Common Drug Review
Pharmacoeconomic Review Report

April 2017

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

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
AE	adverse event
CUA	cost-utility analysis
HD	high-dose
IBD	inflammatory bowel disease
ICUR	incremental cost-utility ratio
LD	low-dose
MMX	Multi Matrix System
MOHLTC	Ministry of Health and Long-Term Care
NMA	network meta-analysis
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
UC	ulcerative colitis

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Budesonide (Cortiment MMX) (referred to as budesonide MMX throughout the report)
Study Question	"The objective of this study was to determine the cost-effectiveness of Cortiment MMX (9 mg/day) compared to standard care with oral 5-ASAs (4.8 g/day) for the induction of complete remission in patients with active, mild to moderate UC."
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with active, mild to moderate UC. The patients were characteristic of those included in the pooled intention-to-treat population of the CORE I and CORE II studies assessing budesonide MMX.
Treatment	Budesonide MMX (9 mg/day) as first-line induction treatment
Outcome	QALYs
Comparator	HD 5-ASA (4.8 g/day) as first-line induction treatment
Perspective	Canadian health care payer
Time Horizon	5 years
Results for Base Case	Initial treatment with budesonide MMX was a dominant strategy compared with initial treatment with HD 5-ASA — i.e., the use of budesonide MMX for induction of remission was more effective and less costly.
Key Limitations	• There are several significant limitations with the manufacturer's NMA informing effectiveness estimates of budesonide MMX and HD 5-ASA (in terms of probability of inducing remission), which are the main drivers of the results of the manufacturer's economic evaluation. In particular, in the NMA, the effectiveness of HD 5-ASA was informed by a single study assessing HD 5-ASA versus LD 5-ASA, which represents a weak connection of the network. As such, estimates for HD 5-ASA from the NMA are uncertain. In addition, available evidence from the CORE studies and from the literature is inconclusive for this comparison. • The use of HD 5-ASA as a comparator does not reflect the most probable place in therapy for budesonide MMX; i.e., as a post 5-ASA option (according to the clinical expert consulted by CDR). A more appropriate comparator would be other second-line therapies, most notably other corticosteroids such as prednisone). There is no direct evidence available comparing budesonide MMX versus another corticosteroid; the results from the manufacturer's NMA informing this comparison are uncertain.
CDR Estimate(s)	In the absence of appropriate evidence, the cost-effectiveness of budesonide MMX versus 5-ASA or another corticosteroid such as prednisone cannot be assessed with robustness. Under the assumption of equal efficacy of budesonide MMX versus 5-ASA and versus prednisone, and considering only the drug cost of treatment, budesonide MMX (daily cost of $8.24) is 62% more expensive than generic 5-ASA (higher daily induction dose of $3.16) and 97% more expensive than prednisone (induction daily dose of $0.22).

5-ASA = 5-aminosalicylic acid; CDR = CADTH Common Drug Review; HD = high-dose; ICUR = incremental cost-utility ratio; LD = low-dose; MMX = Multi Matrix System; NMA = network meta-analysis; QALY = quality-adjusted life-year; UC = ulcerative colitis.

EXECUTIVE SUMMARY

Background

Budesonide (Cortiment Multi Matrix System [MMX]) is an oral formulation of the topically acting corticosteroid budesonide that extends release of the drug to the entire colon. Budesonide MMX is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis (UC).[1] The manufacturer requested reimbursement of budesonide MMX as per the Health Canada indication. Budesonide MMX is available as a 9 mg tablet at the manufacturer-submitted price of $8.24 per tablet. The recommended dose of budesonide MMX is 9 mg daily. At the submitted price and recommended dose of 9 mg daily, the cost of eight weeks of treatment with budesonide MMX is $461.

The manufacturer submitted a cost-utility analysis comparing the use of budesonide MMX to standard care using high-dose (HD) 5-aminosalicylic acid (5-ASA) for the induction of remission among adult patients with active, mild to moderate UC. The analysis also assessed the impact of treatment for patients progressing along the disease and treatment pathway.[2] The analysis was based on a Markov state-transition model using a five-year time horizon, and undertaken from the perspective of the Canadian publicly funded health care system. Patients with active, mild to moderate UC received either budesonide MMX or HD 5-ASA to induce remission. Patients who experienced remission received maintenance therapy while those who failed to achieve remission or who relapsed after remission moved to the modelled next line in therapy, from first-line therapy (budesonide MMX or HD 5-ASA) to prednisone, low-dose (LD) infliximab, HD infliximab, hospitalization with rescue care, and surgery. Treatment effectiveness data (defined in terms of probability of achieving remission) were derived from a manufacturer-commissioned network meta-analysis (NMA).[3] Costs considered were drug acquisition costs, treatment of adverse events, and costs of disease management including routine follow-up visits, hospitalization, and surgery. The manufacturer reported that, compared with HD 5-ASA, use of budesonide MMX for induction of remission was more effective and less expensive and was thus the dominant strategy.

Summary of identified limitations

The CADTH Common Drug Review (CDR) noted two key limitations with the manufacturer's pharmacoeconomic submission. Firstly, there is uncertainty associated with the comparative clinical effectiveness for budesonide MMX versus HD 5-ASA, which drive the pharmacoeconomic results. The results from the NMA providing this comparison are uncertain, and other evidence from the CORE studies and the literature are inconclusive.

Secondly, the choice of HD 5-ASA as the comparator for budesonide MMX is questioned, given that it is not expected that budesonide MMX would displace 5-ASA as first-line therapy, according to the clinical expert consulted by CDR. It is expected that budesonide MMX would be used in practice as a second-line treatment and that more appropriate comparators would be other corticosteroids such as prednisone. Again, given the available evidence, an advantage of one treatment over the other cannot be concluded.

