Budesonide (UCERIS) Extended Release Tablets

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

- Budesonide with multi-matrix system (MMX) technology is an extended release (ER) 9-mg tablet FDA approved for the induction of remission in patients with active, mild to moderate ulcerative colitis for up to 8 weeks. This formulation is designed to be released throughout the colon.
- CORE I and II were high-quality trials that showed budesonide ER 9 mg daily to have a small effect size in terms of clinical and endoscopic remission at 8 weeks.
- Adverse event profile and tolerability of budesonide ER versus placebo were relatively similar.
- Common adverse events included headache, abdominal pain, and gastrointestinal upset.
- Dose adjustments for renal and hepatic impairment are not clearly defined; however, clinicians should consider discontinuing budesonide ER in patients with moderate to severe liver disease or increased monitoring in renal impairment.
- Budesonide ER should be used cautiously in elderly patients especially in those patients with decreased hepatic and renal function and cardiac comorbidities.
- Budesonide is metabolized by CYP 3A4; therefore, potent inhibitors or inducers may increase or decrease budesonide plasma concentrations and their concomitant use with budesonide should be avoided.

Conclusions: Overall, studies evaluating budesonide ER in patients with active, mild to moderate ulcerative colitis consistently showed statistically significant but small benefits with budesonide ER 9 mg in inducing clinical and endoscopic remission within 8 weeks, with initial benefit noted after 4 weeks of treatment. Exploratory, numerical comparisons suggested that budesonide ER is comparable to either mesalamine or budesonide (ENTOCORT) EC capsules in the rates of clinical and endoscopic remission. Use of budesonide ER for longer than 8 weeks has not been established by clinical trial.The adverse event profiles of budesonide ER and placebo were similar, which is notable for a glucocorticoid. The available evidence suggests that budesonide probably has a somewhat lower risk of systemic glucocorticoid effects than prednisolone. Similar to prednisone, concomitant intake of drugs or foods that are inhibitors or inducers of CYP3A4 should be avoided because of the potential for increases or decreases in budesonide plasma concentrations. The most notable issue is that budesonide ER tablets are substantially more costly than conventional alternative therapies. Limitations of the evidence base include lack of head-to-head superiority and non-inferiority clinical trials. Clinically equivalent glucocorticoid (e.g., prednisone, prednisolone) doses for budesonide ER have not been determined in ulcerative colitis; therefore, dosage equivalents are uncertain when switching glucocorticoid therapy. Further studies are needed to confirm the safety and efficacy of budesonide ER compared with alternative therapies (e.g., double-dose mesalamine, prednisone) in inadequate responders to standard 5-ASA therapy. The available evidence and published reviews support the use of budesonide ER in inadequate responders to 5-ASA therapy for active, mild to moderate ulcerative colitis. Budesonide ER may serve as an alternative treatment option in patients with an indication for a trial of a glucocorticoid with potentially lower risks of adrenal suppression and hypercorticism-related adverse effects, taking into consideration comorbid conditions and patient specific factors, such as diabetes, osteoporosis / osteopenia, and immune status.

Introduction

Budesonide is available in multiple formulations with various pharmacokinetic profiles. The enteric coated formulation (ENTOCORT EC 3-mg capsules by AstraZeneca) with controlled ileal release (CIR) was approved for Crohn's disease in the U.S. Budesonide ER tablets with multi-matrix colonic release system by Salix Pharmaceuticals was approved by the Food and Drug Administration (FDA) in September 2014. Budesonide ER is a novel formulation that extends the release of the active ingredient throughout the colon. The multi-matrix system (MMX) technology results in the delayed release of drug and a long dwell time in the colon. Thus, budesonide ER has the FDA approval for use in induction of remission for active, mild to moderate ulcerative colitis based on pharmacokinetic properties associated with the new formulation.[1] Of note, budesonide rectal foam was approved by the FDA in October 2014 for the induction of remission of active, mild to moderate distal ulcerative colitis.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating budesonide ER for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Budesonide, a mixture of the two epimers 22R and 22S, is a potent glucocorticoid and weak mineralocorticoid. Budesonide has a 15-fold greater affinity for glucocorticoid receptors than prednisolone, reflecting higher intrinsic potency; however, the clinically equivalent doses of budesonide ER and other glucocorticoids in ulcerative colitis have not been described.

Budesonide has substantial first-pass elimination and low systemic bioavailability. Compared with the 92% bioavailability of prednisone, the bioavailability of budesonide is 10%-20%, which may translate to less plasma cortisol suppression associated with budesonide.[1]

Budesonide ER tablets are coated with a gastroresistant methacrylic acid copolymer which delays dissolution until a pH of ≥7 in the lower gastrointestinal tract. The active ingredient is further embedded in a sequence of lipophilic and amphiphilic matrices, which provides extended release in a time-dependent manner.[2]

The technology of budesonide ER tablets differs from that of budesonide EC capsules in the pH of dissolution. Budesonide EC capsules dissolves in pH >5.5, therefore drug is available for absorption mostly in the small intestines. Compared to Crohn's disease, ulcerative colitis is restricted to the colon which requires more distal distribution and absorption than budesonide EC can provide, limiting its utility for ulcerative colitis.[2]

Absorption

Cmax for budesonide ER 9 mg is 1.35ng/mL and AUC of 15.16ng·hr/mL. A large difference was noted in the mean arrival time and time to first appearance plasma between budesonide ER tablets and budesonide EC capsules with CIR. When budesonide ER was taken with a high-fat meal, Cmax decreased by 27% with no significant changes in AUC, and after administration with food, absorption lag time was delayed by a mean of 2.4 hours.[2]

Distribution

Mean volume of distribution ranges from 2.2-3.9L/kg with 85-90% plasma protein binding.[1]

Metabolism

High first–pass metabolism (80%-90%). Metabolized via CYP 3A4 into two major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, which have negligible glucocorticoid activity.[1]

Excretion

Urine (60%) and feces as metabolites.[1]

