to 21.2%) in patients older than 43.5 years.

The European Medicines Agency performed a post-hoc subgroup analysis by prior 5-ASA use in the individual CORE studies (Table 13). In CORE I, the mean difference in the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 9.4% (95% CI, –2.2% to 21.0%) in patients who had prior 5-ASA use and 12.5% (95% CI, 1.2% to 23.8%) in patients who did not have prior 5-ASA use. In CORE II, the mean difference in the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 7.6% (95% CI, –2.7% to 18.0%) in patients who had prior 5-ASA use and 23.1% (95% CI, 9.9% to 36.3%) in patients who did not have prior 5-ASA use.

Additional subgroup analyses were performed using pooled data from the CORE I and II studies, where data were presented using odds ratios (ORs) of budesonide MMX versus placebo for achieving remission at week 8 (Table 14). For the primary analysis, the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 17.7% versus 6.2% (OR 3.3; 95% CI, 1.7 to 6.4). For subgroup analysis by age, the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 17.1% versus 6.5% in patients ≤ 60 years old (OR 3.0; 95% CI, 1.5 to 6.0), and 25.0% versus 6.5% in patients older than 60 years (OR 7.7; 95% CI, 0.8 to 77.5). For subgroup analysis by prior 5-ASA use, the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 17.0% versus 7.4% in patients with prior 5-ASA use (OR 2.6; 95% CI, 1.2 to 5.6), and 18.8% versus 3.3% in patients with no prior 5-ASA use (OR 6.8; 95% CI, 1.5 to 31.0). For subgroup analysis by disease severity, the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 36.7% versus 11.1% (OR 4.8; 95% CI, 1.6 to 14.3) for patients with mild UC and 14.1% versus 5.1% (OR 3.1, 95% CI 1.3 to 7.5) for patients with moderate disease. For subgroup analysis by extent of disease, the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 23.5% versus 11.0% (OR 2.5; 95% CI, 1.1 to 6.0) for patients with proctosigmoiditis, 20.3% versus 3.2% (OR 8.9; 95% CI, 1.9 to 42.6) for patients with left-sided disease, and 9.4% versus 3.3% (OR 3.0; 95% CI, 0.6 to 14.7) for patients with extensive disease. For subgroup analysis by duration of disease, the proportion of patients achieving remission at week 8 with budesonide MMX compared with placebo was 23.5% versus 11.0% (OR 2.5; 95% CI, 1.1 to 6.0) for patients who had UC for ≤ 1 year, 19.6% versus 6.3% (OR 2.5; 95% CI, 1.1 to 6.0) for patients who had UC for > 1 to ≤ 5 years, and 17.9% versus 0% for patients who had disease for > 5 years.

3.6.2 Clinical and endoscopic response

a) Clinical and endoscopic improvement

The secondary end points for the CORE studies were clinical improvement (≥ 3-point improvement in UCDAI) and endoscopic improvement (≥ 1-point improvement in UCDAI mucosal appearance subscore) at week 8. In both CORE studies, the proportion of patients with clinical improvement at week 8 was greater in the budesonide MMX group than in the placebo group (CORE I: 33.3% versus 24.8%; CORE II: 42.2% versus 33.7%). The mean difference in the proportion of patients achieving clinical improvement

with budesonide MMX compared with placebo was not statistically significant in both studies (CORE I: 8.5%; 95% CI, –2.8% to 19.9%; *P* = 0.1420; and CORE II: 8.5%; 95% CI, –5.0% to 22.0%; *P* = 0.2215).

In both CORE studies, the proportion of patients with endoscopic improvement at week 8 was greater in the budesonide MMX group than in the placebo group (CORE I: 41.5% versus 33.1%; CORE II: 42.2% versus 31.5%). Because statistical significance was not reached for clinical improvement in both studies, no statistical analyses were performed for the comparison of budesonide MMX versus placebo with regard to endoscopic improvement due to the hierarchical testing procedure.

b) Symptom resolution

Symptom resolution (UCDAI stool frequency and rectal bleeding subscores of 0) was an exploratory end point in the CORE studies. In both CORE studies, the proportion of patients with symptom resolution at week 8 was greater in the budesonide MMX group than in the placebo group (CORE I: 28.5% versus 16.5%; CORE II: 23.9% versus 11.2%). The mean difference in the proportion of patients with symptom resolution versus placebo with budesonide MMX compared with placebo was statistically significant in both studies (CORE I: 11.9%; 95% CI, 1.6% to 22.3%; *P* = 0.0258; and CORE II: 12.6%; 95% CI, 2.3 to 23.0; *P* = 0.0220). However, as this was an exploratory end point for which there was no hierarchical testing procedure, these results should be interpreted with caution because of the potential for type I error.

c) Clinical Activity Index

The proportion of patients who obtained a CAI score of ≤ 4 was an exploratory end point in the CORE studies. In both CORE studies, the proportion of patients with a CAI score of ≤ 4 at week 8 was greater in the budesonide MMX group than in the placebo group (CORE I: 35.0% versus 28.1%; CORE II: 28.4% versus 16.9%). The mean difference in the proportion of patients achieving CAI ≤ 4 versus placebo with budesonide MMX compared with placebo was not statistically significant in both studies (CORE I: 7.6%; 95% CI, –4.3% to 19.6%; *P* = 0.2129; and CORE II: 3.3%; 95% CI, –9.3% to 15.9%; *P* = 0.6090). However, as this was an exploratory end point for which there was no hierarchical testing procedure, these results should be interpreted with caution due to the potential for type I error.

3.6.3 IBD-QoL

Health-related quality of life as measured by the IBD-QoL questionnaire was an exploratory end point in the CORE studies. In CORE I, the mean (SD) IBD-QoL total score at baseline was 146.6 (34.4) in the budesonide MMX group and 141.1 (39.0) in the placebo group. In CORE II, the mean (SD) IBD-QoL total score at baseline was 140.2 (33.9) in the budesonide MMX group and 147.7 (34.7) in the placebo group. In CORE I, the mean (SD) change from baseline in IBD-QoL total score at week 8 was 19.1 (41.4) in the budesonide MMX group and 23.2 (42.3) in the placebo group. In CORE II, the mean (SD) change from baseline in IBD-QoL total score at week 8 was 21.4 (34.3) in the budesonide MMX group and 23.7 (39.4) in the placebo group. The difference in mean change from baseline in IBD-QoL score between the budesonide MMX and placebo groups was not statistically significant in both studies. However, as this was an exploratory end point for which there was no hierarchical testing procedure, these results should be interpreted with caution.

3.6.4 Function and disability

Function and disability were not specifically measured as outcomes in the CORE studies.

TABLE 10: KEY EFFICACY OUTCOMES

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2,400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (ITT)	**123**	**121**	**124**	**109**	**89**	**103**
Clinical remission — primary end point						
Patients with remission at week 8, n (%)	22 (17.9)	9 (7.4)	15 (12.1)	(17.4)	(4.5)	(12.6)
Remission, % (95% CI)	17.9 (11.1 to 24.7)	7.4 (2.8 to 12.1)	12.1 (6.4 to 17.8)			
Mean difference versus placebo, % (95% CI), *P* value[a]	10.4 (2.2 to 18.7), 0.0143	-	4.7 (–2.7 to 12.1), 0.2200[b]			
Clinical improvement (≥ 3-point improvement in UCDAI) — secondary end point						
Patients with improvement at week 8, n (%)	41 (33.3)	30 (24.8)	42 (33.9)	(42.2)	(33.7)	
Improvement, % (95% CI)	33.3 (25.0 to 41.7)	24.8 (17.1 to 32.5)	33.9 (25.5 to 42.2)			
Mean difference versus placebo, % (95% CI), *P* value[a]	8.5 (–2.8 to 19.9), 0.1420	-	9.1 (–2.3 to 20.4), 0.1189[b]			
Endoscopic improvement (≥ 1-point improvement in UCDAI mucosal appearance subscore) — secondary end point						
Patients with improvement at week 8, n (%)	51 (41.5)	40 (33.1)	41 (33.1)		(31.5)	
Improvement, % (95% CI)	41.5	33.1	33.1			
Mean difference versus placebo, % (95% CI), *P* value[a]	8.4[c]	-	0.9991[b]			
Symptom resolution (UCDAI stool frequency and rectal bleeding subscores of 0) — exploratory end point						
Patients with symptom resolution at week 8, n (%)	35 (28.5)	20 (16.5)	31 (25.0)			
Symptom resolution, % (95% CI)	28.5	16.5	25.0			
Mean difference versus placebo, % (95% CI), *P* value[a]	0.0258	-	0.1025[b]			
CAI score ≤ 4 — exploratory end point						
Patients with CAI ≤ 4 at week 8, n (%)						
CAI ≤ 4, % (95% CI)						
Mean difference versus						

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2,400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (ITT)	**123**	**121**	**124**	**109**	**89**	**103**
placebo, % (95% CI), *P* value[a]	[redacted]		[redacted]	[redacted]		[redacted]
IBD-QoL total score — exploratory end point						
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline at week 8, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference versus placebo (95% CI), *P* value[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CAI = Clinical Activity Index; CI = confidence interval; IBD-QoL = Inflammatory Bowel Disease Quality of Life Questionnaire; MMX = Multi Matrix System; SD = standard deviation; UCDAI = Ulcerative Colitis Disease Activity Index.
[a] *P* values were calculated using the chi-square test, with a significance level of 0.025 for comparisons of budesonide MMX versus placebo and 0.05 for comparison of Asacol or Entocort EC versus placebo. Results are presented for the worst-case scenario for missing data.
[b] The study was not powered to detect a difference between Asacol (CORE I) or Entocort EC (CORE II) and placebo.
[c] Statistical comparison of endoscopic improvement of budesonide MMX 9 mg versus placebo were not conducted as this end point fell below a non-statistically significant parameter in the testing hierarchy.
[d] *P* values were calculated using the Wilcoxon rank-sum test, with all tests conducted at a significance level of 0.05. Missing data were imputed using the last observation carried forward method.
Source: Clinical Study Reports.[1,2]

3.6.5 Mucosal healing

Mucosal healing was evaluated by histology using criteria developed by Saverymuttu et al., 1986.[22] Histologic healing at week 8 was an exploratory end point in the CORE studies and defined as having a total histologic score of ≤ 1 for all biopsy specimens. In CORE I, the proportion of patients with histological healing at week 8 was similar between the budesonide MMX and placebo groups (4.1% versus 6.6%), and the mean difference in the proportion of patients achieving histological healing at week 8 for budesonide MMX versus placebo was not statistically significant (–2.5%; 95% CI, –8.2% to 3.1%; *P* = 0.3759) (Table 15). In CORE II, the proportion of patients with histological healing at week 8 was greater in the budesonide MMX group than in the placebo group (16.5% versus 6.7%), and the mean difference in the proportion of patients with histological healing at week 8 for budesonide MMX versus placebo was statistically significant (9.8%; 95% CI, 1.1% to 18.5%; *P* = 0.0361). However, as this was an exploratory end point for which there was no hierarchical testing procedure, these results should be interpreted with caution due to the potential for type I error.

3.7 Harms

Only those harms identified in the review protocol are reported below (see section 2.1 Objectives). See 0 for detailed harms data.

3.7.1 Adverse events

In CORE I, the incidence of AEs was similar between the budesonide MMX and placebo groups (57.5% versus 62.8%) (Table 11). In CORE II, the incidence of AEs was higher in the budesonide group than in the placebo group (55.5% versus 44.2%). The most common AEs included worsening UC, headache, nausea, insomnia, and abdominal pain.

3.7.2 Serious adverse events

The incidence of SAEs was balanced between the budesonide MMX and placebo groups in the CORE studies (CORE I: 2.4% versus 2.3%; CORE II: 3.1% versus 3.9%). The most common SAE was worsening UC.

3.7.3 Withdrawals due to adverse events

In CORE I, the incidence of withdrawals due to AEs was higher in the placebo group than in the budesonide group (18.6% versus 11.8%). In CORE II, the incidence of withdrawals due to AEs was higher in the budesonide group than in the placebo group (18.8% versus 14.7%). The most common reason was worsening UC.

3.7.4 Mortality

There were no deaths in the CORE studies.

3.7.5 Notable harms

In CORE I, glucocorticoid AEs were balanced between the budesonide and placebo groups (11.8% versus 10.1%). In CORE II, glucocorticoid AEs were higher in the placebo group than in the budesonide MMX group (10.1% versus 6.3%). Common glucocorticoid AEs included mood changes, sleep changes, and insomnia.