Key results and conclusions

The comparative effectiveness of budesonide MMX versus 5-ASA and other corticosteroids such as prednisone is uncertain and cannot be concluded to be an efficacy advantage for budesonide MMX over one of these treatments, and vice versa. A cost-effectiveness assessment of budesonide versus these drugs cannot be performed with sufficient robustness. Hence, under the assumption of equal efficacy of budesonide MMX versus 5-ASA and versus prednisone, and considering only the drug cost of treatment, budesonide MMX (daily cost of $8.24) is 62% more expensive than generic 5-ASA (higher daily induction dose of $3.16) and 97% more expensive than prednisone (induction daily dose of $0.22).

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis comparing budesonide MMX to standard treatment with high-dose (HD) 5-aminosalicylic acids (5-ASAs) for the induction of remission in adult patients with active, mild to moderate ulcerative colitis (UC).[2] The use of budesonide MMX and HD 5-ASA were evaluated in the context of a step-up treatment pathway informed by Canadian guidelines[4] in which patients who failed to achieve remission or who subsequently relapsed from remission were switched to next-line therapy. The model population was assumed to have characteristics in alignment with the CORE I and II trials that assessed budesonide MMX:[5] the mean age was 42.8 years, 56.9% were male, and mean body weight was 70 kg.

The cost-utility analysis was based on a Markov state-transition model using a five-year horizon and eight-week cycle length. The time horizon was chosen to capture long-term costs and outcomes without projecting too far beyond available trial data. The cycle time was based on the length of a course of treatment with budesonide MMX. The analysis was undertaken from the perspective of the Canadian publicly funded health care system. Patients enter the model with mild or moderate disease, and receive a first-line treatment, either HD 5-ASA (4.8 g per day) or budesonide MMX (9 mg per day). At the end of the course of treatment (consisting of eight weeks of budesonide MMX or HD 5-ASA), patients either achieve complete remission or they do not (defined in the economic evaluation as achieving both symptomatic and endoscopic remission). Patients in remission stay in that health state and receive maintenance therapy (defined as treatment with HD 5-ASA) until they relapse; otherwise, patients move to receive treatment with prednisone, the modelled second-line intervention. After a course of treatment with prednisone (eight weeks of 24.4 mg per day), patients either achieve remission or they do not. Patients in remission stay in that health state and receive maintenance therapy (consisting of HD 5-ASA) until they relapse; otherwise, patients move to receive treatment with infliximab: patients initially receive eight weeks of low-dose (LD) infliximab (5 mg/kg), at which point they either achieve response to treatment or they do not (based on achieving symptomatic improvement). Patients achieving response stay in that health state and receive maintenance therapy with 5 mg/kg infliximab until they relapse; otherwise, they move to HD infliximab (10 mg/kg). After eight weeks of treatment, patients who respond are maintained on 10 mg/kg infliximab. Patients who fail to respond to HD infliximab or who lose response move to the hospitalization state to receive rescue treatment. Patients who achieved response in the hospitalization state received maintenance therapy with HD infliximab, while those who failed to achieve response moved to the "surgery/post-surgery" state. Patients who received surgery were assumed to discontinue their current treatment and remain in complete remission for the remainder of their time in the model. A proportion of patients were assumed to experience post-surgical complications. The full model structure is provided in Figure 1.

Treatment efficacy for induction of remission among patients with active disease for first-line therapies (budesonide MMX; HD 5-ASA) and prednisone (second-line) were derived from a manufacturer-commissioned network meta-analysis (NMA).[3] The NMA also informed relapse rates after patients gained remission with first-line therapies and prednisone; this led to the next therapy in the treatment pathway. For patients who do not gain remission or who relapse while on prednisone and move on to treatment with a biologic (i.e., infliximab), the transition probabilities for response, for both LD and HD infliximab, were informed from a trial that assessed the use of infliximab in patients with moderate to

severe UC.[6] Rates of relapse for patients on LD and HD infliximab were derived from the same trial. The proportions of hospitalized patients requiring surgery (5.30%) as well as the proportions of patients who experienced post-surgical complications (33.3%) were based on literature values.[7,8] Patients could die at any time throughout the model; the risk of death was based on Canadian-specific general population estimates of all-cause mortality.

The manufacturer undertook a literature review to identify health utility estimates associated with active, mild to moderate UC; drug-induced complete remission (applies to budesonide MMX, 5-ASA, prednisone, clinical response on both infliximab dosages, and achievement of response due on rescue therapy in the hospitalization state); hospitalization, and surgery-induced complete remission.[9-11] Adverse events (AEs) were considered for eight weeks of treatment on corticosteroids (budesonide MMX and oral prednisone), but not for other drug treatments. The incidence of AEs was derived from a safety analysis of budesonide MMX[12] and a clinical trial of prednisolone.[13] A utility decrement was applied to the AEs considered (acne, fluid retention, flushing, hirsutism, insomnia, mood changes, moon face, and sleep changes). These utility decrements were based on literature sources [14-17] and assumptions.

The costs considered in the model were drug acquisition costs, disease management costs, drug AE costs, hospitalization costs, surgery costs, and costs of post-surgical complications. Drug costs were derived from the manufacturer's submitted drug price for budesonide MMX, while the costs of all other drugs came from the Ontario Drug Benefit Formulary.[18] Disease management resource use was based on expert opinion — specifically, patients with controlled disease were assumed to receive two annual gastroenterologist visits and one annual complete blood count, fecal calprotectin, and colonoscopy with biopsy. Patients with active disease were assumed to visit a gastroenterologist, receive a full blood count, and fecal calprotectin every two months and undergo one endoscopy annually. All AEs experienced while on corticosteroids were assumed to result in a gastroenterologist visit. Costs of physician visits were derived from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Schedule of Benefits,[19] while costs of laboratory services came from the Ontario MOHLTC Schedule of Benefits for Laboratory Services.[20] The costs of hospitalization, surgery, and management of post-surgical complications were based on literature values.[8,21] All costs and outcomes after one year were discounted at a rate of 5% annually.