In healthy volunteers, budesonide ER MMX 9-mg tablets and budesonide EC CIR 9 mg capsules were associated with comparable extent (AUC) of systemic drug exposure and Cmax (Table 2). However, the ER MMX tablets were associated with a more delayed appearance and peak concentration of budesonide in plasma, a pharmacokinetic profile consistent with more distal delivery of drug in the gastrointestinal tract.[2]

Table 1: Pharmacokinetic Parameters of Budesonide ER Tablets vs. Budesonide EC Capsules after a Single Dose in Healthy Volunteers under Fasting Conditions

Parameter	Budesonide ER 6 mg	Budesonide ER 9 mg	Budesonide EC 9 mg
AUC (ng/mL/hr)	11.5336(4.7385)	15.1605(10.0209)	14.057(6.3787)
MAT (hr)	13.9(5.7)	16.9(4.7)	8.5(2.7)
Half-life (hr)	6.6(2.4)	7.5(2.9)	7.7(1.8)
Cmax (ng/mL)	1.1585(0.5324)	1.3488(0.9588)	1.5559(0.588)
Tmax (hr)	10	15	5
Tlag (hr)	6	6	1

Sources: References 2, 3. AUC: area under the concentration-time curve; MAT: mean arrival time; Cmax: maximum concentration; Tmax: time to maximum concentration; Tlag: time of first appearance in plasma

FDA Approved Indication(s)

Budesonide ER is FDA approved for the induction of remission of patients with active, mild to moderate ulcerative colitis.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Based on literature review, no published studies were found for potential off-label uses of budesonide ER tablets. Based on the common usage of glucocorticoids in ulcerative colitis, potential off-label uses of budesonide ER include the following:

- Treatment of severe ulcerative colitis
- Use of higher than the 9-mg recommended daily dose
- Treatment for longer than the 8-week recommended treatment duration
- Maintenance of remission / prevention of relapse of ulcerative colitis: Glucocorticoids have not been shown to be effective as maintenance therapy and should be tapered after the patient has been stable for 2 to 4 weeks. There is insufficient data from a study evaluating budesonide ER capsules for maintenance therapy of ulcerative colitis.**Error! Reference source not found.**
- Treatment of other (non-ulcerative colitis) conditions responsive to systemic glucocorticoids

Alternative Therapies for the Approved Indication of Budesonide ER

VA National Formulary

- Balsalazide
- Mesalamine, SA cap, EC tab, oral
- Sulfasalazine tab, EC tab
- Systemic glucocorticoids: dexamethasone, methylprednisolone, prednisone

The following formulary items have indications different from that of budesonide ER tablets:

- Hydrocortisone enema is indicated as adjunctive therapy for distal forms of ulcerative colitis

- Hydrocortisone 10% rectal foam is indicated for ulcerative proctitis
- Mesalamine rectal suppository is indicated for the treatment of mild to moderately active ulcerative proctitis
- Mesalamine rectal suspension (enema) is indicated for the treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis

Non-formulary

- Systemic glucocorticoids: prednisolone, betamethasone
- Budesonide (ENTOCORT EC) CIR:
    - Off-label use for ulcerative colitis is only indirectly supported by a 9-week pilot randomized trial (N = 72) that showed similar efficacy between budesonide EC CIR (10 mg daily, gradually tapered) and prednisolone (40 mg daily, gradually tapered) in terms of mean endoscopic scores in patients with active, mild to moderate extensive and left-sided ulcerative colitis.[4]
    - The off-label use of a budesonide formulation other than the ER MMX tablets for ulcerative colitis may also be indirectly supported by another randomized trial which showed that 70 (39.5%) of 177 patients treated with a U.K. gastro-resistant formulation, BUDENOFALK capsules (9 mg daily), achieved clinical remission at week 8; however, mesalazine / mesalamine (3 g daily) was superior, achieving clinical remission in 91 (54.8%) of 166 patients.[6]
    - Budesonide EC CIR was also used as a reference comparator in one of the budesonide ER trials, as requested by European regulatory authorities.[11] It showed a small benefit (NNT = 13) for combined clinical and endoscopic remission. However, the trial was not powered to test superiority between the two formulations.

Dosage and Administration

Budesonide ER is recommended for the induction of remission in patients with active, mild to moderate ulcerative colitis at a dose of 9 mg once a day in the morning for up to 8 weeks. The tablet should be taken orally in the morning and can be administered with or without food. The tablet should not be crushed, chewed, or broken. Avoid taking this medication with CYP3A4 inhibitors (ketoconazole, grapefruit, etc.).

Taper slowly and cautiously off of systemic glucocorticoids when switching to budesonide ER tablets.

No dosage adjustments for renal insufficiency are recommended.

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism due to systemic availably of orally administered budesonide correlating with disease severity (2.5-fold higher compared to healthy patients). Discontinuation of budesonide should be considered in these patients.

Refer to product information for details.

Efficacy

Efficacy Measures

- CAI: Instrument used to measure ulcerative colitis disease activity through evaluation of objective (ESR, temperature, and hemoglobin) and subjective (endoscopy, degree of abdominal pain, amount of blood in stools, and physician's impression of disease) measures. The total index score ranges from 0 to 29 points, with the higher total scores representing more severe disease.[13] Scores <4: Remission; 4–8: Moderately active; >8: Highly active; Increase of >8: Relapse.
- UCDAI: A numerical disease activity tool which combines clinical and endoscopic assessments in the sum of scores from four components: stool frequency, rectal bleeding, sigmoidoscopic findings, and physician's global assessment. This disease activity index ranges from 0 to 12, with the higher total scores representing more severe disease.[9]
  [≤2: Remission, 3-5: Mild, 6-10: Moderately active, 11-12: Severe]

- Saverymuttu Scale (Histology): Performed to confirm the diagnosis of ulcerative colitis. A scoring system used to grade four items on a 4-point scale for rectal bioptic specimens for elements of ulcerative colitis from the biopsy. Enterocytes, crypts, lamina propria mononuclear cells, and lamina propria neutrophils are the four types of cells observed for diagnosis.[11] Each item is graded on a scale of 0-3 with a grade of 3 being the most severe.
- Rachmilewitz Endoscopic Index (EI): Scoring system based on four items, each scored on a 4-point scale: granulation scattering reflected light, vascular pattern, vulnerability of mucosa, and mucosal damage. Each item is graded on a scale of 0-3 with a grade of 3 being the most severe.
- Biopsy: Performed to confirm the presence of colitis and to exclude the presence of infectious and noninfectious etiologies. Biopsies of the colon obtained can be used to establish the chronicity of inflammation and to exclude other causes of colitis.[10]

The efficacy measures used in the two pivotal COlonic RElease (CORE) budesonide trials are summarized in Table 2.

