Budesonide (UCERIS) Rectal Foam

National Drug Monograph
March 2016
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information	
Description/Mechanism of Action	Budesonide is a potent, non-halogenated, synthetic glucocorticoid with weak mineralocorticoid activity. Prevents or controls inflammation.
Indication(s) Under Review in This Document	Induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.
Dosage Form(s) Under Review	Rectal foam, 2 mg per actuation / metered dose, aerosolized.
REMS	☐ **REMS** ☒ **No REMS** ☐ **Postmarketing Requirements** See Other Considerations for additional REMS information
Pregnancy Rating	Category C

Executive Summary	
Efficacy	• budesonide foam had a small, statistically significant benefit over placebo in inducing remission and resolving rectal bleeding, and produced improvement in rectal bleeding as early as Week 1 • Budesonide foam and hydrocortisone acetate foam were similar in remission efficacy and in safety in patients with ulcerative proctitis or proctosigmoiditis. • twice daily dosing of budesonide foam was shown to be superior to once daily dosing in terms of mucosal healing.
Safety	• Budesonide foam was not shown to have a lower risk of glucocorticoid-related adverse events than hydrocortisone foam enema. • Mean morning cortisol concentrations remained within normal limits throughout therapy with budesonide foam, although cortisol concentrations decreased during twice daily dosing in weeks 1 and 2 then returned to baseline by week 4. • There was a low incidence of clinically relevant effects on adrenal suppression. • The effect of CYP3A4 inhibitors and inducers on the pharmacokinetics of budesonide administered as rectal foam has not been studied.
Other Considerations	• The small volume (25 ml) of each dose of budesonide foam was intended to minimize retention effort, improve distribution to the rectum and sigmoid colon and improve patient comfort relative to conventional liquid enemas and suppositories. • One trial, which compared budesonide (BUDENOFALK) foam with budesonide suspension (ENTOCORT) enema, supports the proposal that budesonide (UCERIS) foam reduces retention problems and is preferred by more patients than the suspension enema. • The prescribing information for budesonide foam does not make any recommendations about tapering the dose upon discontinuation of therapy.
Projected Place in Therapy	• Considering relative drug acquisition costs and similar efficacy and safety, budesonide foam may be reserved for patients with ulcerative proctitis or proctosigmoiditis / distal UC who have an inadequate response or intolerance to hydrocortisone rectal foam. • Since budesonide foam comes in metered-dose aerosolized canisters, it may be considered in patients who, despite repeated patient education, continue to have problems manually measuring or dispensing doses of hydrocortisone foam.

- Rectal glucocorticoid therapy is recommended as second-line treatment after rectal 5-ASA therapies and may be used concomitantly with systemic therapies for additional benefit.

Background

Purpose for Review

Budesonide (UCERIS) extended release tablets were reviewed in March and July 2015 (nonformulary with criteria for use). The rectal foam is a new formulation that has an indication different from the extended-release tablets.

Issues to be determined:

- ✔ Evidence of need
- ✔ Does budesonide rectal foam offer efficacy or safety advantages over currently available formulary and nonformulary alternatives?
- ✔ Are there patient subgroups that have greater efficacy or safety effects?
- ✔ Does budesonide rectal foam have specific characteristics best managed by the nonformulary process, prior authorization, or criteria for use?

Other Therapeutic Options

Formulary Alternatives (Rectal Products)	Other Considerations	Clinical Guidance
Hydrocortisone Enema[1]	100 mg / 60 ml solution in single-dose bottles with lubricated applicator tips. Dosed once nightly usually for 3 weeks, or until remission. Time in left lateral position: ≥30 min. Retention Time: ≥1 h, preferably all night.	Approved for adjunctive treatment of UC
Hydrocortisone Aerosol / Foam[2]	Indication is limited to proctitis (unlike budesonide foam). ~80 mg hydrocortisone (as 90 mg hydrocortisone acetate) per ~900 mg of foam. Body positioning and retention time not stated.	Approved for adjunctive therapy in the topical treatment of UC of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.
Hydrocortisone Suppository	Suppositories generally reach only the distal 5 to 8 cm of the rectum.[3]	Approved for adjunctive treatment of chronic UC, cryptitis.
Hydrocortisone / Pramoxine Aerosol / Foam[4]	1% / 1% concentration. Contains topical anesthetic. Reusable anal applicator. Body positioning and retention time not stated.	Not approved for rectal use or for UC, but seems to be used for UC. Approved for inflammatory and pruritic anal dermatoses.
Mesalamine Enema	Suspension Retention time: overnight, ~8 h	First-line therapy. Approved for treatment of active mild to moderate distal UC, procto-sigmoiditis, or proctitis.
Mesalamine Suppository	Suppositories generally reach only the distal 5 to 8 cm of the rectum.[3]	First-line therapy. Approved for treatment of active ulcerative proctitis.

