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Budesonide MMX®: A Review of Its Use in Patients with Mild to Moderate Ulcerative Colitis

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Abstract Budesonide MMX® (Cortiment®; Uceris®) is a novel once-daily oral formulation of budesonide using Multi Matrix (MMX®) colonic delivery technology to permit the release of budesonide at a controlled rate throughout the colon. It is available in the USA for the induction of remission in patients with active, mild to moderate ulcerative colitis, and in various European countries for the induction of remission in patients with active, mild to moderate ulcerative colitis where 5-aminosalicylic acid (5-ASA) therapy is not sufficient. In three 8-week multinational, phase III studies in patients with active, mild to moderate ulcerative colitis, once-daily budesonide MMX® 9 mg, as monotherapy (CORE I and II studies) or add-on therapy to 5-ASAs (CONTRIBUTE), was significantly more effective than placebo in inducing combined clinical and endoscopic remission. In an 8-week extension of the CORE I study, the efficacy of budesonide MMX® 9 mg monotherapy was demonstrated among patients who completed the CORE I study, but did not achieve clinical remission. In phase III studies, the tolerability profile of budesonide MMX® 9 mg as monotherapy or add-on therapy to 5-ASAs was generally similar to that of placebo. Adverse events were generally mild or moderate in intensity, with exacerbation, relapse or worsening of ulcerative colitis, headache, nausea, abdominal pain and nasopharyngitis the most frequently reported following budesonide MMX® 9 mg monotherapy. Although final data from the CONTRIBUTE study are awaited, current evidence suggests budesonide MMX® 9 mg extends the treatment options currently available for patients with active, mild to moderate ulcerative colitis.

Budesonide MMX® in the management of active, mild to moderate ulcerative colitis: a summary

Novel oral formulation of budesonide using Multi Matrix (MMX®) colonic delivery technology

Primarily absorbed as it passes between the ascending and descending–sigmoid colon

Locally acting agent with low systemic bioavailability

Effective in inducing combined clinical and endoscopic remission as monotherapy or add-on therapy to 5-aminosalicylic acids

Tolerability profile, including the incidence of adverse events, serious adverse events and glucocorticoid-related adverse events, generally similar to that of placebo

1 Introduction

Ulcerative colitis is characterized by a relapsing-remitting course of diffuse mucosal inflammation affecting the colon and rectum [1, 2]. As such inflammation occurs in proximity to the epithelium, and typically does not extend into the small

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intestine [3], treatment necessitates delivery of a locally active drug to the entire colon [4, 5]. Among the pharmacological options for the induction of remission in patients with mild to moderate ulcerative colitis are aminosalicylates [e.g. mesalamine (mesalazine)] and corticosteroids [2].

The standard oral formulation of the corticosteroid budesonide is absorbed in the ileum and ascending colon, thus not permitting targeted delivery to the entire colon [4, 5]. Using Multi Matrix (MMX®) colonic delivery technology, a novel oral formulation of budesonide (hereafter referred to as budesonide MMX®) [Cortiment®; Uceris®] has been developed to provide a controlled release of budesonide throughout the entire colon [6, 7]. This article reviews pharmacological, therapeutic efficacy and tolerability data relevant to the use of oral budesonide MMX® for the induction of remission in patients with active, mild to moderate ulcerative colitis. The use of other formulations of budesonide (i.e. budesonide rectal foam [8]) in this patient population is beyond the scope of this review.

2 Pharmacodynamic Properties

The mechanism of action of budesonide in ulcerative colitis is not yet fully elucidated [6]. Generally, budesonide inhibits a number of inflammatory processes, including cytokine production, the expression of adhesion molecules on endothelial and epithelial cells, and inflammatory cell activation, with data indicating that its effects are localized to the gastrointestinal tract [6]. Budesonide's affinity for glucocorticoid receptors is approximately 200-fold and 15-fold that of cortisol and prednisolone, respectively, reflecting its intrinsic potency [7]. Budesonide has a weak mineralocorticoid effect [7].