2. MANUFACTURER'S BASE CASE

In its base case, the manufacturer reported that treatment with budesonide MMX is associated with a total cost of $144,241 and 4.242 quality-adjusted life-years (QALYs) over the five-year time horizon. When compared with HD 5-ASA treatment, the manufacturer reported that budesonide MMX was $7,209 less costly and associated with a gain of 0.003 QALYs — budesonide MMX is a dominant strategy based on the manufacturer's base-case analysis when compared with use of HD 5-ASA. Further details on the results are available in Table 8.

Summary of manufacturer's sensitivity analyses

The manufacturer undertook univariate and multivariate deterministic sensitivity analyses as well as a probabilistic sensitivity analysis (PSA). The results of the univariate and multivariate deterministic analyses indicated that none of the assessed parameters altered the manufacturer's conclusions that initial treatment with budesonide MMX was a dominant strategy compared with HD 5-ASA (details available in **Manufacturer's Results** section).

The manufacturer's PSA was run for 10,000 simulations, and the majority of simulations indicated that initial budesonide MMX was less costly and more effective than initial HD 5-ASA (Table 11).

3. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Uncertainty regarding clinical effectiveness data comparing budesonide MMX to 5-ASA based on manufacturer's network meta-analysis

As noted in the CADTH Common Drug Review's (CDR's) Clinical Review report, there are several significant limitations with the manufacturer's NMA informing effectiveness estimates of budesonide MMX and HD 5-ASA; these include:

- The inclusion of clinically heterogeneous studies
- The inclusion of studies published across several decades (during which time clinical practice and enrolled populations evolved)
- The variability in study length and its relevance to ascertain clinical remission
- Low numbers of studies overall, including for induction of remission, the use of a single study assessing the effectiveness of HD 5-ASA.

The effectiveness estimates in terms of probability of inducing remission for budesonide MMX and HD 5-ASA are the main drivers of the results of the manufacturer's economic evaluation. To populate the model, the manufacturer used the data from its NMA when both treatments are compared with placebo; the structure of the model was established based on these data. The manufacturer did not use the relative effects of budesonide MMX and HD 5-ASA and the model structure does not allow for the inclusion of treatment effects in this manner (treatment effects can be included only relative to placebo). In addition, the link of HD 5-ASA in the NMA was based on one study comparing 5-ASA HD and LD and represents a weak connection of the network. As such, estimates of HD 5-ASA from the NMA are uncertain.

The CORE I trial assessing budesonide MMX included a reference arm with 5-ASA, which demonstrated a slightly lower proportion of patients reaching clinical remission for 5-ASA. However, the trial was not designed and powered for this comparison. No conclusion can be made from this comparison from CORE I (refer to Clinical Review report). Moreover, the proportion of patients achieving remission for budesonide MMX from the CORE trials 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.

The proportions of patient reaching remission for budesonide MMX and 5-ASA are estimates driving the results of the economic evaluation. However, it cannot be concluded to be an advantage of budesonide MMX over 5-ASA as currently assumed by the manufacturer.

Omission of relevant comparators

The manufacturer's economic analysis compared budesonide MMX to 5-ASA as first-line therapy for the induction of remission. However, budesonide MMX and HD 5-ASA are not expected to occupy the same place in therapy; in particular, budesonide MMX is unlikely to displace 5-ASA as first-line therapy and will likely be a second-line option. CDR's consulting clinical expert explained that given that 5-ASA is not a corticosteroid and given its established safety and efficacy in this indication,[4,22] it would be unlikely that 5-ASA would be displaced as first-line therapy by a corticosteroid. CDR's consulting clinical expert also noted that prednisone may represent a more appropriate comparator to budesonide MMX than HD 5-ASA.

The current cost-effectiveness analysis does not provide an estimate of the cost-effectiveness of budesonide MMX versus other corticosteroids, which are relevant comparators for budesonide MMX. No direct evidence assessed budesonide MMX versus other corticosteroids. The manufacturer's NMA reported a numerical superiority for prednisolone versus budesonide MMX, but this difference was not statistically significant, and the NMA was assessed to provide uncertain results. Hence, it cannot be concluded an advantage for one treatment over the other.

CADTH Common Drug Review reanalyses

As noted above, the comparative effectiveness of budesonide MMX versus 5-ASA and other corticosteroids such as prednisone is uncertain and cannot be concluded to be an effectiveness advantage for budesonide MMX over one of these treatments, and vice versa. Hence, under the assumption of equal efficacy of budesonide MMX versus 5-ASA and versus prednisone, and considering only the drug cost of treatment, budesonide MMX (daily cost of $8.24) is 62% more expensive than generic 5-ASA (higher daily induction dose of $3.16) and 97% more expensive than prednisone (induction daily dose of $0.22) (refer to the cost comparison table in APPENDIX 1).