Nonformulary Alternatives	Other Considerations	Clinical Guidance
None		

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms budesonide, aerosol, foam, rectum and rectal. The search was limited to studies performed in humans and published in the 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. Study results were also obtained from the FDA Medical Review(s).

Review of Efficacy

- The FDA approval of budesonide rectal foam was based on two identically-designed, multicenter, placebo-controlled, Phase 3 randomized clinical trials (RCTs) in the US and Russia that involved adults with active, mild to moderate ulcerative proctitis (limited to the rectum up to approximately 15 cm) or ulcerative proctosigmoiditis (limited to the rectum and sigmoid colon up to approximately 40 cm from the anal verge).[5]
- The FDA determined that data for Dr. Falk Pharma's budesonide (BUDENOFALK) foam, available in Europe since 2006 and which was modified in minor ways to develop Salix's UCERIS foam, could be used to support efficacy and be included in pooled safety analyses for UCERIS foam, without studies to establish bioequivalence.[6]

Budesonide Foam Versus Placebo: Major Efficacy-Safety Trials

- In the two major efficacy-safety trials, Salix's budesonide foam (2 mg / 25 ml) or placebo was given twice daily for 2 weeks, then once daily for 4 weeks. Patients were allowed to use stable doses of oral 5-ASAs up to 4.8 g per day. The combined population consisted mainly of middle-aged (mean age across pooled treatment groups, 42–44 years), white (90.1%) females (56.4%) with established proctosigmoiditis (67%) of moderate activity (89.9%) who were treated concomitantly with 5-ASAs (55.1%).
- The primary efficacy outcome was achievement of remission at Week 6. Remission was defined as an endoscopy score ≤1 (inactive or mild disease), rectal bleeding score of 0, and improvement or no change from baseline in the stool frequency subscore of the Modified Mayo Disease Activity Index (MMDAI). The results of the intent-to-treat (ITT) population analyses were consistent between the two trials and showed that budesonide foam had a small, statistically significant benefit over placebo in inducing remission and resolving rectal bleeding, and produced improvement in rectal bleeding as early as Week 1 (Table 1).

Table 1 Pooled Results in Two 6-Week Placebo-controlled Phase 3 Trials

Measure	BUDF N = 267	Placebo N = 279	Diff	NNT
Achieved Remission, %	41.2	24.0	17.2*	6
MMDAI Rectal Bleeding Subscore of 0 at EOT, %	48.3	28.3	20.0*	5
MMDAI Rectal Bleeding Subscore of 0 at Wk 1, %	16.5	6.8	9.7*	11
Endoscopy Subscore of 0 or 1 at EOT, %	55.8	39.8	16.0*	7

* P ≤ 0.0005. EOT, End of Treatment / Week 6; BUDF, Budesonide foam; MMDAI, Modified Mayo Disease Activity Index.

- Both RCTs showed no significant treatment differences in terms of the percentage of patients with improved or no change in the MMDAI stool frequency subscore. (However, stool frequency may not be a robust outcome measure for rectal therapy in ulcerative proctitis.[7])
- Budesonide rectal foam was significantly better than placebo in terms of remission, rectal bleeding subscore of 0, and endoscopy subscore of 0 or 1 in almost all subgroups (i.e., age, sex, white race, mild or moderate disease activity, established disease, smoking history, extent of disease, baseline use of mesalamine, and country).[5] No statistically significant difference was seen for the endoscopy subscore of 0 or 1 in the proctitis subgroup. No statistically significant differences were also seen in the smaller subgroups of nonwhite patients, those with mild disease activity, and those with newly diagnosed disease.
- Overall, adherence to study treatment was 94.0% and 97.1% with budesonide foam and placebo, respectively.
- Supportive studies showed that therapy with budesonide rectal foam used once daily for 4 weeks[8] or 8 weeks[9] resulted in histologic improvement.

