CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

BUDESONIDE MMX
(Cortiment — Ferring Inc.)
Indication: Ulcerative Colitis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that budesonide MMX not be reimbursed for the induction of remission in patients with active, mild to moderate ulcerative colitis (UC).

Reasons for the Recommendation:

1. Although two randomized controlled trials (RCTs) (CORE I [N = 510] and CORE II [N = 512]) demonstrated that treatment with budesonide MMX was associated with a statistically significantly greater proportion of patients achieving complete remission at week 8 compared with placebo, there was no evidence in these trials to suggest that budesonide MMX has a clinical benefit similar to that of appropriate first-line (5-aminosalicylic acids [5-ASAs]) or second-line (systemic corticosteroids) therapies for the induction of remission in patients with active, mild to moderate UC. A mesalamine (Asacol 2,400 mg) group was included in the CORE I study and a budesonide (Entocort EC 9 mg) group was included in the CORE II study; however, these were included as additional reference arms that were not powered to compare these drugs with budesonide MMX or placebo.
2. In the absence of appropriately designed studies that directly compare budesonide MMX with other active drugs, CDEC considered the indirect comparison submitted by the manufacturer. However, the analysis was limited by a small network of studies, several single-study connections, and clinical heterogeneity across studies with respect to the length of treatment and the use of different definitions of complete remission. Because of these limitations, the results of the network meta-analysis (NMA) for induction of complete clinical remission are uncertain.
3. There was no evidence in the studies submitted for this review to demonstrate that treatment with budesonide MMX is associated with fewer systemic adverse effects than other orally or rectally administered corticosteroids, particularly at the level of the hypothalamic-pituitary-adrenal axis in patients with UC.

Of Note:

- CDEC noted that the CONTRIBUTE study, which 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, was available only in abstract form at the time of the review.

Discussion Points:

- CDEC noted that in both CORE studies, an important clinical parameter — the mean difference (MD) in the proportion of patients achieving clinical improvement with budesonide MMX compared with placebo — was not statistically significant.
- CDEC noted that patient group input for this submission highlighted the importance of patients having access to a treatment option that offers improvements in quality of life and that has fewer side effects than prednisone. The evidence provided in this submission was insufficient to demonstrate that budesonide MMX is associated with improvements in quality of life or offers a favourable safety profile compared with currently available treatment options.

Research Gaps:

- CDEC noted that there is a need for direct comparative studies that assess the efficacy of budesonide MMX compared with active treatments in patients with active mild to moderate UC.
- CDEC recognized the potential for budesonide MMX to offer fewer systemic adverse effects compared with conventional corticosteroids; however, there is a need for appropriately designed studies that compare the systemic adverse effects of budesonide MMX to other orally or rectally administered corticosteroids for patients with active mild to moderate UC.

Background:

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 may decrease systemic bioavailability, and is available in oral and rectal formulations for the management of UC and Crohn's disease. 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. 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 adult patients with active, mild to moderate UC. The recommended dose is one tablet per day in the morning for up to eight weeks.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of budesonide MMX, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals living with active mild to moderate UC, and their caregivers.

Patient Input Information

The following is a summary of information provided by two patient groups (the Gastrointestinal Society and Crohn's and Colitis Canada) that responded to the CDR call for patient input:

- Patients with UC experience physical symptoms such as rectal bleeding, frequent diarrhea, abdominal pain, and fatigue, which may lead to psychological symptoms such as depression, anxiety, and stress. The fear of not knowing when a flare or bowel movement will occur affects every facet of their daily lives.
- Current therapies such as 5-ASAs, topical corticosteroids, and systemic corticosteroids aim to manage both symptoms and disease consequences by decreasing acute inflammation.

They are not always effective and are often accompanied by unwanted side effects, especially in the case of systemic corticosteroids. Biologics are generally used for moderate to severe UC and surgery is used as a last resort.
- Patients expressed a need for more therapy options with fewer side effects and hope that budesonide MMX will provide a safer and more effective option because of its targeted release and prevent or delay the need to progress to biologic treatment.