TABLE 11: HARMS IN THE CORE I AND CORE II STUDIES

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2,400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (safety)	**127**	**129**	**127**	**128**	**129**	**126**
AEs, n (%)						
Patients with > 0 AEs	73 (57.5)	81 (62.8)	80 (63.0)	71 (55.5)	57 (44.2)	69 (54.8)
Most common AEs (≥ 5% in any group), n (%)						
Worsening UC	14 (11.0)	21 (16.3)	13 (10.2)	20 (15.6)	15 (11.6)	16 (12.7)
Headache	8 (6.3)	19 (14.7)	12 (9.4)	21 (16.4)	8 (6.2)	9 (7.1)
Pyrexia	3 (2.4)	9 (7.0)	3 (2.4)	2 (1.6)	2 (1.6)	2 (1.6)
Insomnia	5 (3.9)	9 (7.0)	3 (2.4)	2 (1.6)	3 (2.3)	4 (3.2)
Back pain	5 (3.9)	7 (5.4)	2 (1.6)	1 (0.8)	1 (0.8)	0
Nausea	5 (3.9)	8 (6.2)	10 (7.9)	8 (6.3)	3 (2.3)	3 (2.4)
Abdominal pain	6 (4.7)	8 (6.2)	10 (7.9)	3 (2.3)	7 (5.4)	7 (5.6)
Diarrhea	2 (1.6)	7 (5.4)	8 (6.3)	1 (0.8)	4 (3.1)	4 (3.2)
Flatulence	1 (0.8)	2 (1.6)	7 (5.5)	5 (3.9)	3 (2.3)	7 (5.6)
Nasopharyngitis	3 (2.4)	4 (3.1)	3 (2.4)	1 (0.8)	2 (1.6)	6 (4.8)
Blood cortisol decreased	4 (3.1)	0	0	7 (5.5)	1 (0.8)	4 (3.2)
SAEs, n (%)						
Patients with > 0 SAEs	3 (2.4)	3 (2.3)	4 (3.1)	4 (3.1)	5 (3.9)	1 (0.8)
Most common SAEs, n (%)						
Worsening UC	3 (2.4)	1 (0.8)	1 (0.8)	1 (0.8)	3 (2.3)	1 (0.8)

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2,400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (safety)	**127**	**129**	**127**	**128**	**129**	**126**
WDAEs, n (%)						
Patients with > 0 WDAEs	15 (11.8)	24 (18.6)	14 (11.0)	24 (18.8)	19 (14.7)	22 (17.5)
Most common reason, n (%)						
Worsening UC	10 (7.9)	18 (14.0)	10 (7.9)	19 (14.8)	13 (10.1)	15 (11.9)
Deaths						
Number of deaths	0	0	0	0	0	0
Notable harms, n (%)						
Glucocorticoid effect	15 (11.8)	13 (10.1)	10 (7.9)	8 (6.3)	13 (10.1)	14 (11.1)
Moon face	0	0	1 (0.8)	2 (1.6)	4 (3.1)	1 (0.8)
Striae rubrae	0	2 (1.6)	0	0	0	0
Flushing	0	1 (0.8)	2 (1.6)	0	1 (0.8)	1 (0.8)
Fluid retention	2 (1.6)	1 (0.8)	1 (0.8)	0	2 (1.6)	0
Mood changes	5 (4.0)	3 (2.3)	2 (1.6)	2 (1.6)	7 (5.4)	6 (4.8)
Sleep changes	4 (3.2)	7 (5.4)	1 (0.8)	3 (2.3)	4 (3.1)	7 (5.6)
Insomnia	5 (4.0)	6 (4.7)	2 (1.6)	1 (0.8)	2 (1.6)	3 (2.4)
Acne	3 (2.4)	3 (2.3)	4 (3.1)	1 (0.8)	2 (1.6)	3 (2.4)
Hirsutism	0	0	1 (0.8)	0	0	1 (0.8)

AE = adverse event; MMX = Multi Matrix System; SAE = serious adverse event; UC = ulcerative colitis; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports.[1,2]

4. DISCUSSION

4.1 Summary of available evidence

Two manufacturer-sponsored, multi-centre, double-blind, placebo-controlled RCTs met inclusion criteria for this systematic review. CORE I (N = 510) and CORE II (N = 512) evaluated the efficacy and safety of budesonide MMX 9 mg in adult patients with active, mild to moderate UC. The CORE I study also included a mesalamine (Asacol 2,400 mg) group, while the CORE II study included a budesonide (Entocort EC 9 mg) group, although the studies were not powered for a comparison between these drugs versus placebo or budesonide MMX versus these drugs and were included as reference arms.

The main limitations of the CORE studies included the high percentage of discontinuations, the potential loss of randomization due to the exclusion of patients from the ITT population after a protocol amendment, the placebo effects seen in both trials, the enrolment of a patient population with more advanced disease that may not be reflective of the population who would receive budesonide MMX, and the use of clinical and endoscopic end points that may not be reflective of clinical practice. CORE II may not have been appropriately powered because of the revised definition of the ITT population, where the number of patients did not meet the initial power calculations.

4.2 Interpretation of results

4.2.1 Efficacy

In both CORE studies, there was a statistically significantly greater proportion of patients who achieved the primary end point of clinical and endoscopic remission in the budesonide MMX groups than in the placebo groups. The proportion of patients who achieved complete remission in the budesonide MMX groups (17% to 18%) was lower than was seen in two eight-week mild to moderate UC trials of mesalazine 2.4 g and 4.8 g (30% to 40%) despite having nearly identical definitions of complete remission.[23,24] However, the proportion of patients who achieved complete remission in the placebo groups of the mesalazine studies was also higher than that in the CORE studies (12.9% to 22.1% versus 4.5% to 7.4%), which suggests that these differences may be a result of the differences in the population enrolled. The population enrolled in the CORE studies had a median duration of disease of three to four years, and approximately 65% of patients had a moderate severity of their last flare, suggesting that patients had more advanced disease. More than 50% of patients had prior experience with mesalazine, which may suggest that they would be less responsive to other therapies. In contrast, patients enrolled in the low-dose mesalazine trials had mean times since diagnosis of less than one year and could not have previously failed on 5-ASA therapies.[23,24]

A stringent definition of complete and endoscopic remission was applied in the CORE studies. A composite end point was used in which patients had to have achieved a UCDAI score of ≤ 1 with subscores of 0 for rectal bleeding and stool frequency, no mucosal friability on colonoscopy, and a ≥ 1-point reduction in endoscopy score from baseline at week 8. The clinical expert consulted for this review noted that endoscopy would not normally be done at week 8 in this patient population, and that clinical remission is often determined by qualitative parameters rather than the quantitative scales used in clinical trials.

A modified ITT population was used for all efficacy analyses in the CORE studies, and this definition was updated after a protocol amendment prior to unblinding to include patients who had received at least one dose of study drug, had no major entry criteria or GCP violations (e.g., infectious colitis), and had histologic evidence of active disease at baseline. Few patients were excluded from the ITT using these

criteria in CORE I (6% in the placebo group, 3% in the budesonide MMX group), whereas in CORE II, more patients were excluded from the ITT population (31% in the placebo group, 13% in the budesonide MMX group). This differential in the number of patients excluded may have biased the results, although the direction of the potential bias is unclear. Due to this limitation, the results from the CORE II study should be interpreted with caution.

Although there were statistically significant differences in the proportion of patients who achieved clinical and endoscopic remission between the budesonide MMX and placebo groups across the CORE studies, there were no statistically significant differences between groups for the end point of clinical improvement (≥ 3-point improvement in UCDAI) at week 8, although the proportion of patients achieving this end point was numerically higher in the budesonide MMX groups compared with the placebo groups. For the end point of endoscopic improvement (≥ 1 improvement in UCDAI mucosal appearance subscore) at week 8, approximately 42% of patients achieved this end point in the budesonide MMX groups compared with 32% in the placebo groups. The clinical expert noted that the proportion of patients achieving endoscopic improvement at week 8 was high, and may be due to the use of a ≥ 1 improvement in mucosal appearance subscore rather than a larger improvement, as there is poor inter-observer agreement in this subscore. The UCDAI has been found to be positively correlated with the Mayo Score, the most commonly used disease activity index (see 0).

Quality of life was cited as an important outcome from patient group input as symptoms associated with UC have a negative impact on psychological and emotional well-being (see 0). In the CORE studies, quality of life was assessed using the IBD-QoL as an exploratory outcome. There was no difference in change from baseline at week 8 in the IBD-QoL total score between the budesonide MMX and placebo groups in both CORE studies. As these studies were eight weeks in duration, it may be difficult to detect a difference in quality of life between treatment groups.

UC is a disease that affects the colon, and can be limited to the rectum (proctosigmoiditis), can involve the colon distal to the splenic flexure (left-sided), or extend proximal to the splenic flexure (extensive/pancolitis). Because of its localization to the colon, it is important for oral drugs to be delivered to the colon while being protected from absorption in the stomach or small intestine. Various drugs use polymer-coated, pH-dependent-release tablets that dissolve in the pH environment of the colon.[25] The Multi Matrix System (MMX) technology uses an outer pH-dependent layer containing a hydrophilic and inert polymer matrix that slowly dissolves as the pH of the bowel increases and allows for controlled drug release through the colon.[25] A Cochrane systematic review of oral budesonide formulations for the induction of remission in UC did not identify any studies that compared different formulations of oral budesonide other than CORE II, which included an Entocort EC 9 mg group.[26] Entocort EC are capsules containing granules coated to protect them from gastric juices, and a matrix of ethylcellulose with budesonide controls the release of the drug in a time-dependent manner. Although CORE II was not powered to detect a difference between budesonide MMX and Entocort EC, this study did not find a difference in remission rates at eight weeks between the two formulations. However, Entocort EC is indicated for the treatment and maintenance of active, mild to moderate CD involving the ileum and/or ascending colon, and does not have a Health Canada–approved indication for UC.[27]

The Cochrane review conducted a subgroup analysis of the pooled CORE studies based on disease location, and found that in patients with left-sided disease, budesonide MMX was statistically significantly more likely to achieve complete remission than placebo (risk ratio 2.98; 95% CI, 1.56 to 5.67) but not for patients with extensive disease (risk ratio 2.41; 95% CI, 0.61 to 9.56).[26] Although these analyses are exploratory and not appropriately powered, it is possible that budesonide MMX is

efficacious in patients with left-sided disease because of its mechanism of release throughout the colon.[28]

There were no head-to-head trials comparing budesonide MMX with other active treatments for mild to moderate UC. Although an Asacol 2,400 mg group was included in CORE I and an Entocort EC 9 mg group was included in CORE II, neither trial was designed to compare these groups to budesonide MMX. The manufacturer submitted an NMA to compare budesonide MMX 9 mg to other drugs for the induction of complete clinical remission in patients with active, mild to moderate UC. Based on the induction NMA, budesonide MMX was associated with a statistically significant improvement for induction of complete clinical remission compared with placebo and high-dose mesalazine. Because of significant limitations with the analysis due to a small network informed mainly of single-study connections and the inclusion of studies with different end point definitions and study durations, the results of the NMA for induction of complete clinical remission and maintenance of clinical remission are uncertain.

The Health Canada indication for budesonide MMX is for the induction of remission in patients with active, mild to moderate UC.[6] However, the majority of patients in the CORE studies had previous experience with 5-ASA. The CONTRIBUTE study (N = 510) was an eight-week, double-blind, placebo-controlled RCT evaluating the efficacy and safety of budesonide MMX in patients with active, mild to moderate UC inadequately controlled with oral 5-ASAs.[29] Results from CONTRIBUTE are available only in abstract format. The primary end point was clinical and endoscopic remission at week 8, defined by a UCDAI score of ≤ 1 with subscores of 0 for rectal bleeding, stool frequency, and mucosal appearance. At week 8, there was a great proportion of patients in the budesonide MMX group compared with the placebo group that achieved clinical and endoscopic remission (13% versus 7.5%, *P* = 0.0488), with this result driven primarily by the mucosal appearance subscore. The clinical expert consulted for this review noted that budesonide MMX would likely be positioned after 5-ASA therapy rather than used as a first-line therapy, which corroborates with the available clinical evidence.[30,31]

4.2.2 Harms

Budesonide is a corticosteroid with low systemic bioavailability when administered orally or rectally, due to extensive first-pass hepatic metabolism, which may limit systemic AEs caused by conventional corticosteroids. The proportion of patients reporting an AE was similar across the budesonide MMX and placebo groups in CORE I, and was higher in the budesonide MMX group than in the placebo group in CORE II. The incidence of SAEs was low and similar between treatment groups in both studies. The most common AEs included worsening UC, headache, nausea, abdominal pain, and insomnia.

Corticosteroid-related AEs were low and similar between the budesonide MMX and placebo groups in both studies, with the most common AEs being mood changes, sleep changes, and insomnia. It would be difficult to observe long-term glucocorticoid adverse effects in eight-week studies. A 12-month extension study that enrolled patients who achieved clinical and endoscopic remission in the CORE studies was conducted by the manufacturer, and all patients in this extension were randomized to budesonide MMX 6 mg and placebo to evaluate maintenance of clinical remission. AEs were similar between the budesonide MMX 6 mg and placebo groups.[32] Prolonged treatment did not modify bone mineral density, but 30% of patients were reported to have abnormal adrenal function.[28] However, the long-term effects of budesonide MMX at the 9 mg dose are unknown. The clinical expert noted that it is unlikely that patients taking budesonide MMX for induction of remission would need tapering after an eight-week course of treatment.

The Health Canada product monograph for budesonide MMX recommends a treatment regimen of up to eight weeks and no longer, based on the available data.[6] Budesonide MMX does not have an indication for maintenance of UC. According to the clinical expert consulted for this review, there is a chance that budesonide MMX may be used off-label as maintenance therapy in UC patients whose condition may not be severe enough to warrant biologics, but who are not adequately controlled with 5-ASAs.

4.3 Potential place in therapy

This information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

The current standard of care for first-line therapy for persons with UC with mild to moderate disease activity are oral and/or rectal 5-ASAs.[4] In patients who do not have an adequate response to maximal dose 5-ASA, systemic corticosteroids (most commonly prednisone) may be used in an attempt to induce remission, whereas other patients may simply choose to deal with bothersome symptoms. A medication like budesonide MMX may be a preferred substitute for prednisone in these patients, as it has some efficacy in mild to moderate colitis in promoting treatment response and remission in UC, and may have a favourable side effect profile when compared with systemic corticosteroids.[26,33] Budesonide MMX may be used in place of systemic corticosteroids for patients who developed a disease flare of mild to moderate severity, yet had been maintained in remission on immunomodulators and/or biologics. There is also the possibility that clinicians may attempt to use longer courses of budesonide MMX in an attempt to maintain remission in patients who had a clinical response to a budesonide MMX–based induction course.

It seems unlikely that budesonide MMX will supplant the use of 5-ASAs as first-line therapy for most patients, yet it may have a role for patients with moderate levels of disease activity in combination with a 5-ASA, particularly in patients in whom initial induction therapy with systemic corticosteroids is being considered.

If budesonide MMX is used in clinical practice, it is unlikely that there will be any major changes in the use of diagnostic tests or strategies, and over the short term, it is unlikely that patients will need close monitoring for signs of toxicity.