Budesonide Foam Versus Hydrocortisone Acetate Foam

- A multicenter, open-label, active-controlled RCT conducted in Israel, Germany and Italy showed that budesonide (BUDENOFALK) foam 2 mg / 20 ml and hydrocortisone acetate foam (COLIFOAM, Block Drug Company Inc., Ratingen, Germany) 100 mg / 15 ml (both administered once daily per rectum at bedtime for 8 weeks) were similar in remission efficacy (55% and 51%, respectively) and in safety in 251 patients with ulcerative proctitis or proctosigmoiditis.[9]
- Of 82 patients who had failed prior rectal mesalamine, 23 (52%) of 44 patients responded to budesonide foam and 14 (37%) of 38 responded to hydrocortisone foam (NSD).
- Of 203 patients who had prior experience using glucocorticoid enemas, 62% preferred the foam and 8 percent preferred the enema. The remaining 30% had no preference between the two rectal formulations.
- The relevance of these results to comparing the US products UCERIS and CORTIFOAM is somewhat limited by the difference in volume administered between UCERIS (25 ml) and the study product BUDENOFALK (20 ml) as well as the differences in dose and indication (i.e., whether the product can be used for sigmoid disease) between the US brand CORTIFOAM (90 mg of hydrocortisone acetate per dose, for ulcerative proctitis of the distal portion of the rectum) and the German product used in the study, COLIFOAM (100 mg of hydrocortisone acetate per dose, used for ulcerative proctitis or proctosigmoiditis in the study).

Budesonide Foam Versus Budesonide Suspension

- A noninferiority study (N = 541) compared BUDENOFALK foam (2 mg / 25 ml) with budesonide liquid / suspension (ENTOCORT) enema (2 mg / 100 ml) in patients with active ulcerative proctitis or ulcerative proctosigmoiditis.[8] Analyses of 449 patients comprising the per-protocol population showed that 60% of the foam group and 66% of the suspension group achieved clinical remission (the difference met the predefined noninferiority margin of 15%).
- Retention problems were experienced by 11% of patients in the foam group and 39% in the suspension group.
- More patients (84%) preferred the foam, whereas 6% preferred the suspension and 10% had no preference.

Budesonide Foam Versus Betamethasone Solution: Quality of Life

- In patients with active distal UC, budesonide foam (2 mg / 50 ml) was shown to be comparable to betamethasone solution enema (5 mg / 100 ml) in terms of quality of life.[10] There was a nonsignificant trend towards less clinical improvement in the budesonide group. This pilot, open-label, multicenter RCT (N = 38) did not meet patient enrollment goals for sufficient statistical power and could not confirm previous results suggesting better quality of life with foam than with standard glucocorticoid enema. Both treatments were well tolerated.

Budesonide Foam Versus Mesalamine Suspension

- No studies were found.
- A meta-analysis compared budesonide liquid enema with 5-ASA rectal enemas, but did not include budesonide foam.[11]

Budesonide Foam Once Daily Versus Twice Daily, Placebo-controlled Trial

- Budesonide foam and is being developed in Japan by Ajinomoto Pharmaceuticals, who licensed the product from Dr. Falk Pharmaceuticals.
- In a 6-week multicenter, double-blind, placebo-controlled Phase II RCT involving patients with active mild to moderate distal UC in Japan, twice daily dosing of budesonide foam was shown to be superior to once daily dosing in terms of mucosal healing (46.4% vs. 23.6%; OR 3.024, p =0.0097), and both dosing regimens were superior to placebo (5.6%; $p \leq 0.0156$) (N = 56, 55 and 54, respectively).[12]
- Clinical remission was achieved by 48.2% and 50.9% in the twice-daily and once-daily groups, respectively (NSD), compared with 20.4% in the placebo group ($p \leq 0.0029$).
- In post hoc subgroup analyses, twice-daily dosing was significantly better than once-daily dosing in achieving complete mucosal healing in patients with no previous use of 5-ASA enema or suppository (58.1% vs. 34.4%; p = 0.0431). The difference in complete mucosal healing rates between twice-daily and once-daily dosing did not reach the level of statistical significance (32.0% vs. 8.7%; p = 0.0774) in the subgroup with previous 5-ASA experience.