Therapy with systemically active glucocorticoids, including budesonide MMX®, is associated with the suppression of endogenous cortisol levels and hypothalamus-pituitary-adrenal (HPA) axis function [7]. Compared with prednisolone, HPA axis suppression was significantly lower and the impact on inflammatory markers less with budesonide (doses were clinically equivalent) [6]. However, among patients receiving budesonide MMX® 9 mg once daily in a pilot phase II study, 40 % (6 of 15 patients) and 57 % (8 of 14) at 4 and 8 weeks, respectively, had an abnormal ACTH stimulation test response [9]. The effect of budesonide MMX® 9 mg therapy on blood cortisol levels in patients participating in two phase III studies is discussed in Sect. 5.

3 Pharmacokinetic Properties

Budesonide MMX® contains a gastro-resistant polymer coating that dissolves at a pH $\geq$7 (thereby delaying release during transit through the stomach and duodenum until the lower part of the gastrointestinal tract is reached) and a budesonide-containing lipophilic matrix (permitting the release of budesonide at a controlled rate throughout the colon) [6, 7]. In a single-dose, pharmaco-scintigraphic study in 12 healthy volunteers, budesonide MMX® 9 mg was detectable in the ascending colon 4 to >24 h post dose, with the agent leaving the descending colon 12 to >24 h post dose [10]. Initial tablet disintegration/erosion began a mean of 9.5 h post dose and, for the most part, occurred in the ileum (42 % of subjects) and the ascending and transverse colon (33 %). Most (96 %) absorption occurred during the time period the tablets passed through the region between the ascending and the descending–sigmoid colon [10].

As with other formulations of budesonide, budesonide MMX® is associated with high interindividual variability in terms of gastrointestinal transit and systemic absorption [10]. Both concurrent food intake and tablet size are known to affect gastric emptying [10]. However, the coadministration of budesonide MMX® 9 mg with a high-fat diet has no clinically relevant effect on absorption [6] (Sect. 6).

Plasma concentrations of budesonide were first detected a mean of 6.8 h following a single dose of budesonide MMX® 9 mg, with maximum concentrations reached (t_{max}) a mean of 14.0 h post dose, indicating sustained release [10]. At steady state, t_{max} was reached in 11 h [10]. No drug accumulation was observed following budesonide MMX® 9 mg once daily for 7 days [10]. Plasma budesonide concentrations were below the limit of detection 48 h following the last dose of budesonide MMX® 9 mg [10]. Of note, in a crossover study in healthy volunteers, the systemic exposure of budesonide following a single 9 mg dose of budesonide MMX® was generally similar to that with a single 9 mg dose of budesonide extended release (ER) [Entocort® EC; approved for the induction of remission in patients with active, mild to moderate Crohn's disease in the UK and the USA] [5]. However, the time to first appearance in plasma (median 6 vs. 1 h) and t_{max} (median 15 vs. 5 h) values were delayed with budesonide MMX® versus budesonide ER [5].

Budesonide undergoes extensive (80–90 %) first-pass hepatic metabolism [predominately mediated by cytochrome P450 (CYP) 3A4] to yield several metabolites; the glucocorticoid activity of the two major metabolites, 6β-hydroxybudesonide and 16α-hydroxy-prednisolone, is low (<1 % that of budesonide) [6, 7]. The elimination of budesonide is absorption-rate limited [6], with a plasma elimination half-life following intravenous budesonide of 2.0–3.6 h [7]. Budesonide has a high plasma clearance (0.9–1.8 L/min) and is excreted as metabolites [7]. Following intravenous or oral administration, approximately 60 % of radiolabelled budesonide was recovered in the urine; unchanged budesonide was not detected [7].

Data are limited in patients with hepatic or renal impairment; however, reduced liver function may affect the elimination of glucocorticoids, including budesonide [6, 7]. Caution and patient monitoring are advised when administering budesonide MMX® to these patient populations [6, 7].