4. ISSUES FOR CONSIDERATION

In addition to the problems noted in the Key Limitations section with regard to the comparison to 5-ASA, other problems were noted with the assumed treatment progression and how budesonide MMX was assumed to be used. In particular, CDR's clinical expert noted that:

- In addition to its use as second-line induction therapy, budesonide MMX may be used for treatment of mild flares occurring at any point in therapy, including after use of 5-ASA, systemic corticosteroids, or biologics.
- Use of budesonide MMX in combination with 5-ASA is likely to occur in practice.
- Recurrent use of budesonide MMX may occur in response to successive flares of disease activity.
- While step-up therapy is indicated in the Canadian guidelines,[4] in practice patients may settle for acceptable clinical response to therapy (rather than complete remission) in order to avoid the risks associated with downstream therapies such as biologics. Thus, patients may not universally progress beyond use of oral corticosteroids. As a result, the modelled treatment paradigm may not reflect how many patients are treated, according to CDR's clinical expert.
- Budesonide MMX may be used as maintenance therapy in addition to its indicated use as induction therapy. The assumption that patients who achieve remission will be switched from budesonide MMX to 5-ASA may not occur and patients may continue to receive budesonide MMX.

Patient input

Input was received from two patient groups: the Gastrointestinal Society and Crohn's and Colitis Canada. UC is a chronic inflammatory bowel disease with no cure, characterized by fine ulcerations in the inner mucosal lining of the colon. 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, and anemia. Because of the impacts of the physical, psychological, and emotional symptoms incurred by patients with UC, quality of life can be profoundly affected.

Current treatments for UC are for managing symptoms and disease consequences. First-line treatment is currently 5-ASA, with the goal of decreasing acute inflammation initially, and removing inflammatory symptoms when used as maintenance. Patients noted that 5-ASA often lost efficacy with prolonged use, and although topical corticosteroids can be helpful, they are inconvenient therapies that can alter

routines and be ineffective when symptoms occur. Oral corticosteroids (e.g., prednisone) have been shown to be effective in treating symptoms, but are associated with adverse side effects that may lead to treatment discontinuation. Immunosuppressive drugs (e.g., azathioprine) may reduce dependence on steroids, but the time to onset of effect can be long. In cases where the disease becomes moderate or severe, biologics may be used. Surgery is seen as a last resort for patients whose prior therapies have not been effective.

Patients with mild to moderate UC are looking for safe, effective, and economically accessible treatment options that can improve their quality of life, and potentially delay and limit the progression to biologic treatment. Although the manufacturer's economic analysis reported potential delay in progression to biologic and to surgery with budesonide MMX, no advantage in terms of quality of life improvement and in terms of symptom resolution has been shown by the clinical trials assessing budesonide MMX.

5. CONCLUSIONS

The comparative effectiveness of budesonide MMX versus 5-ASA and other corticosteroids such as prednisone is uncertain and budesonide MMX cannot be concluded to have an efficacy advantage over one of these treatments, and vice versa. A cost-effectiveness assessment of budesonide versus these drugs cannot be performed with sufficient robustness. Hence, under the assumption of equal efficacy of budesonide MMX versus 5-ASA and versus prednisone, and considering only the drug cost of treatment, budesonide MMX (daily cost of $8.24) is 62% more expensive than generic 5-ASA (higher daily induction dose of $3.16) and 97% more expensive than prednisone (induction daily dose of $0.22).

APPENDIX 1: COST COMPARISON

The treatment options presented in the Table 2 below have been deemed to be appropriate by clinical experts. Treatment options may be recommended (appropriate) practice versus actual practice. Treatment options are not restricted to drugs, but may be devices or procedures. Costs are from the Ontario Drug Benefit Formulary, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 2: CDR COST COMPARISON TABLE FOR THE TREATMENT OF MILD TO MODERATE ULCERATIVE COLITIS

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Daily Drug Cost ($)
Budesonide MMX (Cortiment)	**9 mg**	**Tablet**	**8.2400**[a]	**One 9 mg tablet in the morning, for up to 8 weeks**	**8.24**
Aminosalicylates					
5-ASA (generic)	400 mg	Tablet	0.3951	Active: 0.8 g to 3 g daily in divided doses Maintenance: 1.6 g daily in divided doses	0.79 to 3.16 1.58
5-ASA (Asacol, Asacol 800)	800 mg	Enteric tablet	1.0938	4.8 g daily in divided doses	6.56
5-ASA (Mesasal)	500 mg	Enteric tablet	0.6559	Active: 1.5 g to 3 g tabs daily in divided doses Maintenance: 1.5 g daily in divided doses	1.97 to 3.94 1.97
5-ASA (Mezavant)	1.2 mg	Delayed- and extended-release tablet	1.6578	Active: 2.4 g to 4.8 g daily in a single dose Maintenance: 2.4 g daily in a single dose	3.32 to 6.63 3.32
5-ASA (Pentasa)	500 mg	Delayed-release tablet	0.5569	2 g to 4 g daily in divided doses	2.23 to 4.46
	1 g	Extended-release tablet	1.1138	2 g to 4 g daily in divided doses	2.23 to 4.46
	1 g 1 g/100 mL 4 g/100 mL	Suppository Enema Enema	1.6000 3.7000 4.4600	Suppository: 1 g daily Enema: 1 g to 4 g daily	1.60 3.70 to 4.46
5-ASA (Salofalk)	500 mg	Enteric tablet	0.5991	3 g to 4 g daily in divided doses	3.59 to 4.79
	500 mg 1,000 mg	Suppository Suppository	1.3243 1.9453	Suppository: 1 to 1.5 g daily	1.95 to 3.97
	2 g/100 mL 4 g/100 mL	Suppository	4.1500[b] 7.0351	Active: 4 g nightly Maintenance: 2 g nightly or	7.04 3.52 to 4.15