Potential Off-Label Use

- Treatment of pouchitis: A small (N = 26), double-blind, double-dummy RCT showed that budesonide enema (2 mg / 100 ml at bedtime) was similar to oral metronidazole (0.5 g twice daily) in terms of improvement in the pouchitis disease activity index and was associated with a lower rate of adverse effects (25% vs. 57%).[13]

Safety

For more detailed information, refer to the prescribing information.

Boxed Warning	• None
Contraindications	• Known hypersensitivity to budesonide or any of the ingredients
Warnings / Precautions	• Hypercorticism and adrenal suppression • Impaired adrenal function in patients transferred from other glucocorticoids (taper slowly off glucocorticoids with high systemic effects) • Increased risk of infection • Other glucocorticoid effects (monitor patients with co-morbidities) • Flammable contents

Adverse Reactions

The overall incidence of adverse reactions was 22% vs. 4% in the budesonide rectal foam and placebo groups, respectively.[14] Percentages shown below are for budesonide rectal foam versus placebo.

Common Adverse Reactions	• Decreased blood cortisol (< 5 mcg/dl): 17% vs. 2%. Decreases in blood cortisol concentrations were seen in the budesonide rectal foam group at Weeks 1 and 2 during twice-daily treatment, then cortisol concentrations returned to baseline values during the 4 weeks of once-daily treatment.[14,27] • Adrenal insufficiency: 4% vs. 1% (no cases were clinically symptomatic).[27] • Nausea: 2% vs. 1%
Deaths / Serious Adverse Events	• No deaths occurred during clinical trials (pooled data for UCERIS and BUDENOFALK foam). • Serious adverse events: 1.9% vs. 1.1%.[27] • Acute generalized exanthematous pustulosis occurring in a patient who received budesonide rectal foam was the only serious adverse event considered to be treatment related. • Anaphylaxis has occurred. • See Warnings / Precautions.
Discontinuations Due to Adverse Reactions	• 9.7% vs. 4.3%.[27]

Safety Considerations

Glucocorticoid-related Adverse Events	• After topical administration, budesonide has a local-to-systemic exposure ratio of >40,000 to 1.[15] The greater topical than systemic activity is attributed to extensive hepatic first-pass metabolism.[6]
	• Glucocorticoid adverse events were infrequently reported; insomnia, sleep disorder and acne were reported by one patient (0.4%) each.[5]
	• The FDA's safety analyses of clinical trials involving UCERIS or BUDENOFALK foam showed the following:
	  ○ Budesonide foam was not shown to have a lower risk of glucocorticoid-related adverse events than **hydrocortisone** foam enema in one trial.[9]
	  ○ Adrenal suppression (serum cortisol < 5 mcg/ml) occurred in 3% of the budesonide group and none of the hydrocortisone group.
	  ○ Mean cortisol ratios (8 week value to baseline value) were 1.01