As budesonide is primarily metabolized by CYP3A4, its exposure can be affected by CYP3A4 inducers (e.g. carbamazepine) and inhibitors (e.g. ketoconazole) [6, 7]. For instance, an eightfold elevation in systemic budesonide exposure was observed following the coadministration of oral budesonide and oral ketoconazole [7]. Moreover, the release and/or uptake of budesonide MMX® may be altered when administered concurrently with colestyramine and/or gastric acid reducing agents (e.g. antacids) [6, 7]. Local prescribing information should be consulted for recommendations regarding the coadministration of budesonide MMX® with these agents.

4 Therapeutic Efficacy

The therapeutic efficacy of oral budesonide MMX® as monotherapy (Sect. 4.1) or as add-on therapy to 5-aminosalicylic acids (5-ASAs) (Sect. 4.2) for the induction of remission in adults with active, mild to moderate ulcerative colitis has been evaluated in three double-blind, placebo-controlled, multinational, phase III studies: CORE I [11], CORE II [12] and CONTRIBUTE [13]. A pooled analysis [14] of the CORE I and II studies, and an extension study (NCT01100112) [15] of the CORE I study are currently available. Some data are available as abstract presentations [13] or online [15].

4.1 As Monotherapy

Patients aged 18–75 years with active, mild to moderate ulcerative colitis for ≥6 months and an Ulcerative Colitis Disease Activity Index (UCDAI) score of 4–10 were eligible for enrolment in the CORE I and II studies [11, 12]. The key exclusion criteria were prior oral or rectal corticosteroid therapy within 4 weeks; prior immunosuppressive therapy within 8 weeks; prior anti-tumour necrosis factor (TNF) therapy within 12 weeks; evidence or history of toxic megacolon; infectious colitis; proctitis; severe ulcerative colitis (UCDAI score >10); and significant haematopoietic, hepatic or renal dysfunction [11, 12]. Concurrent ulcerative colitis therapy was not permitted during the study, with patients required to washout oral 5-ASAs ≥2 days prior [11, 12] and rectal 5-ASAs 4 weeks prior to randomization [12].

Patients received budesonide MMX® 9 mg once daily (with this dosage based on data from a pilot phase II study [9]), budesonide MMX® 6 mg once daily, oral mesalamine (Asacol®) 800 mg three-times daily (CORE I [11]), oral budesonide ER (Entocort® EC) 9 mg once daily (CORE II [12]), or placebo for 8 weeks [11, 12]. The budesonide MMX® 6 mg dosage was included in CORE I following a request from regulatory authorities to identify the lowest effective dosage for inducing disease remission [11]. The mesalamine and budesonide ER treatment arms were included in CORE I and II, respectively, as internal references; however, the studies were not powered to demonstrate a statistical difference between the budesonide MMX® treatment arms and the reference arms [11, 12]. Thus, discussion in this subsection focuses mainly on the comparison between budesonide MMX® 9 mg (i.e. the recommended dose; Sect. 6) and placebo. It should also be noted that the number of modified intent-to-treat (mITT) patients in the placebo group of the CORE II study [12] ($n = 89$) was smaller than prespecified ($n = 110$), which limited the statistical power of the analysis to detect an effect of budesonide MMX®.

Baseline characteristics were generally similar across the treatment groups of both CORE I and II [11, 12]. Overall, patients in CORE I ($n = 489$) had a median UCDAI score of 7.0 and a median endoscopic index score of 7.0; 65 and 57 % had previous received 5-ASAs or mesalamine [11]. Patients in CORE II ($n = 511$) had a mean UCDAI score of 6.2–6.7 and a mean endoscopic index score of 6.5–7.2; 56 and 23 % of patients had previously received mesalamine or sulfasalazine [12].

The primary efficacy endpoint was the proportion of patients in the mITT population (defined as all randomized patients who had received ≥1 dose of the study medication and had active histological disease at baseline) achieving combined clinical and endoscopic remission at week 8 (see Table 1 for definition) [11, 12].