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Daily Drug Cost ($)
				4 g every 2 nights	
Olsalazine (Dipentum)	250 mg	Capsule	0.5330	Active: 1 to 3 g daily in divided doses Maintenance: 1 g daily in divided doses	2.13 to 6.40 2.13
Sulfasalazine (Salazopyrin and generic)	500 mg 500 mg	Tablet Enteric tablet	0.1804 0.2816	Active: 1 to 2 g 3 to 4 times daily Maintenance: 1 g 2 to 3 times daily	1.08 to 4.51 0.72 to 1.69
Thiopurines/Immunomodulators					
6-MP (Purinethol and generic)	50 mg	Tablet	2.8610	50 mg to 100 mg daily	2.86 to 5.72
Azathioprine (Imuran and generic)	50 mg	Tablet	0.2405	2.5 mg/kg daily	1.20
Corticosteroids (Oral and Rectal)					
Betamethasone (Betnesol)	5 mg/ 100 mL	Enema	10.7314	5 mg nightly	10.73
Betamethasone Sodium Phosphate and Betamethasone Acetate (Betaject)[c]	6 mg/mL	Injectable suspension	10.4830[d]	1 mL IM weekly	1.4976
Budesonide (Entocort)	0.02 mg/mL	Enema	8.8900[b]	2 mg nightly	8.89
Hydrocortisone (Cortenema)	100 mg/ 60 mL	Enema	7.2711	60 mL nightly or every other night	3.64 to 7.27
Hydrocortisone (Cortifoam)	15 g/ package (14 doses)	Rectal aerosol	94.9900	One dose nightly or every other night	3.39 to 6.79
Hydrocortisone (Solu-Cortef)	100 mg 250 mg 500 mg 1 g	Vial	3.9100[b] 6.7700[b] NA NA	300 mg to 400 mg IV daily	8.12 to 15.64
Methylprednisolone (Depo-Medrol)	40 mg/mL 80 mg/mL 100 g/5 mL	Injectable suspension	5.6388 10.8160 12.6271	40 mg to 80 mg IV daily	5.64 to 10.82
Methylprednisolone (Solu-Medrol)	40 mg 125 mg 500 mg 1 g	Sterile powder and diluent	5.0107[d] 10.9018[d] 24.1920[d] 37.1628[d]	40 mg to 120 mg 3 to 7 times per week	2.15 to 10.90

Comparators	Strength	Dose Form	Price ($)	Recommended Dose	Daily Drug Cost ($)
Prednisone (novo-prednisone)	5 mg 50 mg	Tablet	0.0220 0.1735	40 mg to 60 mg daily to induce remission, then lower dose	0.18 to 0.22

5-ASA = aminosalicylic acid; 6-MP = 6-mercaptopurine; IM = intramuscularly; IV = intravenously; min = minute; MMX = Multi Matrix System; NA = not applicable.
Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2016), unless otherwise indicated. Administration fees, dispensing fees, drug delivery system costs, and markups are not included.
[a] Current market price as submitted by manufacturer.
[b] Saskatchewan Drug Formulary (June 2016).
[c] Multi-dose vial.
[d] Delta PA, manufacturer's list price, accessed August 2016.[23]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 3: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS BUDESONIDE MMX RELATIVE TO 5-ASA AND TO PREDNISONE?

Budesonide MMX Vs. 5-ASA	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	Budesonide MMX is more costly than 5-ASA and prednisone					

5-ASA = 5-aminosalicylic acid; CE = cost-effectiveness; NA = not applicable; vs. = versus.
Source: Based on the manufacturer's results.[2]

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 4: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 5: AUTHORS' INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: SUMMARY OF OTHER HEALTH TECHNOLOGY ASSESSMENT REVIEWS OF DRUG

In June 2015, the National Institute for Health and Care Excellence (NICE) published advice regarding budesonide Multi Matrix System(MMX, Cortiment) for the treatment of adults with mild to moderate ulcerative colitis (UC).[24] NICE reviewed data from two eight-week, placebo-controlled studies.[25,26] The results of the studies indicated a statistically significant increase in rates of combined clinical and endoscopic remission, although the effect size was small and clinical relevance is unclear. There was no statistically significant difference for clinical improvement and endoscopic improvement at week 8 (secondary end points). Adverse event rates were not substantially different between groups. The cost of budesonide MMX was £75.00 for 30 tablets, or £140 for an eight-week course; £70 per 28 days). Other comparative treatments available included oral and topical corticosteroids, and oral and topical aminosalicylates. The cost of these treatments was indicated to range from £5.16 to £52.79 for oral corticosteroids, £24.66 to £79.33 for oral aminosalicylates, £14.00 to £272.00 for topical corticosteroids, and £40.01 to £53.44 for topical aminosalicylates.