5. CONCLUSIONS

Two eight-week, manufacturer-sponsored, multi-centre, double-blind, placebo-controlled RCTs met the inclusion criteria for this systematic review. CORE I and CORE II evaluated the efficacy and safety of budesonide MMX 9 mg in adult patients with active, mild to moderate UC. Results from the CORE studies demonstrated that a greater proportion of patients achieved complete clinical and endoscopic remission with budesonide MMX 9 mg than placebo. The proportion of patients achieving remission was lower than has been seen in studies of 5-ASAs for mild to moderate UC, although this may be due to the enrolment of a more severe and difficult-to-treat population in the CORE studies. Although cited as an important outcome from patient input, no differences in quality of life according to the IBD-QoL were observed after eight weeks. As there were no head-to-head trials designed to compare budesonide MMX with active treatment, an indirect treatment comparison was provided, but significant limitations with the analysis made results of the indirect comparison uncertain. Safety results from the CORE studies revealed no increased occurrences of corticosteroid-related AEs with budesonide MMX compared with placebo, although the study duration was short.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief description of patient groups supplying input
Two patient groups provided patient input for this submission: the Gastrointestinal (GI) Society and Crohn's and Colitis Canada (CCC).

The GI Society is committed to improving the lives of individuals with GI and liver conditions by supporting research, advocating for patient access in health care, and promoting GI and liver health. It provides evidence-based information through the BadGut basics patient information pamphlet and the *Inside Tract/Du coeur au ventre* newsletter, BadGut lectures, GI support group meetings, and continuing education events for health care professionals, and has two websites: one in English (www.badgut.org) and French (www.mauxdeventre.org). In the last two years, the GI Society has received funding from AbbVie Corporation, Actavis/Allergan Canada Inc., AstraZeneca Canada Inc., Boehringer Ingelheim, Innovative Medicines Canada, Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Hoffmann-La Roche Limited, Janssen Canada, Johnson & Johnson, LifeScan, Merck Canada Inc., Pfizer Canada Inc./Hospira, Shire Canada Inc., and Takeda Canada Inc.

The CCC is a volunteer-based national charity dedicated to investing in education, awareness, and research for Crohn's disease (CD) and ulcerative colitis (UC). CCC has received funding from individual donors and various pharmaceutical companies. In the 2014-2015 fiscal year, CCC received less than 10% of its total revenue from pharmaceutical companies. Major supporters were AbbVie Corporation, Actavis Allergan, Ferring Inc., Janssen Canada Inc., Shire Canada Inc., Takeda Canada Inc., P&G Canada, and Vertex Pharmaceuticals (Canada) Inc.

No conflicts of interest for this submission were declared by either the GI Society or CCC.

2. Condition-related information
Information was obtained from CCC published reports, educational brochures, the CCC 2011 national online survey (to which more than 430 people responded), telephone interviews, one GI Society questionnaire (completed by 133 Canadians), and one-on-one conversations with patients or caregivers.

UC is a chronic inflammatory bowel disease (IBD) with no cure, which is characterized by fine ulcerations in the inner mucosal lining of the colon. This subsequently causes inflammation that extends varying distances upward above the anus and can include portions of or the entire colon. The highest occurrence of UC is in young children and then peaks again at around 40 to 50 years of age, with an increased risk of development if there is a family history. Canada has both the highest prevalence and incidence in the world, with approximately 104,000 diagnosed individuals. If left untreated, long-standing UC can lead to colon cancer.

Patients with UC experience numerous physical symptoms associated with the chronic inflammation, including rectal bleeding, frequent and often persistent and urgent diarrhea that is accompanied by cramping abdominal pain, weight loss, fatigue, anemia (depending on the severity of the diarrhea and blood loss), and failure to grow (particularly in children). In addition to the aforementioned symptoms, patients can also experience extra-intestinal physical manifestations such as fever, joint and eye inflammation, tender and/or inflamed nodules on the shins, skin lesions, liver disorders, and mouth

ulcers. Patients also experience numerous accompanying psychological and emotional symptoms, such as depression, anxiety, fear, and stress, which often leads to isolation and further social issues.

Due to the impacts of the physical, psychological, and emotional symptoms incurred by patients with UC, quality of life can be profoundly affected. UC affects every facet of patients' lives, including at work and home, in public, and in school. The fear of not knowing whether another flare is in their future or if they are close enough to a bathroom often leads to disempowerment, with patients often foregoing regular daily activities such as eating, running errands, going to work or school, and sports. As one patient stated, *"I am constantly aware of where a bathroom is and always prepared for the urge to go. My activities are limited for the fear of not being able to find a washroom."* Others suffering from UC find the fatigue negatively affects their lives, as evidenced by one patient, who stated, *"My energy levels have decreased and I get fatigued much more easily; the fear of pain, bleeding, incontinence is horrible. The worst part is fearing the next big flare that will prevent me from being a mom to my 18-month-old."* For children who are diagnosed with UC, this comes at a particularly vulnerable age, with many patients' sense of self-worth being affected. For older patients, there are often difficulties with employment, as many are faced with either decreased understanding from employers or having to take many more sick days (sometimes leading to hospitalizations) than the average employee. This can also lead to financial difficulties. In addition, many patients also have to change their diets and can no longer enjoy the types of foods they used to.

Caregivers of those with UC are often negatively affected by the increased burden of having to take time off work to take care of the patient, devoting more of their time to care for and take the patient to appointments and hospitals (if necessary), and in finding their free time decreased because the patient cannot perform everyday activities such as cleaning, cooking, and errands. In caring for patients with UC, caregivers often incur more days off work, which can subsequently be problematic financially. In addition, treatments for UC can be expensive, which often compounds financial difficulties.

3. Current therapy–related information

Treatment of UC includes managing both the symptoms and consequences of the disease. Patients with UC are often treated with 5-aminosalicylate (5-ASA), and the goal of therapy is to decrease acute inflammation and remove inflammatory symptoms for the long term when using it as maintenance therapy. The main issue with 5-ASA is the fact that it often stops working. Topical corticosteroids, such as rectal formulations, can be quite helpful as well; however, they are inconvenient therapies that do not allow the patient to maintain normal routines and may not work if diarrhea is unrelenting. Steroids (e.g., prednisone) have been shown to be effective for UC symptoms, although there are adverse side effects associated with their use that may result in treatment discontinuation. These adverse events include the development of "moon face," challenges related to emotions, and extreme fatigue. Immunosuppressive drugs (e.g., azathioprine) help to reduce the dependence on steroids, but it can take up to six months to see successful results. Biologics, while effective, are generally reserved for cases that are categorized as moderate to severe and are often too costly to access. Surgery is the last resort for patients with UC who have failed all lines of therapy; it is associated with post-surgical complications such as soiling, poor pouch function, pouchitis, sexual dysfunction, and, in some cases, infertility (especially in women). Patients with mild to moderate UC believe there is a gap in currently available treatments and are looking for safer and more effective options.

4. Expectations about the drug being reviewed

While patients with UC would ideally like to take less costly medications with the fewest side effects, many patients do not respond to currently available treatments or will lose their response to these treatments over time. Patients believe that more options, especially those with fewer side effects, are necessary. Patients believe that this new oral formulation of budesonide will help to improve their quality of life in that it may be a safer and more effective treatment, particularly due to its targeted effect (essentially acting only on the colon, with very little systemic exposure). In addition, it is perceived that budesonide MMX may halt the progression to biologic treatment due to the possibility that it may maintain remission in some patients.

Three Canadian patients who had experience with oral budesonide MMX reported that it was easy to use, simple to adhere to, and effective. Patients not only felt better but did not have as many frequent bathroom visits. Some felt that budesonide was successful in reducing the number of flares, and C-reactive protein levels were noted to have declined; both led to less time off work and fewer hospitalizations. While one patient did not achieve full remission, there was still a "remarkable" improvement in their symptoms when compared with their previous therapy. One patient stated that budesonide MMX helped ease the mental health issues caused by prednisone. However, while the treatment has appeared to work in some cases, one patient stated that budesonide MMX *"worked well for a while, reduced my pain and bathroom visits, but I did have to eventually progress to a biologic treatment to control my disease."*

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 21 2016
Alerts:	Weekly search updates until October 19, 2016
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
Adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
Oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1.	budesonide*.ti,ab,hw.
2.	*delayed-action preparations/
3.	*delayed release formulation/
4.	((budesonide* and (multi-matrix or multimatrix or mmx)) or budesonidemmx or cortiment* or uceris* or cb-01-02 or cb0102 or Q3OKS62Q6X).ti,ab,ot,kf,hw,nm.
5.	controlled release formulation/
6.	((budesonide* and (multi-matrix or multimatrix or mmx)) or budesonidemmx or cortiment* or uceris* or cb-01-02 or cb0102 or Q3OKS62Q6X).ti,ab,kw.
7.	1 and 2
8.	4 or 7
9.	8 use pmez
10.	3 or 5
11.	1 and 10
12.	6 or 11
13.	12 use oemezd
14.	9 or 13
15.	conference.pt.
16.	14 not 15
17.	remove duplicates from 16

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	June 16, 2016
Keywords:	Drug name
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Balzola et al., 2012[34]	Abstract
Balzola et al., 2013[35]	
Danese et al., 2014[36]	Review
Lichtenstein et al., 2016[37]	
D'Haens et al., 2010[38]	Phase I/II study
Lichtenstein et al., 2015[39]	Pooled safety analysis

APPENDIX 4: DETAILED OUTCOME DATA

Subgroup analyses

TABLE 12: PRE-SPECIFIED SUBGROUP ANALYSIS BY AGE OF THE PRIMARY END POINT IN THE CORE STUDIES

	CORE I			CORE II		
	Budesonide MMX 9 mg	Placebo	Asacol 2,400 mg	Budesonide MMX 9 mg	Placebo	Entocort EC 9 mg
N (ITT)	**123**	**121**	**124**	**109**	**89**	**103**
Primary Analysis						
Patients with remission at week 8, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference versus placebo, % (95% CI), *P* value[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age ≤ 42 Years (CORE I) or ≤ 43.5 Years (CORE II)						
Patients with remission at week 8, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference versus placebo, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age > 42 Years (CORE I) or > 43.5 Years (CORE II)						
Patients with remission at week 8, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remission, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean difference versus placebo, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intention-to-treat; MMX = Multi Matrix System; SD = standard deviation.
[a] *P* values were calculated using the chi-square test, with a significance level of 0.025 for comparisons of budesonide MMX versus placebo and 0.05 for comparison of Asacol or Entocort EC versus placebo. Results are presented for the worst-case scenario for missing data.
[b] The study was not powered to detect a difference between Asacol (CORE I) or Entocort EC (CORE II) and placebo.
Source: Clinical Study Reports.[1,2]

TABLE 13: POST-HOC SUBGROUP ANALYSIS BY PRIOR 5-ASA USE OF THE PRIMARY END POINT IN THE CORE STUDIES (EUROPEAN MEDICINES AGENCY ANALYSIS)

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (ITT)	**123**	**121**	**124**	**109**	**89**	**103**
Primary analysis						
Patients with remission at week 8, n (%)	22 (17.9)	9 (7.4)	15 (12.1)	19 (17.4)	4 (4.5)	13 (12.6)
Mean difference versus placebo, % (95% CI), *P* value[a]	10.4 (2.2 to 18.7), 0.0143	-	4.7 (–2.7 to 12.1), 0.2200[b]	12.9 (4.6 to 21.3), 0.0047	-	8.1 (0.4 to 15.9), 0.0481[b]
5-ASA use — yes						
Patients with remission at week 8, n (%)	12/64 (18.8)	7/75 (9.3)	8/72 (11.1)	10/70 (14.3)	4/60 (6.7)	12/72 (16.7)
Mean difference versus placebo, % (95% CI)	9.4 (–2.2 to 21.0)	-	1.8 (–8.0 to 11.6)	7.6 (–2.7 to 18.0)	-	10 (–0.7 to 20.7)
5-ASA use — no						
Patients with remission at week 8, n (%)	10/59 (17.0)	2/45 (4.4)	7/52 (13.5)	9/39 (23.1)	0/29 (0)	1/31 (3.2)
Mean difference versus placebo, % (95% CI)	12.5 (1.2 to 23.8)	-	9.0 (–2.0 to 20.1)	23.1 (9.9 to 36.3)	-	3.2 (–3.0 to 9.5)

5-ASA = 5-aminosalicylic acid; CI = confidence interval; ITT = intention-to-treat; MMX = Multi Matrix System.
[a] *P* values were calculated using the chi-square test, with a significance level of 0.025 for comparisons of budesonide MMX versus placebo and 0.05 for comparison of Asacol or Entocort EC versus placebo. Results are presented for the worst-case scenario for missing data.
[b] The study was not powered to detect a difference between Asacol (CORE I) or Entocort EC (CORE II) and placebo.
Source: European Medicines Agency Public Assessment Report.[19]

TABLE 14: SUBGROUP ANALYSES OF POOLED CORE STUDIES

	CORE I + II (pooled)	
	Budesonide MMX 9 mg	**Placebo**
N (ITT pooled)	**232**	**210**
Primary analysis		
Patients with remission at week 8, n (%)	41 (17.7)	13 (6.2)
Odds ratio vs. placebo (95% CI), *P* value[a]	3.3 (1.7 to 6.4), 0.0002	
Age ≤ 60 years		
Patients with remission at week 8, n (%)	37/216 (17.1)	12/186 (6.5)
Odds ratio vs. placebo (95% CI), *P* value[a]	3.0 (1.5 to 6.0), 0.001	
Age > 60 years		
Patients with remission at week 8, n (%)	4/16 (25.0)	1/24 (4.2)
Odds ratio vs. placebo (95% CI), *P* value[a]	7.7 (0.8 to 77.5), 0.0594	
Prior 5-ASA use — yes		
Patients with remission at week 8, n (%)	25/14 (17.0)	11/149 (7.4)
Odds ratio vs. placebo (95% CI), *P* value[a]	2.6 (1.2 to 5.6), 0.0098	
Prior 5-ASA use — no		