Therapy with budesonide MMX® 9 mg was significantly more effective than placebo with regard to the proportion of patients achieving combined clinical and endoscopic remission in the CORE I and CORE II studies (Table 1). Consistent with the primary analysis, prespecified sensitivity analyses from both studies demonstrated that the benefit in this parameter obtained with budesonide MMX® 9 mg was robust to the inclusion of data from patients excluded from the mITT population [11, 12]. The effect of budesonide MMX® 9 mg on combined clinical and endoscopic remission was maintained following adjustment for age, geographical region and sex in the CORE I study [11], with significant ($p < 0.05$) differences in this endpoint favouring budesonide MMX® 9 mg over placebo observed in younger patients, men and Eastern European patients in the CORE II study [12]. Combined clinical and endoscopic remission outcomes significantly ($p < 0.05$) favoured budesonide MMX® 9 mg over placebo in the left-sided disease patient subgroup [11, 12], but

Table 1 Efficacy of oral budesonide MMX® in adults with active, mild to moderate ulcerative colitis. Results in the modified intent-to-treat population at week 8 of two phase III studies [11, 12]

Study	Treatment	No. of pts	Remission[a] (% of pts)	OR (95 % CI) [active therapy vs. PL]	Improvement (% of pts)	
					Clinical[b]	Endoscopic[c]
CORE I[d] [11]	BUD MMX® 9 mg od	123	17.9*	2.71 (1.19–6.16)	33.3	41.5
	BUD MMX® 6 mg od	121	13.2	1.90 (0.80–4.48)	30.6	35.5
	MES 800 mg tid	124	12.1	1.71 (0.72–4.08)	33.9	33.1
	PL	121	7.4		24.8	33.1
CORE II[d] [12]	BUD MMX® 9 mg od	109	17.4**	4.49 (1.47–13.72)	42.2	42.2
	BUD MMX® 6 mg od	109	8.3		25.7	25.7
	BUD ER 9 mg od	103	12.6*		33.0	36.9
	PL	89	4.5		33.7	31.5

BUD budesonide, *ER* extended release, *MES* mesalamine, *od* once daily, *OR* odds ratio, *PL* placebo, *pts* patients, *tid* three times daily, *UCDAI* Ulcerative Colitis Disease Activity Index

* $p < 0.05$, ** $p = 0.0047$ vs. PL

[a] Combined clinical and endoscopic remission (primary endpoint); defined as a total UCDAI score of ≤1, UCDAI mucosal appearance, rectal bleeding and stool frequency subscores of 0 and a reduction from baseline in the endoscopic index score of ≥1

[b] Defined as a reduction from baseline in the total UCDAI score of ≥3

[c] Defined as a reduction from baseline in the UCDAI mucosal appearance subscore of ≥1

[d] Blinding was maintained using a double-dummy procedure

not in the proctosigmoiditis [11] or extensive disease (beyond the splenic flexure) [11, 12] patient subgroups. A significant difference between budesonide ER and placebo in terms of the primary endpoint was observed in the CORE 2 study (Table 1) [12].

In terms of the secondary endpoints, the proportions of budesonide MMX® 9 mg and placebo recipients achieving clinical improvement did not significantly differ in the CORE I and CORE II studies (Table 1). As this endpoint was not significant in either study, the second secondary endpoint (endoscopic healing) was not assessed as per the prespecified hierarchical testing procedure [11, 12]. The proportion of patients in each treatment group in the CORE I and II studies who achieved endoscopic improvement are detailed in Table 1.

Compared with placebo, exploratory analyses revealed significant ($p < 0.05$) differences in the proportion of budesonide MMX® 9 mg (CORE I and II) [11, 12] and budesonide MMX® 6 mg (CORE I) [11] recipients achieving symptom resolution (defined as UCDAI rectal bleeding and stool frequency subscores of 0). The proportion of patients achieving histological healing (defined as a total histological score of 0 or 1 for all biopsy specimens) was significantly ($p < 0.05$) higher following therapy with budesonide MMX® 9 mg versus placebo in the CORE II study [12], but not the CORE I study [11].