Table 2 Efficacy Measures Used in Budesonide ER Pivotal Trials

	CORE I and CORE II	Preliminary Trial
Primary	• Remission: combined clinical and endoscopic remission with UCDAI score ≤ 1 point, with sub-scores of 0 for both rectal bleeding and stool frequency, no mucosal friability on colonoscopy, and ≥ 1 point reduction from baseline in endoscopic score at week 8	• Clinical Remission: CAI ≤ 4 • Clinical improvement : CAI ≤ 4 or CAI reduction by at least 50% of baseline value at week 4 and at week 8
Secondary	• Clinical improvement: ≥ 3 point reduction in UCDAI score week 8 • Endoscopic improvement: ≥ 1 point reduction in UCDAI mucosal appearance score at week 8 • Symptom resolution: score of 0 for both rectal bleeding and stool frequency sub-scores of UCDAI at week 8 • Histologic healing: histologic score ≤ 1 according to Saverymuttu scale for histological assessment of all biopsy specimens at week 8	• Clinical improvement: Reduction by at least 70% of CAI or clinical remission after 8 weeks (after 6 weeks in patients who switched to open-label trial)

Sources: Sandborn (2012)[10] – CORE I; Travis (2014)[11] – CORE II; D'Haens (2010)[12] – Preliminary trial

Summary of efficacy findings

CORE I and CORE II were the two major trials involved in the FDA approval of budesonide ER tablets for induction of remission in patients with active, mild to moderate ulcerative colitis.

Table 1 Summary of Budesonide ER Studies in Mild-Moderate Ulcerative Colitis

Reference	Design, Study Population	Findings
Sandborn (2012) CORE I	8-wk multi-center randomized, double-blind, double-dummy, placebo-controlled trial, with mesalamine as exploratory "reference" 509 patients with active mild-moderate ulcerative colitis	Primary Outcome Measure at Week 8: • Budesonide ER 9 mg showed a small, statistically significant benefit in terms of **clinical and endoscopic remission** rates vs. placebo: 17.9% vs. 7.4%; difference 10.4% (95% CI: 2.2–18.7); p = 0.0143. OR 2.71 (95% CI 1.19–6.16). NNT = 10. • Budesonide ER 6 mg and mesalamine 2.4 g showed no statistically significant benefit compared to placebo. Secondary Outcome Measures at Week 8: • Budesonide ER 9 mg and 6 mg showed small benefits in terms of **symptom resolution rates** (each NNT = 8), whereas mesalamine 2.4 g showed no benefit. • None of the treatments were beneficial in terms of **clinical improvement**, **endoscopic improvement**, and **histologic healing** rates. Generally well tolerated and overall safety profile similar to that of placebo. • Most common adverse events were ulcerative colitis and headache. • No evidence of increase in glucocorticoid effects: 9mg (11.8%), 6mg (5.6%), placebo (10.1%).

Travis (2014)
CORE II
	8-wk Phase III RCT, double-blinded, double-dummy, parallel-group trial, with ENTOCORT EC capsules as exploratory "reference"
	Active mild-moderate ulcerative colitis
		Primary Outcome at Week 8:
		• Budesonide ER 9 mg had a small, statistically significant benefit in terms of **clinical and endoscopic remission**: 17.4% vs. 4.5% placebo; difference 12.9%; p = 0.0047. OR (95% CI): 4.5 (1.5–13.7). NNT = 8.
		• Budesonide (ENTOCORT) EC 9 mg also showed a small benefit (NNT = 13).
		• No statistically significant benefit was seen with budesonide ER 6 mg.
		Secondary Outcomes at Week 8:
		• No statistically significant benefit was seen with the three active treatment groups in terms of
		  • Clinical improvement
		  • Endoscopic improvement
		• Only budesonide ER 9 mg showed a statistically significant benefit in terms of
		  • Histologic healing: 16.5% vs. placebo 6.7%; difference, 9.8%; p = 0.0361; and
		  • Symptom resolution: 23.9% vs. 11.2%; difference, 12.7%; p = 0.0220.
		Most common adverse events:
		• Ulcerative colitis relapse: Budesonide ER 9mg (15.6%) vs. PBO (11.6%)
		• Headache: Budesonide ER 9mg (16.4%) vs. PBO (6.2%)

Reference	Design, Study Population	Findings
D'Haens (2010)	4-8-wk pilot phase II randomized placebo-controlled trial Active ulcerative colitis with a CAI <14, on stable treatment with oral 5-ASA preparation at a dose range between 0-3 g/day for 2 months before the study.	Primary Outcome Measure: Budesonide ER 9 mg failed to show a statistically significant treatment benefit in terms of **clinical improvement** rates at week 4 (46.1% vs. 33.3% placebo); however, the study was underpowered. The most common adverse drug events reported with budesonide ER 9 mg included: • Headache (11.86%) • Abdominal pain (8.47%) • Common cold (6.77%) • Diarrhea, flatulence, and influenza (5.08%).