	CORE I + II (pooled)	
	Budesonide MMX 9 mg	**Placebo**
N (ITT pooled)	**232**	**210**
Patients with remission at week 8, n (%)	16/85 (18.8)	2/61 (3.3)
Odds ratio vs. placebo (95% CI), *P* value[a]	6.8 (1.5 to 31.0), 0.0051	
Disease severity — mild		
Patients with remission at week 8, n (%)	18/49 (36.7)	5/45 (11.1)
Odds ratio vs. placebo (95% CI), *P* value[a]	4.8 (1.6 to 14.3), 0.0039	
Disease severity — moderate		
Patients with remission at week 8, n (%)	22/156 (14.1)	7/137 (5.1)
Odds ratio vs. placebo (95% CI), *P* value[a]	3.1 (1.3 to 7.5), 0.0098	
Disease extent — proctosigmoiditis		
Patients with remission at week 8, n (%)	19/81 (23.5)	9/82 (11.0)
Odds ratio vs. placebo (95% CI), *P* value[a]	2.5 (1.1 to 6.0), 0.0349	
Disease extent — left-sided		
Patients with remission at week 8, n (%)	13/64 (20.3)	2/62 (3.2)
Odds ratio vs. placebo (95% CI), *P* value[a]	8.9 (1.9 to 42.6), 0.0018	
Disease extent — extensive/pancolitis		
Patients with remission at week 8, n (%)	8/85 (9.4)	2/60 (3.3)
Odds ratio vs. placebo (95% CI), *P* value[a]	3.0 (0.6 to 14.7), 0.1585	
Disease duration — ≤ 1 year		
Patients with remission at week 8, n (%)	19/81 (23.5)	9/82 (11.0)
Odds ratio vs. placebo (95% CI), *P* value[a]	2.5 (1.1 to 6.0), 0.7887	
Disease duration — > 1 year to ≤ 5 years		
Patients with remission at week 8, n (%)	18/92 (19.6)	5/80 (6.3)
Odds ratio vs. placebo (95% CI), *P* value[a]	3.7 (1.3 to 10.5), 0.0103	
Disease duration — > 5 years		
Patients with remission at week 8, n (%)	15/84 (17.9)	0/80 (0)
Odds ratio vs. placebo (95% CI), *P* value[a]	NA, < 0.0001	

5-ASA = 5-aminosalicylic acid; CI = confidence interval; ITT = intention-to-treat; MMX = Multi Matrix System; NA = not applicable; vs. = versus.

[a] *P* values were calculated using the chi-square test, with a significance level of 0.025 for comparisons of budesonide MMX versus placebo and 0.05 for comparison of Asacol or Entocort EC versus placebo. Results are presented for the worst-case scenario for missing data.

Source: Sandborn et al., 2015.[40]

Histological healing

TABLE 15: HISTOLOGICAL HEALING IN THE CORE STUDIES

	CORE I			CORE II		
	Budesonide MMX 9 mg	**Placebo**	**Asacol 2,400 mg**	**Budesonide MMX 9 mg**	**Placebo**	**Entocort EC 9 mg**
N (ITT)	**123**	**121**	**124**	**109**	**89**	**103**
Histological healing — exploratory end point						
Patients with histological healing at week 8, n (%)	5 (4.1)	8 (6.6)	14 (11.3)	18 (16.5)	6 (6.7)	14 (13.6)
Histological healing, % (95% CI)	4.1 [redacted]	6.6 [redacted]	11.3 [redacted]	16.5 [redacted]	6.7 [redacted]	13.6 [redacted]
Mean difference versus placebo, % (95% CI), *P* value[a]	–2.5 [redacted] 0.3759	[redacted]	4.7 [redacted] 0.2003	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intention-to-treat; MMX = Multi Matrix System.

[a] *P* values were calculated using the chi-square test, with a significance level of 0.025 for comparisons of budesonide MMX versus placebo and 0.05 for comparison of Asacol or Entocort EC versus placebo. Results are presented for the worst-case scenario for missing data.

Source: Clinical Study Reports.[1,2]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize evidence concerning the reliability, validity, scoring, and minimal clinically important difference (MCID) of the following scales used to assess changes in ulcerative colitis (UC) disease activity, and outcome measurement in the clinical trials:

- Clinical Activity Index (CAI)
- Endoscopic Index Score (EI)
- Histological Score
- Inflammatory Bowel Disease Quality of Life Questionnaire (IBD-QoL)
- Mayo Score
- Ulcerative Colitis Disease Activity Index (UCDAI).

Findings

Table 16: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
CAI (also termed Rachmilewitz Index[20,21])	• Comprises 4 objective measures (extra-intestinal manifestations, number of stools per week, temperature, and lab findings [ESR and Hb]) and 3 subjective measures (general well-being, blood in stool, and abdominal pain and/or cramps); each parameter is assigned a score • Total scores range from 0 to 25: o 0 to 4 inactive (remission) o 5 to 10 mild activity o 11 to 17 moderate activity o ≥ 18 high activity	Yes	Not established	Burri et al.[21] Wolff et al.[20] Hirai et al.[41]
Endoscopic Index Score (according to Rachmilewitz)[a]	• Based on endoscopic data of 4 macroscopic criteria: o vascular pattern of mucosa o granulation scattering reflection of light o damage to mucosa that includes aspects like ulcers, erosions, exudates, fibrin, and mucus o vulnerability of the mucosa	Yes	Not established	Hirai et al.[41] Wolff et al.[20]
Histological score[b]	• Comprises 6 histological features graded on a 4-point scale (none, mild, moderate, or severe): o crypt abscesses o crypt architectural irregularities	Yes	Not established	Riley et al.[42] Wolff et al.[20]

Instrument	Type	Evidence of Validity	MCID	References
	○ acute inflammatory cell infiltrate (this includes polymorphic nuclear cells in the lamina propria) ○ depletion of mucin ○ integrity of surface epithelium ○ chronic inflammatory cell infiltrate (round cells in the lamina propria)			
IBD-QoL	Physician-administered 32-item questionnaire used to assess health-related quality of life in patients with inflammatory bowel disease	Yes	Not established	Irvine et al.[43] Guyatt et al.[44] Pallis et al.[45]
UCDAI	• 4 criteria, with internal scores ranging from 0 to 3, are included in this index: ○ stool frequency ○ rectal bleeding appearance of mucosa upon sigmoidoscopy ○ physician's disease severity assessment • The total score ranges from 0 to 12, with higher scores indicating more severe disease	Yes	Not established	Sutherland et al.[46] Wolff et al.[20]

CAI = Clinical Activity Index; CDR = CADTH Common Drug Review; ESR = erythrocyte sedimentation rate; Hb = hemoglobin; IBD-QoL = Inflammatory Bowel Disease Quality of Life Questionnaire; MCID = minimal clinically important difference; UCDAI = Ulcerative Colitis Disease Activity Index.

[a] While no literature was identified regarding something termed as the Endoscopic Index Score, the most common Endoscopic Index Score is that by Rachmilewitz; however, it is uncertain whether this index was in fact the one used in the Cortiment submission to CDR.

[b] While no literature was identified regarding something termed as the "Histological Score," the most common histological score appears to be that by Riley et al.;[42] however, it is uncertain whether this index was in fact the one used in the Cortiment submission to CDR.

Clinical Activity Index

The CAI is a tool that assesses disease activity in patients with UC. Seven clinical features are evaluated,[20] with the total index score ranging from 0 to 25: 0 to 4 inactive (remission); 5 to 10 mild activity; 11 to 17 moderate activity; and ≥ 18 high activity.[21] It combines objective and subjective measures, for which individual scores are assigned. The objective measures include extra-intestinal UC manifestations (0 = none, 3 = iritis, 3 = erythema nodosum, or 3 = arthritis), number of stools per week (0 = < 18, 1 = 18 to 35, 2 = 36 to 60, or 3 = > 60), sublingual temperature (0 = ≤ 38°C or 3 = > 38°C), and laboratory findings (0 = erythrocyte sedimentation rate [ESR] after one hour of ≤ 50 mm and hemoglobin [Hb] ≥ 10 g/dL; 1 = ESR after one hour of > 50 and ≤ 100 mm; 2 = ESR after one hour > 100 mm, or 4 = Hb < 10 g/dL).[20] The three subjective measures include general well-being during the previous week (0 = good, 1 = average, 2 = poor, 3 = very poor), blood in stool in the previous week (0 = none or once, 2 = a little [≤ 30%], 4 = a lot [> 30]), and a sum of abdominal pain/cramps incidences in the previous week (0 =none, 1 = mild, 2 = moderate, 3 = severe).[20] The following differing degrees of clinical activity indicate the severity of UC, with the total index score ranging from 0 to 25: 0 to 4 inactive

(remission); 5 to 10 mild activity; 11 to 17 moderate activity; and ≥ 18 high activity.[21] Clinical remission for the CAI is defined as CAI ≤ 4.[20]

In one study by Hirai et al.[41] that sought to determine the most frequently applied clinical indices and endovascular indices used to detect changes in UC by doing an extensive literature search, the authors noted that the CAI positively correlated with all the other frequently used clinical indices (Mayo Score [also known as the disease activity Index (DAI)], Truelove and Witts' Severity Index, Lichtiger Index, the Clinical Colitis Activity Index [CCAI], Powell-Tuck Index, and the Seo Index) in detecting change over time points typically used in clinical trials (two, four, and eight weeks) when compared with baseline. This observation indicates that the CAI is effective at assessing clinical improvement and, hence, disease activity over time following treatment.[41] In addition, the CAI and the most frequently reported endovascular indices (including the Baron Score and the Endoscopic Index by Rachmilewitz) were weakly positively correlated at baseline; however, their positive correlation was stronger at four weeks post-treatment and even stronger at eight weeks post-treatment.[41] From this observation, the authors concluded that CAI and endovascular indices had a weaker correlation when disease activity was high and a stronger correlation when there was a decrease in disease activity following treatment.[41] Because of this, the authors concluded that both clinical and endovascular indices should be used concurrently for the assessment of disease activity at baseline of any treatment regimen; however, endoscopy need not be as necessary as the CAI (and other frequently used clinical indices) were sufficient at assessing disease activity due to the positive correlation.[41]

No MCID for the CAI was reported within any of the identified studies.

Endoscopic Index Score (according to Rachmilewitz)
While no literature was identified for an outcome measure termed the "Endoscopic Index Score," the most common Endoscopic Index Score is that by Rachmilewitz; however, it is uncertain whether this index was in fact the one used in the Cortiment submission to the CADTH Common Drug Review (CDR). The following is a description of the EI score according to Rachmilewitz (which appears to be the most common definition).

The EI is a score based on endoscopic data of four macroscopic criteria.[20] Specific score designations are provided with regard to each of the following criteria: vascular pattern of mucosa (0 = normal, 1 = faded/disturbed, or 2 = completely absent), granulation scattering reflection of light (0 = no, 2 = yes), damage to mucosa that includes aspects like ulcers, erosions, exudates, fibrin, and mucus (0 = none, 2 = slight [< 10 ulcers per 10 cm mucosa], or 4 = pronounced [≥ 10 ulcers per 10 cm mucosa), and vulnerability of the mucosa (0 = none, 2 = slightly increased [contact bleeding], or 4 = greatly increased [spontaneous bleeding]).[20] The total score is obtained by summing all of the individual criteria scores, and endoscopic remission is defined as an EI < 4.[20]

A study by Hirai et al.[41] that sought to determine the most frequently applied clinical and endovascular indices used to detect changes in UC by doing an extensive literature search reported that EI effectively evaluated disease activity in UC upon treatment. A positive correlation of determining disease activity with treatment was noted with differing clinical indices (including the Mayo Score [also known as the disease activity Index [DAI], Truelove and Witts' Severity Index, Lichtiger index, the CCAI, Powell-Tuck Index, and the Seo Index) and was similar to another endoscopic index, the Baron Score.[41] However, it should be noted that these positive correlations were weaker at baseline and were more strongly correlated as the post-treatment time increased (from two, four, to eight weeks post-treatment). From these observations, the authors concluded that EI had a weaker correlation with clinical indices when

disease activity was high and a stronger correlation when there was a decrease in disease activity following treatment.[41] The authors also noted that, even though there was a strong correlation post-treatment, it is important to assess the severity of mucosal lesions post-treatment along with performing assessments using clinical indices.[41] In one post-hoc analysis from two randomized controlled trials that looked at the effectiveness of mesalazine granules of differing doses in patients with UC, Wolff et al.[20] determined that there were discrepancies between EI and histological findings in patients with active UC. In addition, the authors noted that there was increased concordance between EI and histological findings during active UC disease than with patients who are in remission.[20]

No MCID for the EI was reported within any of the identified studies.

Histological Score

While no literature was identified for an outcome measure termed the "Histological Score," the most commonly defined histological finding (which includes a score) is by Riley et al.;[42] however, it is uncertain whether this score was in fact the one used in the Cortiment submission to CDR.

One commonly used histological score used to assess microscopic inflammation in patients with UC is that by Riley et al.[42] The authors observed six histological features obtained from mucosal biopsies taken from the anterior wall between 5 cm and 10 cm from the anal margin using sigmoidoscopy in adult patients with chronic UC who were in symptomatic and sigmoidoscopic remission (based on macroscopic appearances of the rectal mucosa) and who were on either oral sulfasalazine or mesalazine maintenance treatment. The six histological features were graded on a 4-point scale (none, mild, moderate, or severe) and included crypt abscesses, crypt architectural irregularities, acute inflammatory cell infiltrate (this included polymorphic nuclear cells in the lamina propria), depletion of mucin, integrity of surface epithelium, and chronic inflammatory cell infiltrate (round cells in the lamina propria).[42]

The authors determined that patients with clinically and macroscopically (using sigmoidoscopy) quiescent colitis still had a high prevalence of histologically abnormal features. While most of these histological features were not of prognostic importance, acute inflammatory indicators were associated with a two- to three-fold risk of relapse in the 12-month follow-up. However, this result should be taken with caution as the sample size of this study was small (N = 82).[42] That being said, the histological concurrence between pathologists with regard to histological scores indicated that there was good inter-observer reproducibility, especially when mucin depletion and crypt abscesses were observed.[42] In one post-hoc analysis from two randomized controlled trials that looked at the effectiveness of mesalazine granules of differing doses in patients with UC, Wolff et al.[20] observed discrepancies between endoscopic and histological findings in patients with active UC. This echoes that observed by Riley et al.[42] From these results, Wolff et al.[20] determined that histological features should still be assessed; however, they should not be used as a prognostic parameter for disease relapse.[20]

No MCID for this histological score was reported within any of the identified studies.