Consistent with the individual study results, a pooled analysis of the CORE I and II studies found that significantly more budesonide MMX® 9 mg than placebo recipients achieved combined clinical and endoscopic remission [17.7 % (41/232) vs. 6.2 % (13/210); $p = 0.0002$], with budesonide MMX® 9 mg recipients three times more likely to achieve this endpoint than placebo recipients [odds ratio 3.3 (95 % CI 1.7–6.4)] [14]. Combined clinical and endoscopic remission rates also favoured budesonide MMX® therapy in most subgroup analyses. As in the individual studies, the proportion of patients achieving clinical improvement did not significantly differ between the budesonide MMX® 9 mg and placebo groups; endoscopic healing was not assessed. Significantly ($p < 0.01$) more budesonide MMX® 9 mg than placebo recipients achieved symptom resolution and mucosal healing (defined as a UCDAI mucosal appearance subscore of 0), but not histological healing, following 8 weeks' therapy [14].

Patients who completed the CORE I study, but did not achieve clinical remission, were eligible to enter a non-comparative extension study (NCT01100112) [15]. Patients ($n = 60$) received budesonide MMX® 9 mg once daily for 8 weeks. Combined clinical and endoscopic remission (primary endpoint) at week 8 was achieved by 25 % of patients, with clinical improvement and endoscopic improvement achieved by 27 and 40 % of patients [15].

4.2 As Add-On Therapy to 5-Aminosalicylic Acids

Patients aged 18–75 years with active, mild to moderate ulcerative colitis inadequately controlled with oral 5-ASA monotherapy, and a UCDAI score of 4–10, a UCDAI mucosal appearance subscore of ≥1 and a UCDAI physician's rating of disease activity score of 1 or 2 were eligible for enrolment in the CONTRIBUTE study (NCT01532648) [13, 15]. The key exclusion criteria were prior rectal

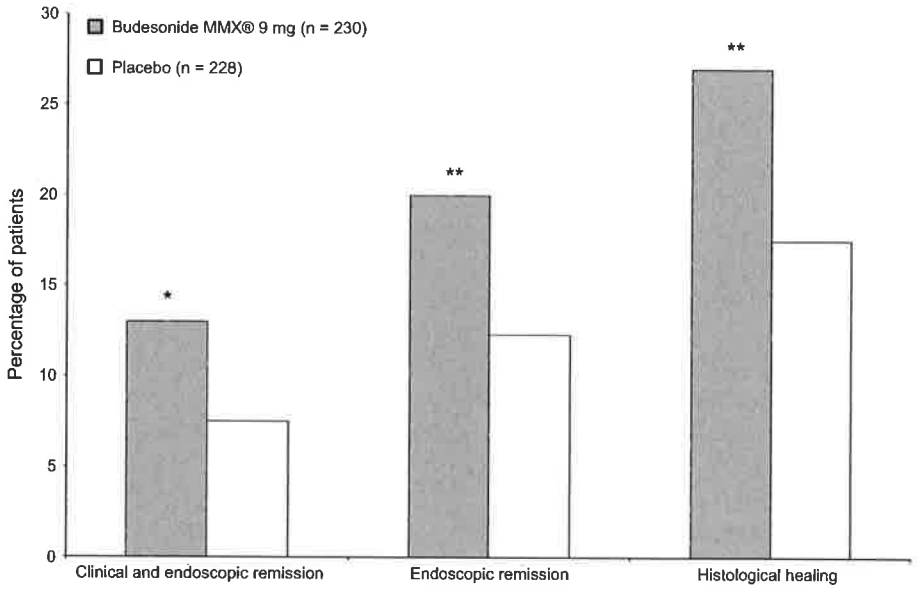

Fig. 1 Efficacy of budesonide MMX® 9 mg as add-on therapy to 5-aminosalicylic acids in adults with active, mild to moderate ulcerative colitis. Proportion of patients achieving clinical and endoscopic remission (primary endpoint), endoscopic remission and histological healing at week 8 in the phase III CONTRIBUTE study [13]. *$p = 0.0488$, **$p < 0.03$ vs. placebo