	(95% CI, 0.92–1.10) for the budesonide group and 1.05 (0.96–1.15) for the hydrocortisone group (NSD). ○ Acne occurred in 2 budesonide patients and 1 hydrocortisone patient. ○ Neither treatment affected bone metabolism (i.e., serum bone-specific alkaline phosphatase and serum osteocalcin). • An integrated analysis[15] of safety data from five Phase 3 studies including an open-label repeat-treatment extension study not included in the FDA review (N = 719) showed that ○ Mean morning cortisol concentrations remained within normal limits throughout therapy with budesonide (pooled UCERIS and BUDENOFALK) foam, although cortisol concentrations decreased during twice daily dosing in weeks 1 and 2 then returned to baseline by week 4. ○ Decreased blood cortisol concentrations were seen in 9.2% versus 2.2% of the budesonide foam and **placebo** groups, respectively. ○ ACTH challenge responses remained normal in 86.1% and 96.2% of patients in the budesonide foam and placebo groups, respectively. ○ There was a low incidence of clinically relevant effects on adrenal suppression, occurring in 1 to 4 budesonide patients for each type of glucocorticoid-related adverse event (budesonide foam vs. placebo): acne (0.6% vs. 0%); agitation (0.1% vs. 0%); depression (0.6% vs. 0.4%); insomnia (0.4% vs. 0.4%); sleep disorder (0.1% vs. 0%) and weight increase (0.3% vs. 0.4%). • In a small open-label multicenter randomized trial (N = 38), suppression of plasma cortisol concentration was seen in 22% of 22 patients treated with budesonide foam (2 mg / 50 ml) compared with 87% of 16 patients treated with **betamethasone** liquid enema (5 mg / 100 ml).[10] Of the 7 patients in each treatment group who experienced at least one adverse event, an association with glucocorticoid therapy was seen in 17.4% of budesonide patients and 43.8% of betamethasone patients. These adverse events included leukocytosis, dizziness, visual disturbances, morning facial edema and increased appetite. • In the 6-week, Phase 2 dose-comparative Japanese trial, the incidence of decreased plasma cortisol was 46.4% and 21.8% in the twice-daily and once-daily budesonide foam groups, respectively. Similarly, decreased plasma corticotrophin occurred in 28.6% and 14.5% of the respective treatment groups.
Postmarketing Experience **(Oral and Rectal Formulations)**	• Hypertension, pancreatitis, pyrexia, peripheral edema, anaphylactic reactions, dizziness, benign intracranial hypertension, mood swings, pruritus, maculopapular rash, allergic dermatitis • Budenofalk rectal foam has been marketed in 30 countries including the UK since 2006. The periodic safety update report for BUDENOFALK describes adverse events for 12 patients, of whom 5 had serious adverse events including pyrexia, dystonia, bloody diarrhea, drug ineffective and pancreatitis.[6]
Other Contraindications	• Local contraindications for the use of intrarectal glucocorticoids include obstruction, abscess, perforation, peritonitis, fresh intestinal anastomoses, extensive fistulas and sinus tracts.

Drug Interactions

Drug-Drug Interactions	• CYP3A4 Inhibitors (e.g., ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, cyclosporine): Avoid concomitant use (may

	increase glucocorticoid effects). The effect of CYP3A4 inhibitors and inducers on the pharmacokinetics of budesonide administered as rectal foam has not been studied.[6]
Drug-Food Interactions	• Grapefruit juice (CYP3A4 inhibitor): Avoid during therapy.

Risk Evaluation	
As of 20 January 2016.	
Sentinel Event Advisories	• None • Sources: ISMP, FDA, TJC
Look-alike / Sound-alike Error Potential	• LA/SA for generic name *budesonide*: Bumetanide; Desonide; Budesonide IR; Budesonide EC capsules; Budesonide ER (multi-matrix system, MMX) tablets • LA/SA for trade name *UCERIS*: Lucentis; Luveris • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations	

Extent of Colonic Spread	• Suppositories: Reach only the distal 5 to 15 cm of the rectum.[3,16]
	• Liquid Enemas: Reach the proximal sigmoid colon and splenic flexure in almost all patients who can retain them.[3] Larger volumes seem to allow more proximal spread, with a volume of 100 ml usually adequate to cover the distal colon and rectum.[17,18]
	• Foam Enemas: Deliver medication to the rectum and distal descending colon,[19,20,21,22] but generally reach only the mid-sigmoid colon.[3]
	  ○ In 12 patients with active disease, budesonide rectal foam was shown to spread to a maximum of 40 cm (range, 11–40 cm) after a mean of 4 hours (range, 2–6 hours), reaching the sigmoid colon in all patients studied.[23]
	  ○ Using gamma-scintigraphy, a crossover RCT in 6 patients with mild distal UC showed that budesonide foam (2 mg) had greater proximal spread in 2 patients and reached the splenic flexure faster compared with budesonide liquid enema (2 mg/115 ml), although both formulations had adequate spread in all cases.[24] The foam had a significantly more homogeneous spread than the liquid enema in the area between rectum and splenic flexure, and the area of distribution was numerically greater with foam (7109 vs. 5849 pixels; p = 0.059).