Inflammatory Bowel Disease Quality of Life Questionnaire

The IBD-QoL was developed by Guyatt et al.[44] as a physician-administered questionnaire and it is widely used for health-related quality of life (HRQoL) assessment in patients with IBD (UC and Crohn's disease [CD]).[45] It is a 32-item Likert-based questionnaire divided into four dimensions: bowel symptoms (10 items), systemic symptoms (five items), emotional function (12 items), and social function (five items). Response to each of the questions is graded from 1 to 7 (1 being the worst situation and 7 the best). Therefore, the total IBD-QoL score ranges between 32 and 224, with higher scores representing better

quality of life. The scores of patients in remission usually range from 170 to 190. An increase in IBD-QoL score of 16 to 32 points constitutes the upper and lower bounds of the clinically meaningful improvement in HRQoL in patients with CD.[43] Information on whether this correlation between score and levels of clinical improvement translates directly to UC was not available through the literature search for this summary.

A systematic review[43] of nine validation studies on the IBD-QoL for UC reported that the IBD-QoL was able to differentiate clinically important differences between patients with disease remission and patients with disease relapse in seven studies by demonstrating significant differences in score.[45] The IBD-QoL can also discriminate changes in the social and emotional state of patients; however, the correlation of this dimension with disease activity is not as high as the correlation with remission of bowel symptoms.[45] The IBD-QoL also demonstrated high test–retest reliability in all the four IBD-QoL dimensional scores. Six studies evaluated IBD-QoL for sensitivity to change and all suggested that it is a sensitive instrument for quantifying changes in HRQoL relative to clinical activity changes in UC.[45]

No MCID for the IBD-QoL was reported within any of the identified studies.

Ulcerative Colitis Disease Activity Index

The UCDAI measures disease activity in patients with UC. Included in the assessment are four criteria, with internal scores ranging from 0 to 3.[46] These include stool frequency (0 = normal, 1 = 1 to 2 stools⁄day > normal, 2 = 3 to 4 stools⁄day > normal, 3 = > 4 stools⁄day > normal), rectal bleeding (0 = none, 1 = streaks of blood, 2 = obvious blood, 3 = mostly blood), appearance of mucosa upon sigmoidoscopy (0 = normal, 1 = mild friability, 2 = moderate friability, 3 = exudation, spontaneous bleeding), and the physician's disease severity assessment (0 = normal, 1 = mild, 2 = moderate, 3 = severe).[46] The total score consists of the sum of all four criteria and can range from 0 to 12, with higher scores indicating more severe disease.[46]

In a randomized, placebo-controlled trial of patients with UC treated with 5-ASA 4g enemas, Sutherland et al.[46] determined that the UCDAI was effective at assessing disease activity upon UC treatment overall and when using each subscale component. Hirai et al.,[41] when seeking to determine the most frequently applied clinical and endovascular indices used to detect changes in UC by doing an extensive literature search, reported that UCDAI was positively correlated to the other most frequently identified clinical indices (including the Mayo Score [also known as the disease activity Index [DAI], Truelove and Witts' Severity Index, Lichtiger Index, the CCAI, Powell-Tuck Index, and the Seo Index) in assessing disease activity post-UC treatment. In addition, the authors noted that this positive correlation extended to endoscopic indices over time post-UC treatment.[41] However, positive correlations with both the other CIs and endoscopic indices were weaker at baseline than in later weeks post-UC treatment, indicating that the correlation strengthened with less disease activity.[41]

No MCID for the UCDAI was reported within any of the identified studies.

Summary

All of the aforementioned clinical indices (CAI, Mayo Score, and UCDAI) were effective at assessing disease activity in patients with UC who received UC treatment. In addition, they were all positively correlated with one another. The EI was also positively correlated with the aforementioned clinical indices; however, it was noted that all of these assessment indices and/or scores were weakly correlated at baseline and strongly correlated eight weeks post-treatment, indicating a stronger correlation associated with weaker disease activity. Both the EI and histological score were also effective at

assessing disease activity, although these items are best implemented alongside clinical indices. Discrepancies were evident between EI and histological score findings; however, histological findings are still an important aspect of assessing inflammation. The IBD-QoL is a physician-administered HRQoL assessment that has been validated and is effective at quantifying changes in HRQoL relative to clinical activity changes in UC.

APPENDIX 6: SUMMARY OF COCHRANE SYSTEMATIC REVIEW OF ORAL BUDESONIDE

1. Objective

To summarize the results from the Cochrane systematic review (SR).[26] This review was undertaken to evaluate both the efficacy and safety of any formulation and dose of oral budesonide in patients with ulcerative colitis (UC). The following summary is based on the published data from the SR.

2. Findings

The objective of the SR was to observe and evaluate the efficacy and safety of oral budesonide (standard and Multi Matrix System (MMX) formulations, along with different doses) in patients with UC. A full SR (with included risk of bias assessment and assessment of heterogeneity) was performed on identified randomized controlled trials (RCTs) (parallel-arm, placebo-controlled or active-comparator, or crossover trials) in patients of any age with a diagnosis of UC (determined using a combination of clinical symptoms and radiologic, endoscopic, and histologic criteria). While heterogeneity in disease activity was expected, the authors of the SR decided to uphold definitions provided by the investigators of the trials, of which the following were acceptable: Beattie's Colitis Symptom Score, the Clinical Activity Index (CAI), the Lichtiger Symptom Score for acute Ulcerative Colitis, the Mayo Index or Score, the Pediatric Ulcerative Colitis Activity Index, the Powell-Tuck Index, the Seo Index, the Simple Clinical Colitis Activity Index (SCCAI), the Truelove and Witt's Severity Index, the Ulcerative Colitis Disease Activity Index (UCDAI), and the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Acceptable interventions included oral budesonide (all formulations and doses) versus control (placebo or active drugs [including corticosteroids (CS) or 5-aminosalicylic acid (5-ASA) drugs]).The primary outcome of interest was the induction of remission (using the intention-to-treat [ITT] population), while secondary outcomes included endoscopic, histological, and clinical improvements, quality of life, endoscopic mucosal healing, change in disease activity score, hospital admissions, surgery, the need for intravenous CS, adverse events (AEs), and study withdrawals. Treatment effects were measured as risk ratios (RRs) and mean differences (MDs) with corresponding 95% confidence intervals (CIs) for dichotomous and continuous outcomes, respectively. Subgroup analyses were planned a priori to look at different durations of treatment, different budesonide doses, disease location, and disease severity. In addition, sensitivity analyses were planned and involved excluding studies of poor methodological quality or those studies only available in abstract form.

Results

Trial characteristics

Six RCTs (N = 1,808) from a systematic search performed in April 2015 were identified and included in the various meta-analyses (MAs). All trials were double-blind, had a duration of eight weeks, and were published between 1996 and 2014. Four trials were placebo-controlled (two of these trials also included active arms [Asacol and Entocort]; however, these were not official comparator arms) and two were active-comparator trials (comparing with either mesalamine or prednisolone, respectively). Three trials were definitively described as multi-centre, with patients from North America, Europe, India, Israel, and Australia. The number of patients per trial ranged from 36 to 509; two trials had a relatively small sample size (range 36 to 72), while the other four were larger (range 343 to 509). Budesonide MMX 9 mg was studied in four of the trials, while standard budesonide (10 mg) was studied in two trials. Of the three large RCTs, all of the patients were on concomitant 5-ASA therapy in the Rubin 2014 study, while patients in the Sandborn 2012 and Travis 2014 studies were excluded if concomitantly taking 5-ASAs.

Primary outcomes of interest in the trials included induction of clinical and endoscopic remission (three trials), clinical remission (two trials), and change in endoscopic and histological scores and improvements in laboratory parameters (one trial). Secondary outcomes included clinical symptom reduction, clinical, endoscopic, and histological remission, mucosal healing, therapeutic success, quality of life, laboratory parameters, evaluation of treatment failures, and AEs (in particular glucocorticoid side effects). One of the included trials was available only in abstract form (Rubin 2014), while the rest were available in full-text format. Detailed trial characteristics with included bias assessments are provided in Table 17.

Patient characteristics

All patients included in the six trials were adults diagnosed with mild to moderate UC. Active UC was defined as having a CAI ≥ 6 and an EI ≥ 4 (one trial), a CAI < 14 (one trial), an EI ≥ 2 in 1 or more colonic segments and having ≥ 4 bloody stools per day (one trial), or having a UCDAI of ≥ 4 and ≤ 10 (three trials). Details regarding proportions of patients with left-sided, proctosigmoiditis, or extensive/pancolitis were not provided in most trials, with the exception of Sandborn 2012. No information was provided regarding mean age, sex, ethnicity, previous treatment, or disease duration. Detailed patient characteristics are provided in Table 17.

TABLE 17: INCLUDED TRIAL AND PATIENT CHARACTERISTICS

Author, Year	Trial[a] and Patient Characteristics	Intervention	Comparator	Outcomes	Bias Assessment						
					RSG	AC	Blinding (All)	Blinding (Tmt Allocation)	IOD	Sel. Rep.	Other
D'Haens, 2010	***Trial:*** • DB RCT • 8 wks ***Patients:*** • Adult pts with active, mild to moderate left-sided UC (N = 36) • Active UC defined as CAI < 14 • Stable doses of immunomodulators[b] or 5-ASAs allowed	Budesonide MMX 9 mg q.d. (n = 18)	PL q.d. (n = 18) x 4 wks then budesonide MMX × 4 wks	***Primary:*** • Clinical remission (CAI ≤ 4) or clinical improvement (50% reduction at 4 wks) ***Secondary:*** • Clinical symptom reduction at 8 wks • Reduction in CAI of 70% • Changes in Rachmilewitz Endoscopic Index Score at 4 and 8 wks	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gross, 2011	***Trial:*** • DB, DD multi-centre (European) RCT • 8 wks ***Patients:*** • Adult pts (18 to 75) with active, mild to moderate UC (N = 343) • Active UC defined as CAI ≥ 6 and EI ≥ 4	Budesonide 9 mg q.d. (n = 177)	Mesalamine 3 g q.d. (n = 166)	***Primary:*** • Clinical remission (CAI ≤ 4) with rectal bleeding and stool frequency subscores = 0 • Subgroup analysis for clinical remission rates of disease location and severity at outset ***Secondary:*** • CAI score changes • Mucosal healing (EI ≤ 1) • Endoscopic remission (EI ≤ 3) • Histological remission • Therapeutic success and benefit (PGA)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lofberg, 1996	***Trial:*** • DB, DD RCT • 8 weeks ***Patients:*** • Adult pts with mild to	• Oral budesonide 6 mg in morning and 4 mg in evening × first 4 wks	• Prednisolone starting dose of 40 mg q.d. • Tapering after first 2 wks, reduction of 5 mg weekly until	***Primary:*** • Change in endoscopic and histological scores of inflammation and improvement in lab parameters	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk

Author, Year	Trial[a] and Patient Characteristics	Intervention	Comparator	Outcomes	Bias Assessment						
					RSG	AC	Blinding (All)	Blinding (Tmt Allocation)	IOD	Sel. Rep.	Other
	moderate extensive and left-sided UC (N = 72) • Active UC defined as EI ≥ 2 in 1 or more colonic segments and ≥ 4 bloody stools/day • Outpatient and hospitalized • Oral sulfasalazine or 5-ASA permitted at constant doses	• Budesonide 4 mg t.i.d. in wks 5 to 7 • Budesonide 4 mg q.d. in wks 8 to 9 (n = 34)	wk 8, during which pts received 7.5 mg q.d. (n = 38)	***Secondary:*** • Clinical symptoms							
Rubin 2014[c]	***Trial:*** • DB RCT • 8 wks ***Patients:*** • Adult pts (18 to 75) with mild to moderate UC (N = 510); mITT n = 458 • Active disease defined as UCDAI ≥ 4 and ≤ 10 with mucosal appearance score ≥ 1 despite use of 5-ASA ≥ 2.4 g daily for ≥ 6 wks)	Budesonide MMX 9 mg (n = 230)	PL (n = 228)	***Primary:*** • Induction of remission (combination clinical and endoscopic) after 8 wks ***Secondary:*** • Clinical remission • Clinical response • Histologic remission and healing • Evaluation of tmt failures • QoL • CRP • Fecal calprotectin levels at 8 wks	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Sandborn 2012 (CORE I)	***Trial:*** • DB, DD, multi-centre (North America and India) RCT • 8 wks ***Patients:*** • Adult pts (18 to 75) with mild to moderate UC (N = 509)	• Budesonide MMX 9 mg (n = 123) • Budesonide MMX 6 mg (n = 121)	• PL (n = 121) • Asacol 2.4 g daily (n = 124)	***Primary:*** • Combined clinical and endoscopic remission at 8 wks (UCDAI ≤ 1, with subscores of 0 for rectal bleeding and stool frequency; no mucosal friability at colonoscopy; and reduction of ≥ 1 point in EI)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Author, Year	Trial[a] and Patient Characteristics	Intervention	Comparator	Outcomes	Bias Assessment						
					RSG	AC	Blinding (All)	Blinding (Tmt Allocation)	IOD	Sel. Rep.	Other
	• Active UC defined as UCDAI ≥ 4 and ≤ 10 • 28.6% had proctosigmoiditis; 29% had left-sided colitis; 40.5% had extensive or pancolitis			***Secondary:*** • Clinical improvement (≥ 3 point reduction in UCDAI) • Endoscopic improvement • Symptom resolution • Histologic healing • Assessment of AEs and potential glucocorticoid side effects							
Travis 2014 (CORE II)	***Trial:*** • DB, DD, multi-centre (Europe, Israel, Russia, Australia) RCT • 8 wks ***Patients:*** • Adult pts (18 to 75) with mild to moderate UC (N = 509); mITT n = 410 • Active UC defined as UCDAI ≥ 4 and ≤ 10	• Budesonide MMX 9 mg (n = 126) • Budesonide MMX 6 mg (n = 128)	• PL (n = 129) • Entocort 9 mg daily (n = 126)	***Primary:*** • Combined clinical and endoscopic remission at 8 wks (UCDAI score ≤ 1, with subscores of 0 for rectal bleeding and stool frequency; no mucosal friability at colonoscopy; reduction of ≥ 1 point in EI) ***Secondary:*** • Clinical improvement (≥ 3-point reduction in UCDAI) • Endoscopic improvement • Symptom resolution • Histologic healing • AEs and potential glucocorticoid side effects	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

5-ASA = 5-aminosalicylic acid; AC = allocation concealment; AE = adverse event; CAI = Clinical Activity Index; CRP = C-reactive protein; DB = double-blind; DD = double-dummy; EI = Endoscopic Index; IOD = incomplete outcome data; mITT = modified intention to treat; MMX = Multi Matrix System; PGA = Physician Global Assessment; PL = placebo; pts = patients; q.d. = once daily; QoL = quality of life; RCT = randomized controlled trial; RSG = random sequence generation; sel. rep. = selective reporting; t.i.d. = twice a day; tmt = treatment; UC = ulcerative colitis; UCDAI = Ulcerative Colitis Disease Activity Index; wks = weeks.