corticosteroid or 5-ASA therapy within 2 weeks; prior oral corticosteroid therapy within 4 weeks; prior immunosuppressive therapy within 8 weeks; prior anti-TNF therapy within 12 weeks; evidence or history of bowel resection or toxic megacolon; infectious colitis; limited distal proctitis; and significant haematopoietic, hepatic or renal dysfunction [13, 15].

Eligible patients were randomized to receive budesonide MMX® 9 mg once daily or placebo, as add-on therapy to 5-ASAs (stable, therapeutic doses throughout the study), for 8 weeks [13]. The primary efficacy endpoint was the proportion of patients in the mITT population achieving combined clinical and endoscopic remission (defined as a total UCDAI score of ≤ 1, and UCDAI mucosal appearance, rectal bleeding and stool frequency subscores of 0) at week 8. Missing data were analysed using a worst case approach, which counted patients with missing data as non-responders [13].

In patients with inadequately controlled mild to moderate ulcerative colitis despite oral 5-ASA monotherapy, add-on budesonide MMX® 9 mg significantly improved combined clinical and endoscopic remission at week 8 compared with add-on placebo (Fig. 1) [13]. In terms of secondary and exploratory endpoints, significant between-group differences were observed in the proportion of patients achieving endoscopic remission (defined as a UCDAI mucosal appearance subscore of 0) and histological healing (defined as a histological activity grade of 0) (Fig. 1) [13].

5 Tolerability

This section focuses on the recommended dosage of oral budesonide MMX® (9 mg; Sect. 6). In phase III studies in adults with active, mild to moderate ulcerative colitis, the tolerability profile of budesonide MMX®, as monotherapy or add-on therapy to 5-ASAs, was generally similar to that of placebo [11–14]. Most treatment-emergent adverse events (TEAEs) were mild or moderate in intensity [11–14]. Severe TEAEs were reported in 5.5–8.1 % of patients across all treatment arms in the CORE I and II studies [11, 12, 14].

In a pooled analysis [14] of the CORE I and II studies, TEAEs were reported in 56.5 % of patients receiving budesonide MMX® 9 mg monotherapy and 53.5 % of patients receiving placebo. The most common (incidence ≥5 %) TEAEs occurring in the budesonide MMX® and placebo groups were exacerbation, relapse or worsening of ulcerative colitis (13.3 vs. 14.0 % of patients), headache (11.4 and 10.5 %), nausea (5.1 and 4.3 %), abdominal pain (3.5 and 5.8 %) and nasopharyngitis (1.6 and 2.3 %) [14]. In the individual CORE I and II studies, TEAEs were reported in 63.0 % of mesalamine and 54.8 % of budesonide ER recipients [11, 12]. A minority of patients in either study discontinued therapy because of TEAEs [15.3 and 16.7 % of budesonide MMX® 9 mg or placebo recipients (pooled data) [14] and 11.0 and 17.5 % of mesalamine or budesonide ER recipients (individual studies) [11, 12]]. Fewer than one-third of patients receiving budesonide MMX® 9 mg or placebo as add-on therapy to 5-ASAs reported TEAEs (31.8 vs. 27.1 %); the respective discontinuation rates because of TEAEs were 4.7 and 3.5 % [13]. Treatment-related adverse events were reported in 27.1 % of budesonide MMX® 9 mg monotherapy recipients [14], 25.2 % of placebo recipients [14], 24.4 % of mesalamine recipients [11] and 23.0 % of budesonide ER recipients [12].

Serious TEAEs were reported in 2.7 % of budesonide MMX® 9 mg monotherapy recipients [14], 3.1 % of

placebo recipients [14], 3.1 % of mesalamine recipients [11] and 0.8 % of budesonide ER recipients [12]. No deaths were reported in the CORE I study [11].