Table 2 Assessment of Evidence Base

Category	Summary
Overall Quality of Studies (GRADE)	Grade: Moderate; one of the studies was a pilot trial and had a complex design with conversion from a double blind to an open-label treatment within the first phase, and another may have suggested a biased title.
Consistency of Results	All studies showed statistically significant findings in improving clinical and endoscopic remission.
Directness of Evidence	Evidence was direct for clinical and endoscopic remission observed after 4 weeks of treatment. Symptom resolution in terms of rectal bleeding and stool frequency as well as histological healing were not considered the primary objective within any study. Evidence was direct for less mean plasma cortisol suppression observed with budesonide ER compared with other glucocorticoids. Prevention of hospitalizations and improvement in terms of quality of life were not assessed.
Precision of Results	The 95% CIs around group differences in clinical and endoscopic remission for budesonide ER 9mg were relatively wide.

Overall, the studies consistently showed statistically significant but small benefits with budesonide ER 9 mg in inducing clinical and endoscopic remission within 8 weeks, with initial benefit noted after 4 weeks of treatment.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 16).

Safety

Deaths and Other Serious Adverse Events

None noted.

Adverse Event Profiles

The adverse event findings from the two pivotal clinical trials are summarized in Table 3 and Table 4.

Table 3 Adverse Events: CORE I Trial

Adverse Event	Placebo (n=129)	Budesonide ER 9 mg (n=127)	Budesonide ER 6 mg (n=126)	Mesalamine 2.4 g/day (n=127)
Any adverse event (AE)	81 (62.8)	73 (57.5)	74 (58.7)	80 (63)
Colitis ulcerative	21 (16.3)	14 (11)	15 (11.9)	13 (10.2)
Headache	19 (14.7)	8 (6.3)	17 (13.5)	12 (9.4)
Pyrexia	9 (7)	3 (2.4)	5 (4)	3 (2.4)
Insomnia	9 (7)	5 (3.9)	6 (4.8)	3 (2.4)
Back pain	7 (5.4)	5 (3.9)	4 (3.2)	2 (1.6)
Nausea	8 (6.2)	5 (3.9)	5 (4)	10 (7.9)
Abdominal pain	8 (6.2)	6 (4.7)	2 (1.6)	10 (7.9)
Diarrhea	7 (5.4)	2 (1.6)	5 (4)	8 (6.3)
Flatulence	2 (1.6)	1 (0.8)	1 (0.8)	7 (5.5)
Treatment related AE	34 (26.4)	36 (28.3)	35 (27.8)	31 (24.4)
Severity of AE				
Mild	31 (24)	30 (23.6)	33 (26.2)	39 (30.7)
Moderate	34 (26.4)	35 (27.6)	29 (23)	34 (26.8)
Severe	16 (12.4)	8 (6.3)	12 (9.5)	7 (5.5)
AE leading to discontinuation	24 (18.6)	15 (11.8)	18 (14.3)	14 (11)
Any serious AE	3 (2.3)	3 (2.4)	2 (1.6)	4 (3.1)
Treatment related serious AE	0	1 (0.8)	1 (0.8)	0
Serious AE leading to discontinuation	2 (1.6)	2 (1.6)	2 (1.6)	1 (0.8)
Any potential glucocorticoid effect	13 (10.1)	15 (11.8)	7 (5.6)	10 (7.9)

Source: Sandborn (2012)[10] ** Reported as n (%)

Table 4 Adverse Events: CORE II Trial

Adverse Event	Placebo (n=129)	Budesonide ER 9 mg (n=128)	Budesonide ER 6 mg (n=126)	Budesonide EC 9 mg/day (n=126)
Any adverse event (AE)	57 (44.2)	71 (55.5)	80 (62.5)	69 (54.8)
Ulcerative colitis	15 (11.6)	20 (15.6)	27 (21.1)	16 (12.7)
Headache	8 (6.2)	21 (16.4)	20 (15.6)	9 (7.1)
Abdominal Pain	7 (5.4)	3 (2.3)	5 (3.9)	7 (5.6)
Flatulence	3 (2.3)	5 (3.9)	7 (5.5)	7 (5.6)
Nausea	3 (2.3)	8 (6.3)	7 (5.5)	3 (2.4)
Nasopharyngitis	2 (1.6)	1 (0.8)	8 (6.3)	6 (4.8)
Blood cortisol decrease	1 (0.8)	7 (5.5)	3 (2.3)	4 (3.2)
Treatment Related AE	31 (24.0)	33 (25.8)	28 (21.9)	29 (23.0)
Severity of AE				
Mild	18 (14)	27 (21.1)	36 (28.1)	30 (23.8)
Moderate	32 (24.8)	32 (25)	38 (29.7)	29 (23.0)
Severe	5 (3.9)	12 (9.4)	5 (3.9)	10 (7.9)
AE leading to discontinuation	19 (14.7)	24 (18.8)	30 (23.4)	22 (17.5)
Any serious AE	5 (3.9)	4 (3.1)	3 (2.3)	1 (0.8)
Treatment related serious AE	0	1 (0.8)[a]	2 (1.6)[b]	1 (0.8)[c]
Serious AE leading to discontinuation	2 (1.6)	2 (1.6)	2 (1.6)	1 (0.8)
Any potential glucocorticoid effect	13 (10.1)	8 (6.3)	6 (4.7)	14 (11.1)
Plasma cortisol concentrations mean (nmol/litre)	365	253	315	323

Source: Travis (2014)[11]
** Reported as n (%) except as noted. [a] Treatment failure. [b] UC (relapse/nausea/urge incontinence). [c] Gastric ulcer/UC relapse

The adverse event profiles of budesonide ER and placebo were similar. In exploratory comparisons, budesonide ER 9 mg was associated with numerically lower rates of gastrointestinal adverse events (nausea, abdominal pain,

diarrhea, flatulence) than mesalamine and numerically higher rates of headache than budesonide (ENTOCORT) EC 9 mg.

Glucocorticoid Effects

The greatest decrease in mean serum cortisol concentration (ug/dL) was seen after 2-4 weeks of treatment with budesonide ER 6-mg and 9-mg tablets; however, on final visit (week 8) there were no statistically significant differences among study arms. Mean morning plasma cortisol concentrations decreased from baseline to final visit in a dose-dependent manner; however, there was no associated increase in the frequency of reported potential glucocorticoid effects.