[a] Unless otherwise stated, concomitant mediations were not allowed.

[b] Including methotrexate or azathioprine.

[c] Only available in abstract form at the time of this systematic review and meta-analysis.

Clinical efficacy outcomes

Primary outcome — clinical remission (Table 18)

Five studies (D'Haens 2010, Gross 2011, Sandborn 2012, Rubin 2014, and Travis 2014) were included in the meta-analysis of the primary outcome of induction of clinical remission.

Budesonide MMX 9 mg versus placebo

Budesonide MMX 9 mg daily was observed to be superior to placebo at inducing remission at eight weeks in three studies (N = 900) (Sandborn 2012, Rubin 2014, Travis 2014); RR of 2.25 (95% CI, 1.50 to 3.39). The quality of evidence was considered moderate due to sparse data. A subgroup analysis performed to assess remission rates according to those patients not concurrently using mesalamine (Sandborn 2012 and Travis 2014) suggested that there were significant differences in favour of budesonide MMX when compared with placebo; RR of 2.89 (95% CI, 1.59 to 5.25). A subgroup analysis performed to assess remission rates according to disease location (Sandborn 2012 and Travis 2014) determined that budesonide MMX was significantly more efficacious than placebo at treating the proctosigmoiditis and/or left-sided disease subgroup (n = 289); RR of 2.98 (95% CI, 1.56 to 5.67). No statistically significant differences were observed in patients with extensive disease.

Budesonide MMX 9 mg versus standard budesonide 9 mg

Although not powered to make this comparison, Travis 2014 observed no significant differences in the rate of remission at eight weeks between budesonide MMX 9 mg and Entocort (budesonide controlled ileal release) 9 mg daily; RR of 1.38 (95% CI, 0.72 to 2.65).

Standard budesonide 9 mg versus mesalamine

Data were not pooled for meta-analysis because of the differences in outcomes and in drug regimens between studies. Meta-analysis on the data from one study (Gross 2011) determined that significantly fewer patients experienced clinical remission at eight weeks in the budesonide 9 mg group than in the mesalamine group (RR of 0.72 [95% CI, 0.57 to 0.91]); the quality of evidence was determined as moderate due to sparse data. In addition, the authors from the Sandborn 2012 study determined that there were no significant differences in eight-week remission rates between budesonide MMX 9 mg and Asacol 2.4 g; however, this study was not powered to assess this comparison.

Budesonide versus prednisolone

The only study that compared budesonide (10 mg/day for the first four weeks, 8 mg/day for weeks 5 to 7, 4 mg for weeks 8 to 10) with prednisolone (Lofberg 1996) did not assess this outcome.

Secondary clinical outcomes (Table 18)

Endoscopic improvement

Statistically significant rates of improvement at eight weeks were observed in favour of budesonide MMX 9 mg when compared with placebo when the data from two studies were pooled (N = 442): RR of 1.29 (95% CI, 1.01 to 1.66). When comparing standard budesonide 9 mg to mesalamine, a statistically significant difference favouring mesalamine was observed: RR of 0.84 (95% CI, 0.74 to 0.95); however, this was based on the results from only one study. No statistically significant differences were observed between the other comparisons (budesonide versus Entocort or prednisolone).

Endoscopic remission (mucosal healing)
A statistically significant difference in the rates of endoscopic remission was observed in favour of budesonide MMX 9 mg when compared with placebo in a pooled analysis of two studies (N = 695): RR of 1.56 (95% CI, 1.13 to 2.16). No other comparison (budesonide compared with mesalamine or prednisolone) showed any statistically significant differences in this end point. Based on the results from only one study, no statistically significant differences between budesonide MMX 9 mg and placebo were observed when endoscopic remission was based on disease location (proctosigmoiditis, left-sided disease, or extensive disease).

Histological remission (or improvement)
When compared with placebo in a pooled analysis of three studies (N = 900), budesonide MMX 9 mg showed a statistically significant difference in rates of histological remission at eight weeks. Statistically significant rates of histological remission favoured mesalamine when compared with budesonide 9 mg: RR of 0.81 (95% CI, 0.66 to 0.99); however, this was based on the results from only one study. No statistically significant differences were observed between the other comparisons (budesonide versus Entocort or prednisolone).

Symptom resolution
When compared with placebo, the analysis of the data from two pooled studies (N = 442) showed that a resolution of symptoms was significantly more likely to occur when using budesonide MMX 9 mg compared with placebo: RR of 1.86 (95% CI, 1.25 to 2.77).

Therapeutic success (based on Physician Global Assessment):
Using the Physician Global Assessment (PGA), Gross 2011 assessed therapeutic success between budesonide 9 mg and mesalamine and observed a statistically significant difference favouring mesalamine: RR of 0.75 (95% CI, 0.63 to 0.89).

Other secondary analyses and subgroup/sensitivity analyses
No statistical significant differences were observed between budesonide and any other comparator (placebo, budesonide MMX, mesalamine, or prednisolone) for clinical improvement, endoscopic remission based on disease location, or change in disease activity score (data not shown). In addition, no studies included assessments of quality of life, hospital admissions, the need for intravenous CS, or surgery. With regard to the subgroup analyses, no significant differences were observed based on concurrent mesalamine use or extensive disease. For the sensitivity analyses, no significant differences were observed with regard to either histological or endoscopic remission (see Table 18).

TABLE 18: PRIMARY AND SECONDARY EFFICACY OUTCOME MEASURES

Outcomes	Budesonide MMX 9 mg vs. PL	Budesonide MMX 9 mg vs. Entocort EC 9 mg	Budesonide 9 mg vs. Mesalamine	Budesonide 10 mg vs. Prednisolone 40 mg
Remission,[a] RR (95% CI) Number of studies N	**2.25 (1.50 to 3.39)**[b] 3 900	1.38 (0.72 to 2.65)[c] 1 212	1.48 (0.81 to 2.71)[c] 1 247	NA
Clinical remission, RR (95% CI) Number of studies N	NA	NA	**0.72 (0.57 to 0.91)**[b] 1 343	NA
Clinical Improvement, RR (95% CI) Number of studies N	1.30 (0.99 to 1.70)[b] 2 442	1.28 (0.9 to 1.82)[b] 1 212	0.98 (0.69 to 1.4)[b] 1 247	NA
Symptom resolution, RR (95% CI) Number of studies N	**1.86 (1.25 to 2.77)** 2 442	NA	NA	NA
Endoscopic improvement, RR (95% CI) Number of studies N	**1.29 (1.01 to 1.66)**[b] 2 442	1.14 (0.82 to 1.60)[b] 1 212	**0.84 (0.74 to 0.95)**[b] 1 343	0.94 (0.66 to 1.33)[c] 1 72
Histological remission, RR (95% CI) Number of studies N	**1.51 (1.11 to 2.06)**[c] 3 900	1.21 (0.64 to 2.31)[c] 1 212	**0.81 (0.66 to 0.99)**[b] 1 343	0.56 (0.15 to 2.06)[d] 1 72
Therapeutic success (using PGA), RR (95% CI) Number of studies N	NA	NA	**0.75 (0.63 to 0.89)** 1 343	NA
Endoscopic remission, RR (95% CI) Number of studies N	**1.56 (1.13 to 2.16)**[b] 2 695	NA	0.78 (0.58 to 1.04)[b] 1 343	0.75 (0.23 to 2.42)[d] 1 72
Endoscopic Remission Based on Disease Location				
Proctosigmoiditis, RR (95% CI) Number of studies N	1.66 (0.75 to 3.65) 1 75	NA	NA	NA
Left-sided disease, RR (95% CI) Number of studies	1.53 (0.76 to 3.09)	NA	NA	NA

Outcomes	Budesonide MMX 9 mg vs. PL	Budesonide MMX 9 mg vs. Entocort EC 9 mg	Budesonide 9 mg vs. Mesalamine	Budesonide 10 mg vs. Prednisolone 40 mg
N	1 66			
Extensive disease, RR (95% CI) Number of studies N	1.97 (0.65 to 6.00) 1 105	NA	NA	NA
Subgroup Analyses — Remission				
Mesalamine use				
Concurrent mesalamine, RR (95% CI) Number of studies N	1.75 (0.99 to 3.08) 1 458	NA	NA	NA
No mesalamine, RR (95% CI) Number of studies N	**2.89 (1.59 to 5.25)** 2 442	NA	NA	NA
Disease Location				
Combined proctosigmoiditis and left-sided disease, RR (95% CI) Number of studies N	**2.98 (1.56 to 5.67)** 2 289	NA	**0.74 (0.58 to 0.96)** 1 274	NA
Extensive disease, RR (95% CI) Number of studies N	2.41 (0.61 to 9.56) 2 145	NA	0.64 (0.39 to 1.05) 1 69	NA
Sensitivity Analyses				
Histological remission, RR (95% CI) Number of studies N	1.44 (0.75 to 2.75) 2 442	NA	NA	NA
Endoscopic remission, RR (95% CI) Number of studies N	1.48 (0.91 to 2.40) 1 237	NA	NA	NA

CI = confidence interval; MMX = Multi Matrix System; NA = not applicable; PGA = Physician Global Assessment; PL = placebo; RR = risk ratio; vs. = versus.

Note: Statistically significant results are bolded. RR > 1 in favour of budesonide.

[a] Combined clinical and endoscopic remission.

[b] Moderate quality (based on GRADE): Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.

[c] Low quality (based on GRADE): Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.

[d] Very low quality (based on GRADE): Very uncertain about the estimate.

Safety outcomes

Adverse events and serious adverse events

No statistically significant differences in adverse events (AEs) were observed when comparing budesonide MMX with placebo or Entocort or when comparing budesonide with mesalamine or prednisolone. The only exception to this was a statistically significant reduction in plasma cortisol below the lower reference limit, which was observed in the prednisolone group when compared with standard budesonide: RR of 0.02 (95% CI, 0 to 0.3); however, this result was based on only one study (N = 67). In addition, no statistically significant differences in serious adverse events (SAEs) were observed between budesonide (or budesonide MMX) and any other comparator (placebo, mesalamine, or Entocort).

Of the studies (n = 2) that provided sufficient information regarding withdrawals due to AEs, no statistically significant differences were observed between budesonide MMX and Entocort or standard budesonide and prednisolone. No statistically significant differences between budesonide and prednisolone were observed in the one study that contained sufficient information regarding study withdrawals. Detailed results are provided in Table 19.

TABLE 19: HARMS AND WITHDRAWALS

Outcomes	Budesonide MMX 9 mg vs. PL	Budesonide MMX vs. Entocort EC 9 mg	Budesonide vs. Mesalamine	Budesonide 10 mg vs. Prednisolone 40 mg
AEs, RR (95% CI) Number of studies N	 1.09 (0.95 to 1.26)[a] 3 971	 1.01 (0.81 to 1.26)[a] 1 254	 1.05 (0.73 to 1.50)[a] 1 343	NA
AE — reduction in plasma cortisol below lower reference limit, RR (95% CI) Number of studies N	NA	NA	NA	 **0.02 (0 to 0.3)[b]** 1 67
SAEs, RR (95% CI) Number of studies N	 0.88 (0.33 to 2.4)[c] 2 513	 3.94 (0.45 to 34.74)[c] 1 254	 0.75 (0.17 to 3.28)[c] 1 254	NA
WDAEs, RR (95% CI) Number of studies N	NA	 0.94 (0.56 to 1.58)[a] 1 254	NA	 0.98 (0.40 to 2.41)[b] 1 72
Study withdrawals, RR (95% CI) Number of studies N	NA	NA	NA	 1.12 (0.47 to 2.65)[b] 1 72

AE = adverse event; CI = confidence interval; MMX = Multi Matrix System; NA = not applicable; PL = placebo; RR = risk ratio; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Moderate quality (based on GRADE): Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.

[b] Very low quality (based on GRADE): Very uncertain about the estimate.

[c] Low quality (based on GRADE): Further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.