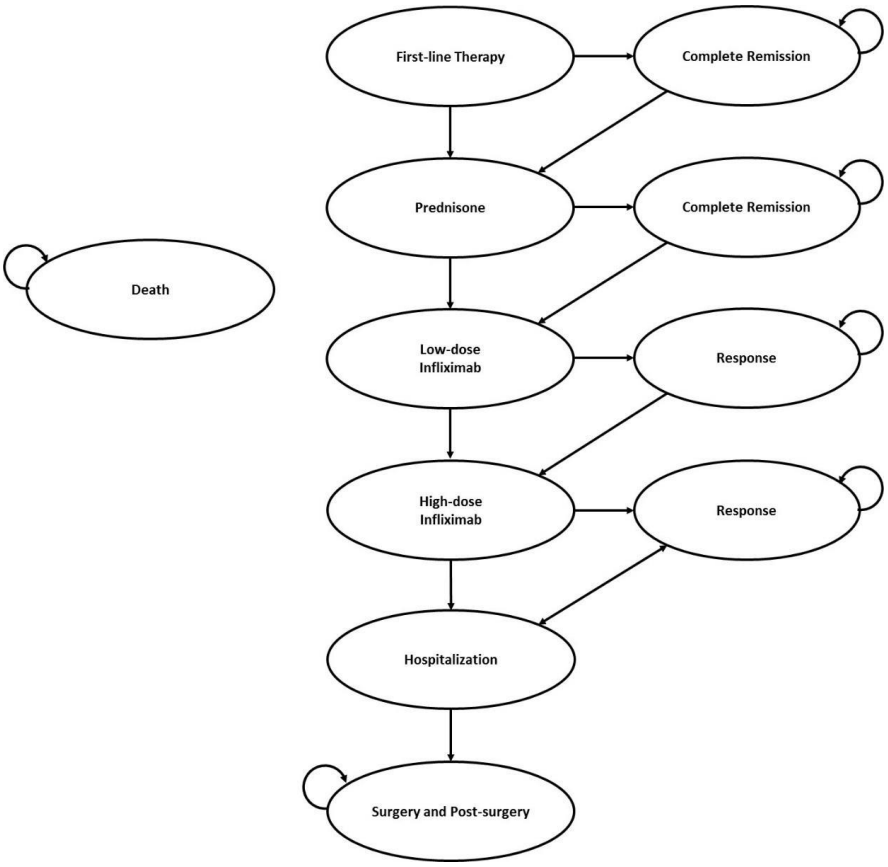
Upon review of the available data, NICE noted that there are several important pieces of information that are not known or uncertain:

- The place in therapy is uncertain; whether budesonide MMX will be used first-line (prior to ASA) or second-line (post-ASA).
- The effect of budesonide MMX when used in combination with an ASA is not known, and neither is the effect in patients who do not respond to ASAs.
- The comparative effectiveness of budesonide MMX compared with topical or oral corticosteroids (the recommended second-line treatments for UC) is not known.
- How well the effect is maintained is not known, affecting potential off-label use.
- The speed of onset of effect is not known.

APPENDIX 5: REVIEWER WORKSHEETS

Manufacturer's model structure

FIGURE 1: MODEL STRUCTURE



Source: Manufacturer's Pharmacoeconomic Submission.[2]

TABLE 6: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Efficacy estimates for achievement of remission came from a manufacturer-sponsored NMA for first-line therapies (budesonide MMX, HD 5-ASA) and subsequent prednisone treatment. Estimates of relapse among patients achieving remission on first-line therapies or prednisone were also derived from the manufacturer's NMA. Estimates of response and relapse rates on LD and HD infliximab were based on the results of a clinical trial investigating the use of infliximab in patients with moderate to severe UC.[6]	The CDR clinical report identified substantial limitations and uncertainty with the manufacturer's NMA. Given the sensitivity of the model to transition probabilities, this is problematic. Various sources, including the CDR Clinical Review report, have noted that the CORE I and II trials

Data Input	Description of Data Source	Comment
	Surgery was assumed to be curative for all patients. The efficacy of budesonide MMX compared with placebo was derived from two phase III, double-blind, double-dummy randomized controlled trials, CORE I and CORE II.[5,25,26]	were problematic for several reasons.[24,27] Of note, both SMC and NICE felt that the drug did not adequately demonstrate efficacy against relevant comparators. The use of the Rutgeerts et al. trial[6] for infliximab values is problematic, as it uses a population with more severe UC.
Natural History	Rates of surgery among hospitalized patients were based on a meta-analysis of patients receiving rescue therapy (based on corticosteroids with or without concurrent antibiotics) during an exacerbation of UC.[7] Rates of complications from surgery were based on a study by Swenson et al.[8]	Rates of surgery are of questionable appropriateness, given differences between the populations studied in Gupta et al. (patients on corticosteroids with or without concurrent antibiotics, where new initiation of infliximab was among outcomes of interest) vs. the patients modelled (patients who had failed HD infliximab therapy). It is unclear whether these are comparable populations. Rates of complications seem reasonable.
Utilities	Utilities for active, mild to moderate UC, drug-induced remission, hospitalization, and surgery-induced remission were chosen by the manufacturer from studies identified through a literature review. Utilities for active mild to moderate UC and drug-induced remission were derived from a study by Poole et al.[9] that reported EQ-5D utilities from the PINCE and PODIUM clinical trials, which evaluated mesalazine for the treatment of UC among a European population. This publication was chosen based on its consideration of active, mild to moderate UC patients and its use of validated methods. Utilities for hospitalization were based on values used in a previous economic evaluation by Yen et al. assessing the cost-effectiveness of 5-ASA for maintenance of remission in UC.[10] The choice of these data was not justified.	The Poole[9] estimate for active, mild to moderate disease may be questionable in the Canadian context, given that these data come from European populations. The value of 0.608 reported by Yen et al.[10] for hospitalization utilities is of questionable appropriateness, given that the studies referred to are more than 20 years old and given the improvements in health care over that time.