In the FDA's pooled analyses across Phase III randomized trials, glucocorticoid effects were seen most frequently with budesonide EC (ENTOCORT) (14% of 126 patients), then next most frequently with mesalamine (12% of 127 patients), followed by placebo (11% of 258 patients), and budesonide ER 9 mg (10% of 255 patients) and 6 mg (8% of 254 patients).**Error! Reference source not found.** The most frequent specific glucocorticoid effects reported with budesonide ER 9 mg were mood changes (3.5%), sleep changes (2.7%), and insomnia and acne (2.4% each). Mood changes, sleep changes and insomnia were numerically less frequent with budesonide ER 9 mg than with placebo (4.3%, 4.7% and 3.1%, respectively), whereas acne was seen in 1.9% of placebo patients. Glucocorticoid effects seen numerically more frequently in the ENTOCORT group than in the budesonide ER groups were moon face (1.6% vs. 1.2%), flushing (0.8% vs. 0%), mood changes (4.8% vs. 3.5%), sleep changes (7.1% vs. 2.7%), insomnia (4.0% vs. 2.4%) and hirsutism (0.8% vs. 0.4%).

The FDA also reviewed long-term glucocorticoid effects during administration of budesonide ER 6 mg relative to placebo for up to 12 months of maintenance therapy in study CB-01-02/04.**Error! Reference source not found.** There were no clinically important treatment differences in terms of bone density scans at the last study visit and no clinically meaningful changes in bone mineral density after 12 months of treatment with budesonide ER 6 mg. The following potential glucocorticoid effects occurred numerically more frequently (but in only one to three patients each) with budesonide ER 6 mg (N = 62) than with placebo (N = 61): cushinoid (5% vs. 3%), acne (5% vs. 0%), flushing (3% vs. 2%), hirsutism (5% vs. 0%) and blood cortisol decreased (3% vs. 2%). There were no trends related to abnormal changes in hematologic or chemistry laboratory test results.

The literature search found no studies comparing budesonide ER 9 mg with other glucocorticoids in terms of glucocorticoid effects in patients with ulcerative colitis. Since the lower bioavailability of budesonide is the basis for reducing both deficient cortisol and hypercorticism rather than the particular formulation, studies involving other budesonide formulations were sought to thoroughly evaluate this potential advantage. Budesonide with Eudragit-S technology had a numerically lower percentage of patients with deficient cortisol response to ACTH than prednisolone 7.5 mg (34% versus 46%) for rheumatoid arthritis.[21] In another study, 8 weeks' therapy for Crohn's disease with tapering doses of budesonide EC (ENTOCORT) CIR capsules (9 mg once daily or 4.5 mg twice daily) had a better glucocorticoid safety profile in certain respects than prednisolone (40 mg once daily, tapering schedule): moon face (13.8% and 11.5% versus 37.9%; $p = 0.0005$); normal cortisol response on ACTH testing (42% and 50% vs. 16%; $p \leq 0.013$) and significantly higher mean morning plasma cortisol concentrations (188 and 242 versus 117 nmol/l; $p = 0.0035$).[23] In a pilot randomized trial evaluating budesonide EC (ENTOCORT) CIR capsules (10 mg / day to week 4, tapering off through week 9) in comparison with prednisolone (40 mg / day to week 2 then tapering off through week 9) in 72 patients with active, mild to moderate extensive and left-sided ulcerative colitis, none of the budesonide-treated patients developed mean plasma cortisol concentrations below the lower limit of normal (<150 nmol/l) at any time during the study, whereas a significantly greater percentage of prednisolone-treated patients had low cortisol concentrations (25 (75.8%) of 33 patients after 2 weeks, 21 (61.7%) of 34 patients after 4 weeks, and 6 (17.6%) of 34 patients after 9 weeks; p-values ≤ 0.047) and one patient on prednisolone developed a Cushing-like syndrome.[4] In children with Crohn's disease, budesonide (9 mg/day for 8 weeks, 6 mg/day for 4 weeks; N = 22) was associated with significantly higher mean morning plasma cortisol concentration than prednisolone (1 mg/kg/day for 4 weeks, tapering for 8 weeks; N = 26) (200 versus 98 nmol/l) and significantly lower incidences of any treatment-

emergent glucocorticoid effects (50.0% vs. 76.9%; p = 0.03), moon face (22.7% vs. 57.7%) and acne (4.5% vs. 26.9%).[22]

Common Adverse Events

Central nervous system: headache, emotional liability, fatigue
Dermatologic: acne vulgaris
Endocrine and metabolic: hirsutism, decreased cortisol
Gastrointestinal: nausea, upper abdominal pain, flatulence, abdominal distension, diarrhea
Genitourinary: urinary tract infection
Neuromuscular and skeletal: arthralgia

Tolerability

CORE I

- Placebo: 18.6% discontinued due to AE
- Budesonide ER 9mg: 11.8% discontinued due to AE
- Budesonide ER 6mg: 14.3% discontinued due to AE

CORE II

- Placebo: 14.7% discontinued due to AE
- Budesonide ER 9mg: 18.8% discontinued due to AE
- Budesonide ER 6mg: 23.4% discontinued due to AE

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 21).

Contraindications

Hypersensitivity to budesonide or any of the ingredients
Previous anaphylactic reaction with other budesonide formulations

Warnings and Precautions

Hypercorticism /Adrenal axis suppression

Immunosuppression

Liver impairment/Cirrhosis: May increase systemic glucocorticoid susceptibility

Co-morbidities: Caution should be used when administering glucocorticoid to individuals with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma/cataracts, or with a family history of the following conditions.

Systemic glucocorticoid treatment alteration: Risk of impaired adrenal function when transferring from glucocorticoid treatment with higher systemic effects to glucocorticoids with lower systemic effects.