Clinical Trials

The CDR systematic review included two phase 3, double-blind, placebo-controlled RCTs assessing the efficacy and safety of budesonide MMX 9 mg in adult patients with active, mild to moderate UC. The CORE I study (N = 510) also included a mesalamine (Asacol 2,400 mg) treatment group, while the CORE II study (N = 512) included a budesonide (Entocort EC 9 mg) treatment group, although the studies were not powered to compare these drugs with placebo or budesonide MMX and were included as reference arms. The CORE studies included patients aged 18 to 75 years with active, mild to moderate UC for at least six months, as determined by Ulcerative Colitis Disease Activity Index (UCDAI) score of 4 to 10.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Clinical and endoscopic remission — defined as a UCDAI score ≤ 1 with subscores of 0 for rectal bleeding and stool frequency; a normal mucosa by endoscopy; and a ≥ 1-point reduction in endoscopic index score from baseline. 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).
- Clinical improvement — defined as a ≥ 3-point improvement in UCDAI score.
- Endoscopic improvement — defined as a ≥ 1-point improvement in the UCDAI mucosal appearance subscore.
- Mucosal healing — defined as having a total histologic score of ≤ 1 for all biopsy specimens according to criteria that assign 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).
- Inflammatory Bowel Disease Quality of Life Questionnaire (IBD-QoL) — a 32-item questionnaire that assesses symptoms, general health, mood, and social or work problems resulting from UC. An increase in score indicates alleviation of the disease, and a decrease in score indicates aggravation.
- Serious adverse events, total adverse events, glucocorticoid-related adverse events, withdrawals due to adverse events.

The primary outcome in the CORE studies was clinical and endoscopic remission at week 8.

Efficacy

- The proportion of patients who achieved complete remission at week 8 was statistically significantly greater in the budesonide MMX group than in the placebo group in both CORE studies (CORE I: MD 10.4%; 95% confidence interval [CI], 2.2% to 18.7%; *P* = 0.0143; and CORE II: MD 12.9%; 95% CI, 4.6% to 21.3%; *P* = 0.0047).

- The proportion of patients with clinical improvement at week 8 was not statistically significantly greater in the budesonide MMX group than in the placebo group in both CORE studies (CORE I: MD 8.5%; 95% CI, –2.8% to 19.9%; *P* = 0.1420; and CORE II: MD 8.5%; 95% CI, –5.0% to 22.0%; *P* = 0.2215).
- The proportion of patients with endoscopic improvement at week 8 was greater in the budesonide MMX group than in the placebo group in both CORE studies (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, because of the hierarchical testing procedure.
- In CORE I, the MD 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). In CORE II, the MD 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).
- In CORE I, the mean (standard deviation [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.

Harms (Safety and Tolerability)

- 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 MMX group (18.6% versus 11.8%). In CORE II, the proportion of patients with withdrawals due to adverse events was higher in the budesonide MMX group than in the placebo group (18.8% versus 14.7%).
- 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.

Cost and Cost-Effectiveness

Budesonide MMX is available as a 9 mg tablet at a manufacturer-submitted price of $8.24 per tablet. At a recommended dose of 9 mg daily, eight weeks of treatment (the maximum duration of treatment recommended in the product monograph) with budesonide MMX costs $461.

The manufacturer submitted a cost-utility analysis comparing budesonide MMX to standard of care (high-dose 5-ASA, 4.8 g/day) for the induction of remission in adults with active, mild to moderate UC. The impact of treatment on patients progressing along the disease and treatment pathway was assessed in the analysis, which was based on a Markov state-transition model using a five-year time horizon, undertaken from the perspective of the Canadian publicly funded health care system. Patients with active, mild to moderate UC received either budesonide MMX

or high-dose 5-ASA to induce remission. Patients who experienced remission received maintenance therapy (high-dose 5-ASA), 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 high-dose 5-ASA) to prednisone, then low-dose infliximab, high-dose infliximab, hospitalization with rescue care, and surgery. Treatment effectiveness data (defined in terms of probability of achieving remission) were derived from a manufacturer-commissioned NMA.

CDR identified the following key limitations with the manufacturer's economic submission:

- Uncertainty associated with the comparative clinical effectiveness for budesonide MMX versus high-dose 5-ASA, which drives the results of the economic analysis. The results from the NMA used in this comparison are uncertain and the CORE I study, which included a mesalamine (5-ASA) reference arm, was not powered to compare this drug to budesonide MMX.
- The choice of high-dose 5-ASA as the comparator for budesonide MMX is questionable given it is not expected that budesonide MMX would displace 5-ASA as first-line therapy, according to the CDR clinical expert. It is expected that budesonide MMX would be used in practice as a second-line treatment, with corticosteroids (such as prednisone) as a more appropriate comparator. Based on available evidence, one cannot conclude that there is an advantage of one treatment over the other.

The cost-effectiveness of budesonide MMX versus 5-ASA or other corticosteroids, such as prednisone, is directly affected by the quality of the comparative clinical evidence. Given the limitations in available comparative evidence, the cost-effectiveness of budesonide MMX is considered highly uncertain. The daily cost of budesonide MMX ($8.24) is 62% more expensive than generic 5-ASA ($3.16) and 97% more expensive than prednisone ($0.22).

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

Regrets

October 19, 2016 Meeting: None
March 15, 2017 Meeting: None

Conflicts of Interest: None

About This Document:

CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information.

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