In the pooled analysis, glucocorticoid-related adverse events were reported in 9.0 versus 10.1 % of patients receiving budesonide MMX® 9 mg monotherapy versus placebo, with mood changes (2.7 vs. 3.9 %) and sleep changes (2.7 vs. 4.3 %) being the most frequent [14]. Other individual glucocorticoid-related adverse events occurred in ≤2.4 and ≤3.1 % of patients in the respective treatment groups [14]. In the individual studies, glucocorticoid-related adverse events occurred in 7.9 % of mesalamine recipients [11], with acne (3.1 %) being the most common, and 11.1 % of budesonide ER recipients, with sleep changes and mood changes (5.6 and 4.8 %) being the most common [12].

Therapy with systemically active glucocorticoids such as budesonide MMX® is associated with the suppression of endogenous cortisol (Sect. 2) [7]. Reductions in blood cortisol levels were observed in 4.3 % of budesonide MMX® 9 mg recipients versus 0.4 % of placebo recipients in the CORE I and II studies [7]. However, in both studies, mean levels remained within the normal reference range (138–690 nmol/L) for all treatment groups at all timepoints [11, 12].

The incidence of adverse reactions and glucocorticoid-related effects with budesonide MMX® 9 mg monotherapy across the entire 16-week course of the CORE I study and its extension was generally similar to that observed in the CORE I study [7]. In the 8-week extension study (NCT01100112) [15], 48.3 % of 60 patients receiving budesonide MMX® 9 mg experienced other (not including serious) adverse events, with a reduction in blood cortisol levels (15.0 %) being the most frequent. Two (3.3 %) patients experienced serious adverse events (one case each of endometrial hyperplasia and ulcerative colitis) [15].

6 Dosage and Administration

Oral budesonide MMX® is approved in various European countries, including the UK [6], under the EU Mutual Recognition Procedure [16], for the induction of remission in patients with active, mild to moderate ulcerative colitis where 5-ASA therapy is not sufficient. In the USA, it is approved for the induction of remission in patients with active, mild to moderate ulcerative colitis [7]. The recommended dosage is 9 mg once daily, administered in the morning with or without food, for up to 8 weeks [6, 7], with the UK summary of product characteristics stating that gradual dose tapering prior to cessation may be useful [6].

Local prescribing information should be consulted for detailed information, including administration procedures, contraindications, drug interactions, patient monitoring, precautions and use in special patient populations, including those transferring from other glucocorticoid therapy.

7 Current Status of Budesonide MMX® in Mild to Moderate Ulcerative Colitis

Treatment selection for active ulcerative colitis should take into consideration the level of clinical activity (mild, moderate or severe) and the distribution (extensive, left-sided, proctitis) and pattern (e.g. course of the disease, extra-intestinal manifestations, relapse frequency, response to previous medication) of the disease [3, 17]. Current guidance from professional bodies states that oral and/or rectal mesalamine is the first-line therapy for the induction of remission in patients with active, mild or moderate ulcerative colitis [2, 17], with the use of topical and/or systemic corticosteroid therapy considered if patients fail to respond to mesalamine [17]. Of note, at the time of publication of these treatment guidelines [2, 17] the role of budesonide MMX® was yet to be determined. A recent review suggests that budesonide MMX® should be considered as an alternative to systemic corticosteroids in patients with mild-to moderate ulcerative colitis who have an unsatisfactory response to 5-ASAs, and that a revision of current treatment algorithms is needed [18]. In addition, it has been noted that some patients may benefit from initial therapy with budesonide MMX® [6, 19].