*Warnings and precautions of budesonide ER do not differ from those of budesonide EC

Special Populations

Pregnancy

Teratogenic Effects: Pregnancy Category C
There are not adequate and well controlled studies in pregnant women. Budesonide ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
No data from controlled trials on the use of budesonide ER by nursing mothers or their infants at this time but potential for serious adverse reaction in nursing infants is still a consideration. Providers and mothers should make a decision on whether to discontinue nursing or to discontinue budesonide ER.

Geriatrics
Budesonide ER should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Clinical studies of budesonide ER did not include sufficient numbers of subjects greater than or equal to 65 year to determine whether they respond differently from younger subjects.

Hepatic Impairment
Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Studies showed that an increase in systemic availability among patients with cirrhosis was approximately 2.5-folds higher compared to healthy patients. Patients with liver cirrhosis and mild liver disease showed no difference in absorption or clearance compared to patients with normal hepatic function. Patients with severe liver dysfunction have not been studied.

Renal Impairment
Renal impairment studies have not been performed.

Post-marketing Safety Experience

According to product information, oral budesonide has been associated with anaphylactic reactions, benign intracranial hypertension, and mood swings.

Sentinel Events

None

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

- LA/SA for generic name *Budesonide ER*: Bumetanide; Desonide; Budesonide IR; Budesonide EC
- LA/SA for trade name *UCERIS*: Lucentis; Luveris

Drug Interactions

Ingestion of grapefruit or grapefruit juice should be avoided during budesonide ER therapy, and if therapy with CYP3A4-inhibiting antiinfectives is indicated, discontinuation of budesonide ER should be considered.

Drug-Drug Interactions

Drug	CYP Activity	Description of Interaction
Major		
Ritonavir	CYP3A4 inhibitor	may result in increased steroid concentrations
Boceprevir	None	may result in increased budesonide plasma concentrations
Eslicarbazepine	CYP3A4 inducer	may result in decreased budesonide plasma concentrations
Dabrafenib	CYP3A4 inducer	may result in decreased budesonide plasma concentrations
Siltuximab	CYP3A4 substrate	may increase the metabolism of budesonide and decrease its effectiveness
Cobicistat	CYP3A4 inhibitor	may result in increased budesonide plasma concentrations and increased risk for systemic corticosteroid effects
Buproprion	None	may result in lowering of the seizure threshold
Primidone	CYP3A4 substrates	may result in decreased budesonide plasma concentration
Idelalisib	CYP3A inhibitor	may increase budesonide concentrations and increase the risk of adverse effects
Mitotane	CYP3A4 inducer	may result in decreased budesonide plasma concentrations
Carbamezepine	CYP3A4 inducer	may result in decreased budesonide plasma concentrations
Piperaquine	CYP3A4 inhibitor	may result in increased budesonide concentrations
Pixantrone	P-gp substrate and P-gp inducer	may result in decreased exposure of pixantrone
Teleprevir		may result in increased budesonide plasma concentrations and significantly reduce serum cortisol concentrations
Ceritinib	CYP3A substrate	may increase budesonide plasma concentrations
Moderate		
Itraconazole	CYP3A4 inhibitors	may increase budesonide plasma concentrations
Erythromycin	CYP3A4 inhibitors	may increase budesonide plasma concentrations
Ketoconazole	CYP3A4 inhibitors	may increase budesonide plasma concentrations which may be reduced by administration of budesonide and ketoconazole separated by 12 hours.
Clarithromycin	CYP3A4 inhibitor	may increase budesonide plasma concentrations
Ranolazine	CYP3A4 inhibitor	may increase budesonide plasma concentrations
Sargramostin	None	may potentiate the myeloproliferative effects of sargramostim
Deferasirox	CYP3A4 inducer	may decrease budesonide plasma concentrations
Testosterone	None	may result in increased risk of edema
Crizotinib	CYP3A4 inhibitor	may increase budesonide plasma concentrations
Glycerol phenylbutyrate	None	may result in increased plasma ammonia levels
Low		
Amiodarone	CYP3A4 inhibitor	may result in increased risk of developing Cushing's syndrome.

Sources: References 4,5
*Budesonide is metabolized by CYP3A4. CYP3A4 potent inhibitors can increase budesonide plasma concentrations, whereas CYP3A4 potent inducers can decrease the plasma concentration.
*Caution with gastric reducing agents due to altered release properties

Drug-Food Interactions
Grapefruit may result in two-fold increase in systemic exposure of budesonide, possibly increasing cortisol suppression.

Drug-Lab Interactions
None noted.

Pharmacoeconomic Analysis
No data.

Reviews on Potential Place in Therapy

Review articles and tertiary references discuss the potential place in therapy of budesonide ER tablets for the induction of remission of active mild to moderate ulcerative colitis. Danese, et al.(no pharmaceutical or other

support or sponsorship) evaluated the integration of budesonide ER tablets into current treatment algorithms. The authors concluded that budesonide ER tablets should be trialed after orally (with or without rectally) administered aminosalicylates (5-ASA) products but before other oral glucocorticoids such as prednisone because of the lower bioavailability and better adverse effect profile with the budesonide product.[16]

Additionally, a Cochrane review published in 2010 concluded that, compared with other systemic steroids, budesonide may have a better adverse effect profile; however, mesalamine products were superior to budesonide for treatment of active ulcerative colitis.[17]

Oral budesonide is not addressed by the American College of Gastroenterology (ACG)[18] or the UK's NICE[19] guidelines for ulcerative colitis, both of which were published prior to the FDA approval of budesonide ER tablets. Both the ACG and NICE guidelines recommended oral aminosalicylates first for induction of remission for active mild to moderate distal, left-sided, or extensive ulcerative colitis. The ACG and NICE guidelines recommend oral corticosteroid use for patients who have 5-ASA–refractory, mild to moderate extensive colitis.