Limitations

While the SR itself was of good quality (with all appropriate bias and study quality assessments included), limitations were still evident, albeit more from the individual included studies perspective. There were distinct differences in the study sample sizes that ranged from 36 to 509. It appeared that two of the studies with small sample sizes were not adequately powered to assess the primary end point of clinical remission or change in endoscopic and histological scores of inflammation (D'Haens 2010 [N = 36]; and Lofberg 1996 [N = 72], respectively). In addition, the authors had the Rubin 2014 information only in abstract form and were therefore unable to obtain the full compilation of results from the other studies. Many of the outcomes, including the meta-analysis performed on the primary outcome of remission, were based on moderate quality evidence (most often due to sparse data); however, there were other secondary outcomes that were based on low (histological remission [budesonide MMX versus standard budesonide]; SAEs [budesonide MMX versus placebo]; study withdrawals [budesonide MMX versus placebo]) or very low (histological remission [budesonide versus prednisolone]; endoscopic remission [budesonide versus prednisolone]; AEs [budesonide versus prednisolone]; study withdrawals or WDAEs [budesonide versus prednisolone]) quality evidence. Potential confounders such as concurrent 5-ASAa and the harder to treat population observed in the Rubin 2014 study could have influenced the results, thereby introducing uncertainty surrounding the effect estimates. Even though all patients had to meet the criteria for having mild to moderate UC as per their individual study requirements, the authors did note that they accepted all possible definitions. Therefore, there may have been some discrepancy regarding UC disease severity between patients in differing studies and, hence, the results may not pertain or be generalizable to all patients with mild to moderate UC. Finally, even though the standard appears to treat patients for eight weeks, this time duration may not, in fact, be sufficient to identify true clinical remission.

Summary

Six studies were included in this SR. Of the six included trials, pooled data from three recent, large randomized controlled trials (N = 900) provided evidence that budesonide MMX, when compared with placebo, was more than two times more likely to induce combined endoscopic and clinical remission (classified as remission) at eight weeks. Subgroup analyses (pooled data from two studies) indicated that budesonide MMX was more effective than placebo in inducing remission at eight weeks in patients with combined proctosigmoiditis and left-sided disease and in patients; however, it was less effective than mesalamine (results from one study included). In addition, a subgroup analysis including only patients not taking concurrent mesalamine demonstrated that budesonide MMX was almost three times as likely to induce remission than placebo (pooled data from two studies was included).

With regard to other outcomes, it appeared that budesonide MMX resolved symptoms and induced endoscopic remission at eight weeks and was also more effective at inducting histological remission and endoscopic improvement when compared with placebo; however, it was less effective with regard to the aforementioned latter end points when compared with mesalamine (based on the results from one study). No differences between budesonide MMX, standard budesonide, mesalamine, prednisolone, or placebo were observed with regard to AEs or serious adverse events. The only exception to this was the one study (N = 67) whereby prednisolone appeared to cause a reduction in plasma cortisol below the lower reference limit.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

Introduction

Background

The studies included in the systematic review did not provide head-to-head comparisons of budesonide MMX with other relevant drugs used in the treatment of mild to moderate ulcerative colitis (UC). Although the CORE I study included a mesalazine 2.4 g group, the study was not designed or powered for comparisons between budesonide MMX and mesalazine. The objective of this section is to summarize and critically appraise the indirect evidence comparing the efficacy and safety of budesonide MMX with other drugs used for treatment of mild to moderate UC.

Methods

One network meta-analysis (NMA) was provided by the manufacturer in the submission.[47] The CADTH Common Drug Review (CDR) literature search results were also reviewed to identify any additional published relevant indirect evidence.

Description of indirect comparisons identified

One manufacturer-submitted network meta-analysis (NMA) was relevant to the analysis of treatments for mild to moderate UC. No additional published indirect comparisons relevant to this review were identified. A summary of the characteristics of the NMA for the two outcomes assessed (complete clinical remission and relapse from clinical remission) is presented in Table 20.

TABLE 20: CHARACTERISTICS OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS

	Manufacturer-submitted NMA[47]
Study designs	RCTs
Population	Adults ≥ 18 years with mild to moderate UC
N of included studies (complete clinical remission)	7 RCTs
N of patients (complete clinical remission)	1,849 (ITT)
N of included studies (relapse from clinical remission)	16 RCTs
N of patients (relapse from clinical remission)	1,902 (ITT)

ITT = intention-to-treat; NMA = network meta-analysis; RCT = randomized controlled trial; UC = ulcerative colitis.

Review and Appraisal of Indirect Comparisons

Review of manufacturer-submitted network meta-analysis for treatment of mild to moderate ulcerative colitis

Objectives and rationale

The primary objective for the indirect comparison was to compare the efficacy of budesonide MMX to 5-ASA therapies and other corticosteroid therapies available in Canada for the treatment of mild to moderate UC.

Methods

Study eligibility and selection process

Study evidence for inclusion in the NMA was derived from a systematic literature search conducted to identify randomized controlled trials (RCTs) of therapies used to treat mild to moderate UC. The search strategy was based on a review conducted by National Institute for Health and Care Excellence (NICE) in 2013, which included studies from 1946 to November 2012.[48] An updated search of electronic medical

databases (OVID MEDLINE, OVID Embase, and the Cochrane Library) between the dates of November 15, 2012 and November 26, 2015 was conducted using a predefined search strategy. Additional articles of relevance were identified from Internet searches (conference abstracts) and bibliography searches. Inclusion criteria for the systematic literature review are presented in Table 3. The following exclusion criteria were applied, and were based on the NICE 2013 review:

- Studies that used rectal treatment for induction of remission in patients with left-sided and/or extensive disease as this does not reflect current clinical practice
- Studies comparing different brands of mesalazine for induction of complete clinical remission
- Studies that compared different preparations, volumes, or regimens of the same drug, as there were no clinically relevant differences for these comparisons
- Studies that did not included patients with left-sided and/or extensive disease (or if this population made up < 50% of the total population)
- Studies that did not report the extent of disease of the enrolled population
- Studies that looked at immunomodulators were excluded from the induction of complete clinical remission network, as they would not add much power to the network if included
- Studies of treatments unavailable in Canada.

TABLE 21: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults ≥ 18 years with mild to moderate UC
Intervention	Budesonide MMX 9 mg
Comparators	• Oral 5-ASAs (mesalazine, olsalazine, sulfasalazine) • Oral corticosteroids (prednisolone, budesonide, beclomethasone) • Rectal 5-ASAs (mesalazine) or rectal corticosteroids (hydrocortisone, budesonide) in combination with oral treatments • Immunomodulators (azathioprine, 6-mercaptopurine)[a] • Placebo
Outcomes	• Induction of clinical and endoscopic remission • Relapse from clinical remission (6 months minimum)
Study Design	Published RCTs

5-ASA = 5-aminosalicylic acid; RCT = randomized controlled trial; MMX = Multi Matrix System; UC = ulcerative colitis.
[a] Used as comparator only for relapse from clinical remission end point.
Source: Manufacturer-submitted network meta-analysis.[47]

Two reviewers independently reviewed study records, citation titles, and abstracts in the literature search to assess study eligibility, and potentially eligible articles were independently reviewed in full-text form for formal inclusion in the review. Disagreements between reviewers were resolved by a consensus meeting. Two reviewers independently extracted data from the RCTs, and disagreements between reviewers were resolved by consensus.

Data extraction

For the induction NMA, seven RCTs (published between 1960 and 2014) were included, which provided a combined total of 1,849 patients in the ITT population. The following treatments were included: low-dose olsalazine (1 g to 1.49 g), low- (1.6 g to 2.4 g) and high-dose (> 2.4 g per day) mesalazine, low-dose sulfasalazine (4 g to 6 g), and budesonide MMX 9 mg. The mean age of patients ranged from 32 years to 43 years. Three studies included patients with prior 5-ASA use, two studies did not include patients with prior 5-ASA use, and two studies did not report prior 5-ASA use in patients. Five studies were eight weeks in duration, one study was six weeks, and one was four weeks in duration.

For the maintenance NMA, 16 RCTs (published between 1973 and 2005) were included, which provided a combined total of 1,902 patients in the ITT population. The following treatments were included: low-dose olsalazine (≤ 1 g), low- (≤ 1.5 g, ≤ 2 g for Pentasa) and high-dose (> 1.5 g, > 2 g for Pentasa) mesalazine, low- (≤ 2 g) and high-dose (2 g) sulfasalazine, and azathioprine 100 mg. The mean age of patients ranged from 38 years to 48 years. Eight studies included patients with prior 5-ASA use, one study did not include patients with prior 5-ASA use, and the remaining studies did not report prior 5-ASA use. Nine studies were 12 weeks in duration, and seven studies were six weeks in duration.

Comparators

The intervention of interest was budesonide MMX. Comparators of interest included oral 5-ASAs, oral corticosteroids, rectal 5-ASAs in combination with oral treatments, and rectal corticosteroids in combination with oral treatments. Immunomodulators were included as a comparator only for the relapse from clinical remission end point.

Outcomes

Two analyses were conducted: one for complete remission (induction NMA), and another for relapse from clinical remission (maintenance NMA). As budesonide MMX is not indicated for maintenance of remission, this intervention was not included in the relapse NMA. No safety outcomes were analyzed.

The definition of complete remission differed between studies included in the induction NMA and are defined in Table 22.

TABLE 22: DEFINITIONS OF COMPLETE REMISSION IN STUDIES INCLUDED IN THE INDUCTION NETWORK META-ANALYSIS

Study	Definition of Complete Remission
Jiang 2004 (low-dose vs. high-dose olsalazine)	Subsidence of clinical symptoms with relative normal mucous membrane in colonoscopy
Kamm 2007 (low-dose mesalazine vs. placebo)	Modified UCDAI score ≤ 1 with rectal bleeding and stool frequency subscores of 0, no mucosal friability, ≥ 1-point reduction in sigmoidoscopy score from baseline
Lennard-Jones 1960 (prednisolone vs. placebo)	Freedom from symptoms combined with finding of an inactive or rarely active, normal mucosa on sigmoidoscopy
Lichtenstein 2007 (low-dose mesalazine vs. placebo)	Modified UCDAI score ≤ 1 with rectal bleeding and stool frequency subscores of 0, ≥ 1-point reduction in sigmoidoscopy score from baseline
Sandborn 2009 (low-dose vs. high-dose mesalazine)	PGA score of 0 (complete resolution of or normalization of stool frequency)
Sandborn 2012 (CORE I, budesonide MMX 9 mg vs. placebo)	Modified UCDAI score ≤ 1 with rectal bleeding and stool frequency subscores of 0, no mucosal friability on colonoscopy, ≥ 1-point reduction in endoscopy score from baseline
Travis 2014 (CORE II, budesonide MMX 9 mg vs. placebo)	Modified UCDAI score ≤ 1 with rectal bleeding and stool frequency subscores of 0, no mucosal friability on colonoscopy, ≥ 1-point reduction in endoscopy score from baseline

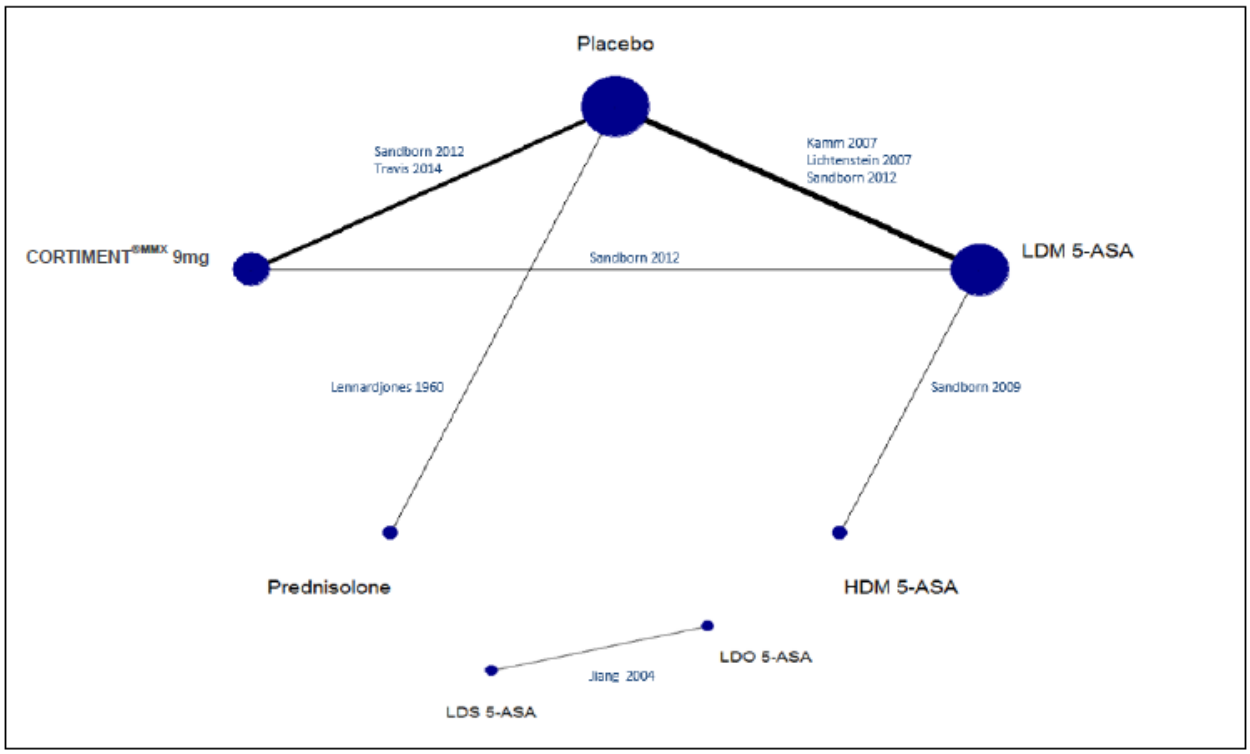
MMX = Multi Matrix System; PGA = Physician Global Assessment; UCDAI = Ulcerative Colitis Disease Activity Index; vs. = versus.