Advantage of Small Volume	• Budesonide rectal foam expands once it is administered. • The small volume (25 ml) of each dose of budesonide foam was intended to minimize retention effort, improve distribution to the rectum and sigmoid colon and improve patient comfort relative to conventional liquid enemas and suppositories.[6] • The use of rectal suppositories is limited by lack of distribution to the sigmoid colon and problems with retention and leakage. Patients may have problems retaining enemas because of the volume and pain during flares of proctitis or proctosigmoiditis. • One trial, which compared budesonide (BUDENOFALK) foam with budesonide suspension (ENTOCORT) enema, supports the proposal that budesonide (UCERIS) foam reduces retention problems and is preferred by more patients than the suspension enema.[8]
Differences in Dispensers	• Budesonide foam: No measuring is necessary. Dose is delivered via single-

	use applicator nozzles attached to an aerosolized canister. Pushing down on the canister dome delivers one dose. The canister must be held in an upside down position to work properly. • Hydrocortisone foam: Requires filling a reusable rectal applicator by placing the applicator on the nose of an aerosolized canister and pressing down on the cap flanges. The canister must be kept in an upright position to work properly.
Pharmacokinetics / Low Systemic Exposure	• Budesonide plasma concentrations were below detectable limits in 39% and 27% of patients in the two major RCTs.[5] Of those with detectable drug, the mean budesonide plasma concentrations were about 0.37 ng/ml at Week 1 on twice daily treatment and 0.18 ng/ml at Week 6 on once-daily treatment.[5] The mean maximal plasma concentration across the two major RCTs was 0.57 ng/ml.[5] • In pharmacokinetic studies, systemic absorption of rectally administered budesonide foam (a single 2-mg dose and multiple doses of 2 mg twice daily) also remained low and showed no evidence of significant accumulation of serum budesonide.[6] Peak budesonide concentrations were 0.84 ng/ml and 0.90 ng/ml after 1 and 9 consecutive doses, respectively. Corresponding estimates of $AUC_{0–12}$ were 4.59 ng.h/ml and 4.30 ng.h/ml, respectively.
No Recommendations for Tapering Upon Discontinuation	• The prescribing information for budesonide foam does not make any recommendations about tapering the dose upon discontinuation of therapy. • This is in contrast to hydrocortisone liquid enema and foam, which recommend gradual tapering of the dose.[1,2]

Dosing and Administration

- Administer one metered dose rectally twice daily for 2 weeks followed by 1 metered dose rectally once daily for 4 weeks.
- See prescribing information and medication guide for administration instructions.
- Body positioning for rectal administration: standing, lying or sitting (e.g., on the toilet).
- Retention time: All night, if possible.
- How Supplied: The budesonide rectal foam kit contains 2 aerosol canisters with 28 PVC applicators coated with paraffin lubricant, and applicator disposal bags. Each canister contains 14 metered doses.