Conclusions

Overall, studies evaluating budesonide ER in patients with active, mild to moderate ulcerative colitis consistently showed statistically significant but small benefits with budesonide ER 9 mg in inducing clinical and endoscopic remission within 8 weeks, with initial benefit noted after 4 weeks of treatment. Exploratory, numerical comparisons suggested that budesonide ER is comparable to either mesalamine or budesonide (ENTOCORT) EC capsules in the rates of clinical and endoscopic remission. Use of budesonide ER for longer than 8 weeks has not been established by clinical trial.The adverse event profiles of budesonide ER and placebo were similar, which is notable for a glucocorticoid. The available evidence suggests that budesonide probably has a somewhat lower risk of systemic glucocorticoid effects than prednisolone. Similar to prednisone, concomitant intake of drugs or foods that are inhibitors or inducers of CYP3A4 should be avoided because of the potential for increases or decreases in budesonide plasma concentrations. The most notable issue is that budesonide ER tablets are substantially more costly than conventional alternative therapies. Limitations of the evidence base include lack of head-to-head superiority and non-inferiority clinical trials. Clinically equivalent glucocorticoid (e.g., prednisone, prednisolone) doses for budesonide ER have not been determined in ulcerative colitis; therefore, dosage equivalents are uncertain when switching glucocorticoid therapy. Further studies are needed to confirm the safety and efficacy of budesonide ER compared with alternative therapies (e.g., double-dose mesalamine, prednisone) in inadequate responders to standard 5-ASA therapy. The available evidence and published reviews support the use of budesonide ER in inadequate responders to 5-ASA therapy for active, mild to moderate ulcerative colitis. Budesonide ER may serve as an alternative treatment option in patients with an indication for a trial of a glucocorticoid with potentially lower risks of adrenal suppression and hypercorticism-related adverse effects, taking into consideration comorbid conditions and patient specific factors, such as diabetes, osteoporosis / osteopenia, and immune status.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to August 2014) using the search terms <budesonide> and <Uceris>. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Table 5 Study Summaries: Budesonide ER in Ulcerative Colitis

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
Sandborn WJ, Travis S, Moro L, Jones R, Gautille T, Bagin R, Huang M, Yeung P, Ballard ED. Once-daily budesonide MMX extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: Results from CORE I study. Gastroenterology 2012; 143: 1218-1226				
8-wk randomized, double-blind, double-dummy, placebo-controlled trial Study locations: USA, Mexico, Canada, India	Inclusion: Age up to 75 years; active ulcerative colitis for at least 6 months; UCDAI score 4-10. Washout of prior oral 5-ASA tx: ≥ 2 d Exclusion: Oral or rectal steroids within 4 weeks; immunosuppressive within 8 weeks; anti-TNF or experimental study within 3 months; UCDAI >10; toxic megacolon; disease limited to rectum; infectious colitis; severe anemia; leukopenia; granulocytopenia; pregnant/lactating; hepatic or renal disease; severe disease or organs; type 1 diabetes mellitus; glaucoma; hepatitis B/C; HIV 509 patients with 489 included in intent-to-treat analysis Median age: 42 y 55.8% Male 50.1% White 34.4% Asian 57.3% Prior mesalamine 65.2% Prior use of any 5-ASA	Randomized 1:1:1:1 Budesonide ER 9mg daily: n=123 Budesonide ER 6mg daily: n=121 Mesalamine 400mg TID*: n=124 Placebo: n=121 *Active control, internal reference	Efficacy: Measure / Placebo / Budesonide ER 9mg / Budesonide ER 6mg / Mesalamine 2.4gm Primary Outcome Measure Clinical and endoscopic remission (95%CI): 7.4% (2.8,12.1) / 17.9% (11.1,24.7) / 13.2% (7.2,19.3) / 12.1% (6.4,17.8) Difference between active and placebo (95%CI): - / 10.4% (2.2,18.7) / 5.8% (-1.8,13.4) / 4.7% (-2.7,12.1) P-value: - / 0.0143 / NS / NS Odds ratio (95% CI): - / 2.71 (1.19,6.16) / 1.9 (0.8,4.48) / 1.71 (0.72,4.08) NNT: - / 10 / - / - Secondary Outcome Measures Clinical improvement: [difference (P-value)]: 24.8% / 33.3% [8.5% (NS)] / 30.6% [5.8% (NS)] / 33.9% [9.1% (NS)] Endoscopic improvement [difference]: 33.1% / 41.5% [8.4%] / 35.5% [2.5%] / 33.1% [0%] Histologic healing [difference (P-value)]: 6.6% / 4.1% [-2.5% (NS)] / 7.4% [0.8% (NS)] / 11.3% [4.7% (NS)] Symptom resolution [difference (P-value)]: 16.5% / 28.5% [11.9% (0.0258)] / 28.9% [12.4% (0.0214)] / 25% [8.5% (NS)]	Sponsor: Santarus Inc, and Cosmo Pharmaceuticals SpA GRADE: High Notes: Title of study portray results which may be misleading External Validity to VA: Possible

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes

Safety:

Measure	Placebo	Budesonide ER 9mg	Budesonide ER 6mg	Mesal 2.4g
Any AE	62.8%	57.5%	58.7%	63%
Tx related AE	26.4%	28.3%	27.8%	24.4%
AE leading to discontinuation	18.6%	11.8%	14.3%	11%
Glucocorticoid effect	10.1%	11.8%	5.6%	7.9%

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes

Travis SP, Danese S, Kupcinskas L, et al. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. Gastroenterology 2014; 63 (3):433-41.

8-wk
Phase III RCT, double-blinded, double-dummy, parallel-group trial

Study locations: Western/Eastern Europe, Russia, Israel, Australia

Inclusion:
Age 18-75 years; active mild-moderate ulcerative colitis for ≥ 6 months; UCDAI score ≥ 4 and ≤ 10. Washout of current 5-ASA tx: 2 d for oral; 4 wk for rectal.