Data Input	Description of Data Source	Comment
	The utility associated with surgery-induced remission was based on a study by Waljee et al.[11] The choice of these data was not justified. Utility decrements associated with AEs due to corticosteroid use were derived from literature sources for acne, hirsutism and insomnia.[14-17] Disutilities for all other AEs (fluid retention, flushing, mood changes, moon face, and sleep changes) were assumed to be –0.02.	Utility for surgery-free remission seems reasonable. Utility decrements are of questionable appropriateness: literature sources reflect non-UC patients; assumption lacked face validity — i.e., neuropsychiatric side effects (e.g., mood change) had less impact on quality of life than cosmetic AEs (e.g., acne, hirsutism); and similar AEs had different utilities (insomnia vs. sleep changes: 0.09 vs. 0.02). Altering these did not make any difference to results.
AEs	AEs were considered only for corticosteroids (i.e., budesonide MMX and oral prednisone). The specific AEs considered were acne, fluid retention, flushing, hirsutism, insomnia, mood changes, moon face, and sleep changes. The incidence of each type of AE was based on a pooled safety analysis of the CORE trials for budesonide MMX[12] and on a clinical trial of prednisolone to estimate rates for prednisone.[13] Each AE was assumed to require a visit to a gastroenterologist. The total resource use (in terms of gastroenterologist visits) was based on the expected number of AEs per patient given by a weighted average of the incidences.	Incidence of AEs is uncertain. The incidence of AEs for prednisone did concur with the estimates of CDR's clinical expert, but we acknowledge a paucity of published sources in this respect. Further, assuming that patients require a gastroenterologist visit for all steroid-related AEs likely does not reflect clinical practice. The more "cosmetic" AEs may be a minor annoyance, while more severe neuropsychiatric side effects may necessitate a visit.
Mortality	Transitions to the "death" health state were based on Canadian-specific general population estimates of all-cause mortality. Of note, age-adjusted mortality was not used. A fixed death rate based on age at model entry was used. No disease-specific mortality was applied to the model.	Age-adjusted mortality is the optimal method to use.

Data Input	Description of Data Source	Comment
Resource Use	Estimates of resource use were obtained from the published literature and clinical opinion.	Appears reasonable.
Costs	First-line induction therapy, additional therapies, disease management, AEs, hospitalization, and surgery.	Generally appropriate.
Drug	The price of budesonide MMX was from the manufacturer's submitted market price. The price of all other medications (5-ASA, prednisone, infliximab).	Appropriate, apart from using price of branded infliximab price instead of price for SEB infliximab.
Event	Costs of hospitalization and surgery were based on a costing study examining administrative data from Manitoba in 2005-2006.[21] Costs for management of AEs were derived from the Swenson et al. study.[8]	Reasonable.
Disease management	Patients in complete remission were assumed to have 2 gastroenterologist visits per year, along with 1 each of a complete blood count, fecal calprotectin, and colonoscopy. Patients with active disease were assumed to have a gastroenterologist visit, fecal calprotectin, and complete blood count every 2 months, as well as an annual endoscopy. Costs for physician services and laboratory tests were derived from the OHIP schedule of benefits and Ontario MOHLTC Schedule of Laboratory Services.[19,20]	Schedule of follow-up for patients with active disease may not reflect clinical practice, according to CDR's consulting clinical expert. Data sources were appropriate.

5-ASA = 5-aminosalicylic acid; AE = adverse event; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions Questionnaire; HD = high-dose; LD = low-dose; MOHLTC = Ministry of Health and Long-Term Care; MMX = Multi Matrix System; NICE = National Institute for Health and Clinical Excellence (UK); NMA = network meta-analysis; OHIP = Ontario Health Insurance Plan; SEB = subsequent entry biologic; SMC = Scottish Medicines Consortium; UC = ulcerative colitis; UK = United Kingdom; vs. = versus.

TABLE 7: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
All patients who received surgery were cured and required no further treatment.	Questionable.
The treatment paradigm that was modelled reflects the most common or meaningful clinical pathway.	CDR's consulting clinical expert noted that the model structure was not representative of the Canadian clinical practice.
Budesonide MMX would occupy the same place as 5-ASA in the treatment algorithm (i.e., as first-line therapy for maintenance of remission).	Highly questionable. A review based on the CORE studies[28] and feedback from the CDR clinical expert suggested that in practice, budesonide MMX is more likely to be used as second-line therapy. It is unclear whether budesonide MMX, which is both more expensive than 5-ASAs and is a corticosteroid, would be broadly adopted as first-line therapy.
Use of HD 5-ASA for maintenance after achieving remission on 5-ASA, budesonide MMX, or prednisone.	Appropriate, but the lack of a stopping rule may be an issue in clinical practice.
Definition of remission in the clinical trials (consisting of both clinical and endoscopic remission; also used in the model for first-line therapies and prednisone) reflects remission as it would be assessed in practice.	Highly questionable, as most patients will be assessed for clinical improvement after initiating a treatment but only a minority will receive an endoscopy. It is unknown how this affects cost-effectiveness estimates.
Constant death rate.	Not optimal, but acceptable considering the 5-year time horizon.
Efficacy and withdrawals from HD infliximab are the same as those from LD infliximab.	Seems appropriate.
AEs only for steroids, post-surgery.	Questionable
The disutilities associated with corticosteroid AEs lacking literature values was set to –0.02.	Highly questionable. Likely to be an overestimate, and lacks in face validity.
Surgery is offered only to those who have been hospitalized and failed infliximab.	Generally appropriate.
All steroid-related AEs result in a gastroenterologist visit.	Inappropriate. Feedback from the CDR clinical expert suggested that some of the more minor AEs would not require a physician visit.
Use of a 5-year time horizon.	Likely inappropriate. This was chosen by the manufacturer to balance capturing long-term costs and outcomes without projecting too long beyond available clinical data — further, it was noted that a 5-year time horizon has been used in other CDR submissions for UC. However, given that this drug is indicated only for induction of remission, and given the uncertainty associated with the available clinical data, a shorter time horizon is likely more appropriate for this evaluation.

5-ASA = 5-aminosalicylic acid; AE = adverse event; CDR = CADTH Common Drug Review; EQ-5D = EuroQol 5-Dimensions questionnaire; LD = low-dose; HD = high-dose; MMX = Multi Matrix System.