Quality assessment of included studies

Quality assessment of RCTs was conducted using the checklist provided in the NICE single technology appraisal template. Assessment of the risk of bias of eligible RCTs was performed by two reviewers.

Evidence network

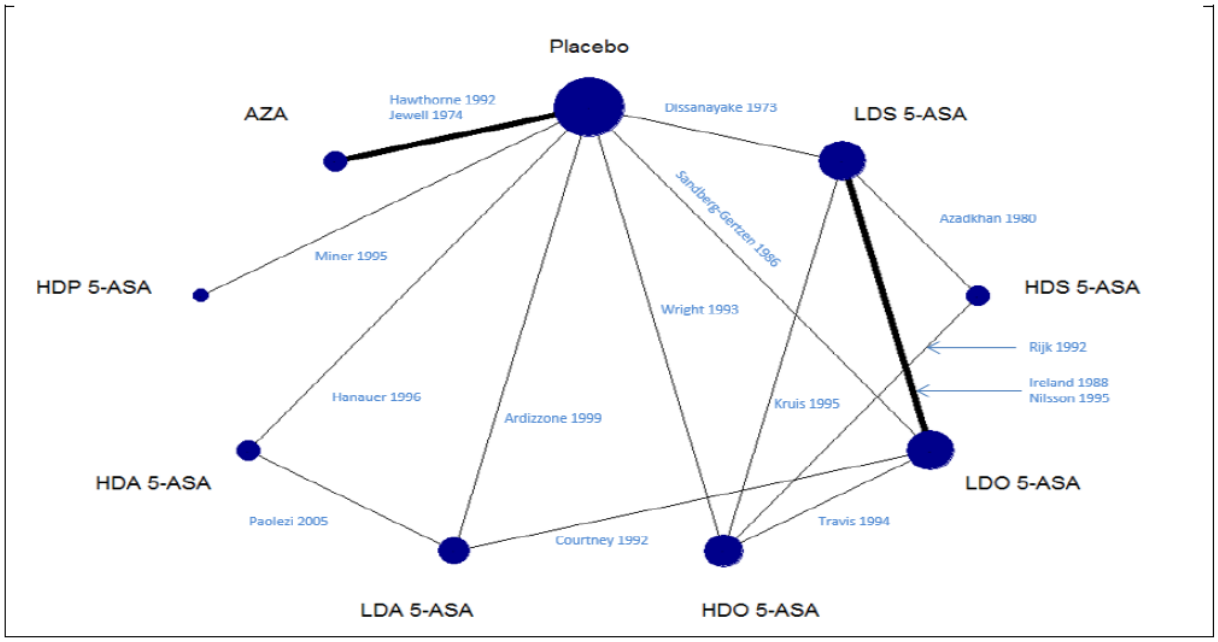
FIGURE 2: INDUCTION NETWORK META-ANALYSIS



KEY: 5-ASA = 5-aminosalicylic acid; HDM = high-dose mesalazine; LDM = low-dose mesalazine; LDO = low-dose olsalazine; LDS = low-dose sulphasalazine.

Source: Manufacturer-submitted network meta-analysis.[47]

Figure 3: Maintenance Network Meta-Analysis



KEY: 5-ASA = 5-aminosalicylic acid; AZA = Azathioprine; LDA = Low-dose Asacol® (5-ASA); LDO = Low-dose Olsalazine (5-ASA); LDS = Low-dose Sulphasalazine (5-ASA); HDA = High-dose Asacol® (5-ASA); HDO = High-dose Olsalazine (5-ASA); HDP = High-dose Pentasa® (5-ASA); HDS = High-dose Sulphasalazine (5-ASA).

Source: Manufacturer-submitted network meta-analysis.[47]

Indirect comparison methods

A Bayesian NMA was performed for each outcome using methods outlined by the NICE technical support document.[49-52] For the induction NMA, the number of individuals in clinical remission was treated as a binary outcome, and estimates were presented as relative risks by converting odds ratios. For the relapse NMA, the number of individuals unable to maintain clinical remission was treated as cumulative count statistics to generate hazard ratios. For both outcomes, both fixed-effects and random-effects analyses were performed. To assess model fit, posterior residual deviance was compared with the corresponding number of unconstrained data points, and the deviance information criterion (DIC) was also assessed. The NMAs were performed using WinBUGS and R using burn-in samples of 20,000 iterations or more and sampling iterations of 60,000 iterations or more.

Heterogeneity was assessed by summarizing relevant information using boxplots or tables and performing subgroup and sensitivity analyses where appropriate. The following potential factors for heterogeneity were considered: age, prior 5-ASA use, placebo response, blinding, and year of study. A placebo-adjusted meta-regression analysis was conducted for induction NMA. For the relapse NMA, the presence of several single-study connections between interventions prevented the use of a meta-regression analysis.

To assess consistency, deviance and DIC statistics were compared in fitted consistency and inconsistency models. The posterior mean deviance of the individual data points in the inconsistency model was also plotted against their posterior mean deviance in the consistency model to identify loops where inconsistency was present.

Results

Both fixed-effects and random-effects models were conducted. However, because of networks that mainly comprised single-study connections, between-study variance was difficult to estimate and the FE model was used for the main analyses. The results of both analyses are presented below.

Induction network meta-analysis

A total of seven RCTs (1,849 patients) informed the network for induction of complete clinical remission. Data from head-to-head trials were available for six pairwise comparisons in the network, with single studies informing four of these comparisons. The Jiang 2004 study that assessed low-dose versus high-dose olsalazine was disconnected from the network, and therefore this study did not inform the network. The DIC was 77.30 for the fixed-effects model and 78.88 for the random-effects model. With the fixed-effects model, budesonide was associated with a statistically significant improvement for induction of complete clinical remission compared with placebo and high-dose mesalazine. There was one study that compared high-dose (4.8 g/day) versus low-dose (2.4 g/day) mesalazine (ASCEND III, N = 772, Sandborn 2009[53]) in patients with active mild to moderate UC, and a greater proportion of patients in the low-dose mesalazine group achieved complete remission (PGA score 0) compared with the high-dose mesalazine group (2.6% versus 5.0%), although partial response rates were higher in the high-dose group compared with the low-dose group.

TABLE 23: INDUCTION OF COMPLETE CLINICAL REMISSION

	Fixed-Effects Model		Random-Effects Model	
Drug	Treatment vs. placebo, RR [95% CrI]	Budesonide MMX vs. treatment, RR [95% CrI]	Treatment vs. placebo, RR [95% CrI]	Budesonide MMX vs. treatment, RR [95% CrI]
Budesonide MMX	2.79 [1.83 to 4]	-	2.83 [1.32 to 5.08]	-
Prednisolone	3.21 [1.02 to 6.68]	0.87 [0.37 to 2.89]	3.22 [0.69 to 7.22]	0.88 [0.29 to 4.5]
High-dose mesalazine	1.16 [0.5 to 2.34]	2.4 [1.13 to 5.69]	1.17 [0.24 to 3.97]	2.4 [0.64 to 11.82]
Low-dose mesalazine	2.06 [1.48. 2.78]	1.36 [0.89 to 2.01]	2.07 [0.96 to 3.64]	1.36 [0.61 to 2.91]

CrI = credible interval; MMX = Multi Matrix System; RR = relative risk; vs. = versus.

Maintenance network meta-analysis

A total of 16 RCTs (1,902 patients) informed the network for relapse from clinical remission. Data from head-to-head trials were available for 14 of the pairwise comparisons in the network, with single studies informing 12 of these comparisons. Because budesonide MMX does not have an indication for maintenance of UC remission, it was not included as an intervention in the maintenance NMA. The DIC was 205.187 for the fixed-effects model and 206.371 for the random-effects model. The hazard ratios of treatment versus placebo for relapsing from clinical remission ranged from 0.25 (95% CrI, 0.1 to 0.6) for high-dose sulfasalazine to 0.62 (95% CrI, 0.39 to 0.97) for azathioprine.

TABLE 24: RELAPSE FROM CLINICAL REMISSION

	Fixed-Effects Model	Random-Effects Model
Drug	Treatment vs. placebo, HR [95% CrI]	Treatment vs. placebo, HR [95% CrI]
Azathioprine	0.62 [0.39 to 0.97]	0.61 [0.3 to 1.23]
High-dose Pentasa	0.52 [0.34 to 0.78]	0.51 [0.21 to 1.23]
High-dose Asacol	0.54 [0.35 to 0.85]	0.55 [0.26 to 1.16]
Low-dose Asacol	0.61 [0.39 to 0.95]	0.62 [0.32 to 1.27]
High-dose olsalazine	0.35 [0.21 to 0.55]	0.32 [0.14 to 0.59]
Low-dose olsalazine	0.44 [0.28 to 0.68]	0.42 [0.21 to 0.77]
High-dose sulfasalazine	0.25 [0.1 to 0.6]	0.23 [0.07 to 0.71]
Low-dose sulfasalazine	0.33 [0.2 to 0.53]	0.31 [0.15 to 0.6]

CrI = credible interval; HR = hazard ratio; MMX = Multi Matrix System.

Inconsistency

In the induction NMA, there was only one closed loop and no inconsistency was detected. There was also no inconsistency detected for the maintenance NMA. Caution should be used in interpreting these results as there may not have been sufficient power to detect inconsistency in these networks.

Subgroup analysis of prior 5-ASA use

A subgroup analysis based on prior 5-ASA treatment for the induction NMA was performed by separating studies into the following groups: naive to 5-ASA; prior use of 5-ASA; mixed (both naive and experienced); insufficient data. Additional data for budesonide MMX were taken from the pooled analysis of the CORE studies and the CONTRIBUTE study (patients who were on a therapeutic background of 5-ASA) were used to allow for further analyses. Subgroup analysis of the induction NMA by 5-ASA use was limited without the use of additional data, as studies either reported a mix of prior 5-ASA use or did not report 5-ASA use. Using additional data, the results of the analyses showed that budesonide MMX was associated with statistically significant improvements in the induction of remission compared with placebo in 5-ASA naive, 5-ASA experienced, and 5-ASA failures. However, these results were based only on the CORE I, CORE II, and CONTRIBUTE studies, with the addition of two studies comparing low-dose mesalazine with placebo in the 5-ASA naive network, thereby limiting the usefulness of this analysis.

Sensitivity analysis of placebo response

Placebo response rates differed between studies and were a potential source of heterogeneity in the induction NMA. Sensitivity analyses were conducted by separating the studies published prior to and after 2000 to reduce variation in clinical practice over time. Only one study in the induction NMA was conducted prior to 2000 (Lennard-Jones 1960,[54] prednisolone vs. placebo). When this study was removed from the network, budesonide MMX was associated with a slightly improved induction of complete clinical remission compared with placebo, low-dose mesalazine, and high-dose mesalazine. A meta-regression was also conducted to adjust for placebo responses, centering on the pooled placebo response calculated from the seven studies in the induction NMA. Results from the meta-regression were similar to that of the primary analysis.

Critical appraisal

There were several limitations with the NMA. The induction NMA was informed by few studies, limiting the strength of the network. Although the maintenance NMA had a greater number of studies, most of the network was made up of single-study connections. The studies that were included in the NMAs were

clinically heterogeneous. The studies were published across several decades, where clinical practice and the enrolled populations would have been variable, although sensitivity analyses were conducted separating studies by year of publication. In the induction NMA, study duration ranged from four weeks to eight weeks, which would be an appropriate length of time to ascertain clinical remission. In the maintenance NMA, study duration was either six weeks or 12 weeks. According to the clinical expert, a minimum of 12 weeks should be employed for a study looking at maintenance treatment for UC; otherwise, it may be difficult to observe a difference between treatments. The dosing of 5-ASAs employed in the studies was appropriate and the categorization of low-dose and high-dose 5-ASAs was consistent between studies. For the induction NMA, one study informed the comparison of low-dose versus high-dose mesalazine, and this study showed that the low-dose mesalazine group had a higher proportion of patients achieving clinical remission than the high-dose mesalazine group. As there was only one study informing this comparison, the results of the NMA also mirrored the results of this study, which may not be robust.

Model fit statistics were presented, and generally showed that both fixed-effects and random-effects models had similar fit. According to the manufacturer, because the networks mainly comprised single-study connections, between-study variance was difficult to estimate and the fixed-effects model was used for the main analyses. While the use of a fixed-effects model appears reasonable, there were some differences in reported treatment effects between the fixed- and random-effects models.

Though subgroup and sensitivity analyses were performed to mitigate sources of heterogeneity, the lack of data available in the network limited the amount of information gleaned from these analyses. Several studies were excluded with the reason of complete clinical remission not being defined. Although the definition may not have been defined, a sensitivity analysis including these studies could have been considered.

The only outcome that was assessed that included budesonide MMX was induction of remission. Other outcomes, such as clinical response, quality of life, histological healing, and harms, were not assessed.

Discussion

One manufacturer-submitted NMA was summarized and critically appraised. Two outcomes were assessed: induction of complete clinical remission (induction NMA), and maintenance of clinical remission (maintenance NMA). As budesonide MMX is not indicated for the maintenance of remission in UC, it was not included as an intervention in the maintenance NMA. The analyses were limited by a sparse network, a network that consisted mainly of single-study connections, and clinical heterogeneity between studies with regard to the length of treatment, potential differences in clinical practice over the decades the studies were conducted, and the use of different definitions of complete remission across studies.

Due to these limitations, the results of the NMA for induction of complete clinical remission and maintenance of clinical remission are uncertain.

Conclusion

One manufacturer-submitted NMA was summarized and critically appraised. The NMA assessed the induction of complete clinical remission and maintenance of clinical remission. Based on the induction NMA, budesonide MMX was associated with a statistically significant improvement for induction of complete clinical remission compared with placebo and high-dose mesalazine. However, these analyses were subject to significant limitations, including networks that were informed mainly by single-study

connections, and clinical heterogeneity across studies with regard to length of treatment and the use of different definitions of complete remission. Due to these limitations, the results of the NMA for induction of complete clinical remission and maintenance of clinical remission are uncertain.

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