Exclusion:
Current infection, UC limited to the rectum ≤15cm above the dentate line, oral or rectal steroids in last 4 weeks, immunosuppressives in the last 6 weeks, tumor necrosis factors in the last 3 months, UCDI > 10, history of toxic megacolon, Hgb < 10.5g/dL, leukopenia or granulocytopenia, pregnancy or lactation, use of CYP450 3A4 inducers or inhibitors, liver cirrhosis, hepatic or renal disease / insufficiency, type I diabetes, glaucoma, Hepatitis B and C, and HIV infection

54.8% Men
99.6% White
Mean disease duration: 6 yr
56.3% Prior mesalazine
23.1% Prior sulfasalazine

Randomized 509 patients: 1:1:1:1

Budesonide ER 9mg N:126

Budesonide ER 6mg N: 128

Budesonide EC 9mg (3mgx3cap) N:126

Placebo N:129

Efficacy:

Measure	Placebo	Budesonide ER 9mg	Budesonide ER 6mg	Budesonide EC 9mg
Primary Outcome Measure:				
Clinical and endoscopic remission (95%CI)	4.5%	17.4%	8.3%	12.6%
Difference (95%CI)	Ref	12.9%	3.8%	8.1%
P-value		0.0047	NS	0.0481
Odds ratio (95% CI)	Ref	4.5 (1.5,13.7)	-	-
NNT	-	8	-	13
Secondary Outcome Measures:				
Clinical improvement: [diff (P-value)]	33.7%	42.2% [8.5% (NS)]	25.7% [-8(NS)]	33% [-0.7(NS)]
Endoscopic improvement [diff (P-value)]	31.5%	42.2% [10.7%(NS)]	25.7% [-5.8%(NS)]	36.9 [5.4(NS)]
Histologic healing [diff (P-value)]	6.7%	16.5% [9.8%(0.0361)]	9.2% [2.5%(NS)]	13.6 [-6.9(NS)]
Symptom resolution [diff (P-value)]	11.2%	23.9% [12.7(0.0220)]	13.8% [2.6(NS)]	18.4% [7.2(NS)]

Safety:

Adverse Event	Placebo	Budesonide ER 9mg	Budesonide ER 6mg	Budesonide EC 9mg
Any ADE	44.2%	55.5%	62.5%	54.8%
Treatment Related ADE	24%	21.1%	21.9%	23%

Sponsor: Santarus Inc., and Cosmo Pharmaceuticals SpA

GRADE: High

Notes:

External Validity to VA: Possible

D'Haens GR, Kovács A, Vergauwe P, et al. Clinical trial: Preliminary efficacy and safety study of a new Budesonide-MMX® 9 mg extended-release tablets in patients with active left-sided

Methods	Participants	Interventions	Outcomes	Funding, Quality, Notes
ulcerative colitis. J Crohns Colitis. 2010;4(2):153-60.				
4-8 wk pilot phase II RCT; Phase I double blinded; Phase II open-labelled Primary efficacy measure: **Clinical improvement,** defined as either (symptomatic) remission (CAI ≤4) or a CAI reduction by at least 50% of the baseline value after 4 weeks of treatment Secondary efficacy measures: Clinical improvement defined as clinical remission or CAI reduction by at least 70% of after 8 weeks. Clinical efficacy through endoscopic and histological evaluations.	Inclusion: Men and women with diagnosis of active moderate left-sided ulcerative colitis (CAI <14) on stable treatment with oral 5-ASA at a dose ranging between 0-3g/day for at least 2 months before the study. Exclusion: Distal proctitis (<15cm above the anal verge from the pectineal line), severe left-sided UC (CAI >14), extensive colitis proximal to the splenic flexure, and infections as a cause of relapse, patients using oral or topical steroids in the last 4 weeks, patients using immunosuppressive medications, prior treatment with anti-TNF agents, use of NAIDs or drugs affecting the colonic motility including antidiarrheal, using drugs that alter the pH of intestinal content, pregnancy, and severe	<u>Phase I, Double-blind (4-wks)</u> Randomized N:36 (18 budesonide, 18 placebo) After week 2, those without improvement or worsening disease could switch to open-label treatment (n = 5) <u>Phase II, Open-label (4-wks)</u> All patients received active treatment • Continued from double blinded tx: 24 • Open label: 5	Efficacy: Measure | Budesonide ER 9 mg | Placebo **4-wks** Clinical Improvement, % | 46.1% | 33.3% Difference, pp | 13.7 (NS) | Ref CAI | 4.47 (± 3.04) N= 17 | 5.33 (± 3.62) N=15 Endoscopic Index | 6.44 (± 3.27) N=16 | 6.33 (± 2.64) N=15 Histology | 1.69 (± 1.25) N=16 | 1.8 (± 0.77) N=15 ≤ 50% (70%) or CAI ≤ 4 | 8 (47.06%) | 5 (33.33%) Improved clinical status | 8 (47.06%) | 5 (33.33%) **8-wks** CAI | 4.92 (± 3.62) N=13 | Endoscopic Index | 4.9 (± 4.48) N=10 | Histology | 1.2 (± 0.79) N=10 | ≤ 50% (70%) or CAI ≤ 4 | 7 (53.85%) | 5 (33.33%) Improved clinical status | 3 (23.08%) | 5 (33.33%) **Last 4 wks** CAI | 4.69 (± 3.66) N=13 | Endoscopic Index | 5.22 (± 4.38) N=9 | Histology | 1.33 (± 1) N=9 | ≤ 50% (70%) or CAI ≤ 4 | 8 (61.54%) | 5 (33.33%) Improved clinical status | 1 (7.69%) | 5 (33.33%) Unchanged or worsened clinical status | 4 (30.77%) | 5 (33.33%) Safety: Most frequent AEs (Budesonide ER 9 mg): headache (11.9%), abdominal pain (8.5%), common cold (6.8%), diarrhea / flatulence / influenza (5.1%)	Sponsor: Crinos S.p.A; Cosmo Technologies Ltd GRADE: Low Notes: Study not adequately designed External Validity to VA: Possible