Manufacturer's Results and CADTH Common Drug Review Reanalysis

TABLE 8: MANUFACTURER'S BASE-CASE RESULTS

Model Outcomes per Patient	Budesonide	HD 5-ASA	Difference
Health Outcomes			
Weeks in drug-induced remission	235.18	234.13	1.05
Deaths (%)	0.63	0.63	0.00
Surgery (%)	2.83	3.00	–0.18
Number of hospitalizations	0.56	0.60	–0.03
Weeks on oral prednisone	7.71	7.87	–0.16
Weeks on infliximab	202.76	213.61	–10.85
QALYs	**4.242**	**4.239**	**0.003**
Costs ($)			
First-line induction therapy	461	368	94
Additional therapies	132,507	139,282	–6,775
Disease management	2,634	2,638	–5
Adverse events	138	131	7
Hospitalization	7,874	8,364	–489
Surgery	627	667	–40
Total	**144,241**	**151,450**	**–7,209**
ICUR	**DOMINATES 5-ASA[a]**		

HD 5-ASA = high-dose 5-aminosalicylic acid (4.8 g/day); ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
[a] I.e., treatment with budesonide costs less and produces more QALYs than treatment with HD 5-ASA.

In the course of providing comments, the manufacturer provided an analysis assessing the use of budesonide MMX versus prednisone as second-line treatment (Table 9). The use of budesonide MMX was associated with fewer QALYs and lower costs (savings per QALY lost: $1,389,019). In this analysis, budesonide MMX was used before prednisone. CDR also undertook a scenario analysis where budesonide MMX was used in place of prednisone (i.e., patients started on budesonide MMX or prednisone and, in both cases, moved to infliximab). This analysis made use of the price of subsequent entry biologic (SEB) infliximab in place of branded infliximab (Remicade) as was used in the manufacturer's original base case. CDR's reanalysis found that use of budesonide MMX was associated with an ICUR of $433,251 per QALY gained (Table 10).

TABLE 9: MANUFACTURER ANALYSIS: BUDESONIDE MMX VERSUS PREDNISONE

Model Outcomes per Patient	Budesonide	Prednisone	Difference
Health Outcomes			
Weeks in drug-induced remission	235.48	241.06	–5.59
Deaths (%)	0.63	0.63	0.00
Surgery (%)	2.77	3.22	–0.45
Number of hospitalizations	0.55	0.64	–0.09
Weeks on oral prednisone	7.71	8.00	–0.29
Weeks on infliximab	199.03	224.97	–25.94
QALYs	**4.243**	**4.256**	**–0.013**
Costs ($)			
First-line induction therapy	$461	$0	$461
Additional therapies	$130,173	$147,339	–$17,166
Disease management	$2,633	$2,555	$78
Adverse events	$138	$135	$3
Hospitalization	$7,706	$8,975	–$1,270
Surgery	$614	$717	–$103
Total	**$141,724**	**$159,720**	**–$17,996**
ICUR	**Savings per lost QALY: $1,389,019**		

ICUR = incremental cost-utility ratio; MMX = Multi Matrix System; QALY = quality-adjusted life-year.

TABLE 10: CADTH COMMON DRUG REVIEW ANALYSIS — BUDESONIDE MMX VERSUS PREDNISONE

Model Outcomes per Patient	Budesonide	Prednisone	Difference
Health Outcomes			
Weeks in drug-induced remission	240.48	241.06	–0.59
Deaths (%)	0.63	0.63	0.00
Surgery (%)	3.34	3.22	0.12
Number of hospitalizations	0.66	0.64	0.02
Weeks on oral prednisone	0.00	8.00	–8.00
Weeks on infliximab	232.31	224.97	7.34
QALYs	**4.263**	**4.256**	**0.007**
Costs ($)			
First-line induction therapy	$461	$0	$461
Additional therapies	$81,242	$78,918	$2,324
Disease management	$2,556	$2,555	$1
Adverse events	$10	$135	–$125
Hospitalization	$9,322	$8,975	$346
Surgery	$745	$717	$28
Total	**$94,336**	**$91,300**	**$3,037**
ICUR	**$433,251 per QALY gained**		

ICUR = incremental cost-utility ratio; MMX = Multi Matrix System; QALY = quality-adjusted life-year.

Sensitivity analyses

The manufacturer tested the robustness of the model through both deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA). One-way sensitivity analyses all produced the same conclusion as the base-case analysis — i.e., budesonide MMX dominated HD 5-ASA.

TABLE 11: MANUFACTURER'S ONE-WAY SENSITIVITY ANALYSES

Parameter Type	Specific Parameters Assessed	Results
Model characteristics	Time horizon; discount rates for outcomes and costs	Budesonide MMX dominates HD 5-ASA
Baseline population characteristics	Age; body weight	
Clinical efficacy and outcomes	Probability of remission and relapse on placebo, budesonide MMX, HD 5-ASA, and prednisone; probability of remission and relapse on infliximab; risk of surgery during hospitalization; risk of surgical complications; mortality rate; exclusion of hospitalization and surgery risks	Budesonide MMX dominates HD 5-ASA
Exclusion of AEs for corticosteroids	NA	Budesonide MMX dominates HD 5-ASA
Utility values and decrements	Active, mild to moderate UC; drug-induced complete remission; hospitalization; surgery-induced remission	Budesonide MMX dominates HD 5-ASA
Costs	Costs of all drugs; costs of disease management; costs of hospitalization; surgery; post-surgical complications	Budesonide MMX dominates HD 5-ASA

AE = adverse event; HD 5-ASA = high-dose 5-aminosalicylic acid (4.8 g/day); MMX = Multi Matrix System; NA = not applicable; UC = ulcerative colitis.

The manufacturer also provided the results of a PSA with 10,000 iterations in which the majority of simulations showed initial treatment with budesonide MMX to have fewer costs and more effectiveness (i.e., higher QALYs) than treatment of 5-ASA.

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