Budesonide MMX® is primarily absorbed as it passes through the section of bowel between the ascending and descending–sigmoid colon (Sect. 3). It acts locally to inhibit a number of inflammatory processes (Sect. 2) and has low systemic bioavailability (Sect. 3), reducing the potential for systemic effects. The approval of budesonide MMX® was primarily based on the CORE I and II studies (Sect. 4.1). In these studies, budesonide MMX® 9 mg was significantly more effective than placebo in inducing combined clinical and endoscopic remission. However, significant benefits over placebo were not observed for the secondary endpoints of clinical improvement and endoscopic improvement, which may have been due to a high placebo response (Sect. 4.1). Of interest, combined clinical and endoscopic remission rates observed in the CORE I and CORE II studies (Table 1) are lower than those reported for other ulcerative colitis therapies (29.2–59.5 %), with such differences potentially thought to be due to the more stringent criteria for remission used in the CORE I and II studies [14]. In addition, combined clinical and endoscopic remission rates for placebo were low in the

CORE I and II studies (Table 1). It is worth noting that in an 8-week extension of the CORE I study, one-quarter of patients achieved clinical remission, approximately one-quarter achieved clinical improvement and two-fifths achieved endoscopic improvement (Sect. 4.1). Budesonide MMX® 9 mg, as add-on therapy to 5-ASAs, significantly improved combined clinical and endoscopic remission, and endoscopic remission at week 8 compared with add-on placebo in patients with inadequately controlled mild to moderate ulcerative colitis despite oral 5-ASA therapy (Sect. 4.2). A previous Cochrane review concluded that there was no evidence to recommend the clinical use of oral budesonide for the induction of remission in active ulcerative colitis [20]. Of note, only one (a pilot phase II study [9]) of the three studies included in this review assessed budesonide MMX® as the CORE I and II studies were not published at that time. An updated Cochrane review is awaited with interest, as are head-to-head comparisons of budesonide MMX® 9 mg with active treatments.

The tolerability profile of budesonide MMX® 9 mg as monotherapy or add-on therapy to 5-ASAs in adults with active, mild to moderate ulcerative colitis was generally similar to that of placebo (Sect. 5). Moreover, the experiences over the entire 16-week course of the CORE I study and its extension was consistent with that observed in the CORE I study. In a pooled analysis of the CORE I and CORE II studies, the most frequently reported TEAEs with budesonide MMX® 9 mg monotherapy were exacerbation, relapse or worsening of ulcerative colitis, headache, nausea, abdominal pain and nasopharyngitis (Sect. 5). The incidence of glucocorticoid-related adverse events with budesonide MMX® 9 mg monotherapy was also generally similar to that of placebo, with mean morning cortisol levels remaining within the normal reference range following budesonide MMX® 9 mg monotherapy (Sect. 5).

A recently completed 12-month extension study has assessed budesonide MMX® 6 mg as maintenance therapy in patients who completed the CORE I or II studies, or the CORE I extension study and achieved clinical and endoscopic remission (NCT00801723) [21]. Patients were randomized to receive budesonide MMX® 6 mg once daily or placebo for 12 months. Efficacy data have not yet been reported; however, preliminary results indicate that the tolerability and safety profile (including potential glucocorticoid-related effects and effects on bone mineral density) of budesonide MMX® 6 mg once daily for up to 12 months is generally similar to that of placebo [21, 22].

The allocation and utilization of resources attracts ever increasing scrutiny in contemporary healthcare systems, with the recommendation or adoption of any agent/regimen dependent not only on its efficacy and tolerability but also on pharmacoeconomic considerations. Given the recent approval of budesonide MMX®, it is not unexpected that robust pharmacoeconomic data are lacking.

In the absence of head-to-head studies, definitive conclusions on the comparative efficacy and tolerability of budesonide MMX® versus existing therapies are not yet possible. However, current evidence suggests budesonide MMX® 9 mg extends the treatment options currently available for patients with active, mild to moderate ulcerative colitis.

Data selection sources: Relevant medical literature (including published and unpublished data) on Budesonide MMX® was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 13 April 2015], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Budesonide, controlled*release, CR, MMX, Uceris, Cortiment, ulcerative colitis, mild to moderate UC.
Study selection: Studies in patients with active, mild to moderate ulcerative colitis who received Budesonide MMX®. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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