Special Populations (Adults)	
Elderly	• Insufficient data to determine whether the elderly respond differently from younger patients. • Use caution; generally start at low end of dosing range.
Pregnancy	• Category C. No adequate and well controlled studies in pregnant women. Teratogenic and embryocidal in rats and rabbits. Weigh risks and benefits. • Hypoadrenalism may occur in fetuses and neonates (carefully observe for signs and symptoms).
Lactation	• Budesonide from rectal foam administration is likely to be present in human milk. Weigh risk and benefits; exercise caution.
Renal Impairment	• No data identified.
Hepatic Impairment	• Mild (Child-Pugh Class A): No dosage adjustment is needed. • Moderate to Severe (Child-Pugh Class B or C): Monitor for increased signs and/or symptoms of hypercorticism. Consider discontinuing budesonide rectal foam therapy if signs of hypercorticism develop.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- Ulcerative colitis is a recurrent, incurable, likely immune-mediated disorder characterized by continuous superficial mucosal inflammation that almost always starts in the rectum and extends to varying degrees to the proximal colon. Over the past 50 years, UC has become more common in the West particularly in developed countries, with an incidence of up to 8–14 / 100,000 persons and a prevalence of 120–200 / 100,000 persons.[25,26] Based on 2009 data, about 46% of UC patients are affected by ulcerative proctitis and 17% by ulcerative proctosigmoiditis or distal UC.[27] Patients with ulcerative colitis present with mild symptoms in the majority of cases.[28] About 27% of patients present with moderate disease, and 1% with severe disease. Within 10 years of diagnosis, 67% of patients relapse at least once.[28] About 50% of patients with proctitis will have extension, and 20% of patients with colonic disease extend within 5 years.[28] Overall, 20% to 30% of patients will require colectomy, although the need for colectomy within 10 years is lower (5%) among patients who present with proctitis alone.[28] Analysis of a large US health insurance database (2005–2007) showed that, of 636 patients with new-onset ulcerative proctitis, 10% were treated with rectal hydrocortisone.[29] The majority of patients received prescriptions for mesalamine products: suppositories (42%), oral formulations (19%), combination (14%) and enema (11%).
- One important consideration when deciding treatment approaches for UC is that separate therapy is required for the rectum; patients receiving systemic therapies may need additional agents for relieving rectal symptoms such as tenesmus, urgency or fecal incontinence.[16] Another consideration is that mild to moderate disease activity by standard definitions can have severe effects on quality of life (e.g., incontinence). Patient preferences should be taken into account when deciding whether to start rectal therapy. Rectal suppositories and enemas have several limitations in the treatment of active, mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis. They may be difficult to administer, require retention in recumbent positions for a specified period of time and do not spread proximally. Liquid enemas may be difficult to retain because of their volume and low viscosity.
- Practice guidelines recommend using topical glucocorticoids to induce remission of mild or moderate, active ulcerative proctitis or proctosigmoiditis in patients who cannot tolerate, who decline, or who have contraindications to first-line 5-aminosalicylic acid (5-ASA) therapy.[3,30]
    - UpToDate suggests using glucocorticoid foam preparations or enemas twice daily plus glucocorticoid suppositories twice daily for colitis involving greater than 8 cm of the rectum or the sigmoid colon in patients who cannot tolerate rectal 5-ASA products (enemas plus suppositories twice daily).[3] A response is usually seen in 3 to 4 weeks, after which the topical glucocorticoid regimen can be tapered gradually to once-nightly dosing. Topical glucocorticoids should also be used in combination with topical 5-ASA products in patients who do not respond to topical 5-ASA monotherapy in 4 to 6 weeks. Topical glucocorticoids should not be used for maintenance of remission.
    - NICE Guidelines (2013) suggest considering oral prednisolone as an alternative to topical glucocorticoids.[31]
    - The 2010 American College of Gastroenterology guideline on management of mild to moderate distal colitis states the following:[30]
        - Patients with mild to moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine or topical glucocorticoids (Grade A recommendation).
        - Topical mesalamine agents are superior to topical glucocorticoids or oral aminosalicylates (Grade A).
        - The combination of oral and topical aminosalicylates is more effective than either alone (Grade A).
        - In patients refractory to oral aminosalicylates or topical glucocorticoids, mesalamine enemas or suppositories may still be effective (Grade A).
        - The unusual patient who is refractory to all of the above agents in maximal dose, or who is systemically ill, may require treatment with oral prednisone in doses up to 40–60 mg per day, or infliximab with an induction regimen of 5 mg/kg at weeks 0, 2 and 6, although the latter two agents have not been studied specifically in patients with distal disease (Grade C).
- The quality of evidence is high for the efficacy and safety of budesonide foam, except evidence is of moderate quality for relative risk of glucocorticoid-related adverse events. Budesonide foam is likely to be effective in US Veterans, although there is some uncertainty as to whether the treatment effect sizes seen in the clinical trials will be seen in actual clinical practice.
- In comparison with hydrocortisone foam, budesonide foam seems to be just as safe and efficacious in the treatment of ulcerative proctitis and proctosigmoiditis / distal UC, with apparently no safety advantage in terms of glucocorticoid-related adverse effects. The foam formulation seems to be preferred over liquid enemas by

patients. Considering relative drug acquisition costs and similar efficacy and safety, budesonide foam may be reserved for patients with ulcerative proctitis or proctosigmoiditis / distal UC who have an inadequate response or intolerance to hydrocortisone rectal foam. Those who have intolerance to hydrocortisone liquid enemas may be given a trial of hydrocortisone foam. Since budesonide foam comes in metered-dose aerosolized canisters, it may be considered in patients who, despite repeated patient education, continue to have problems manually measuring or dispensing doses of hydrocortisone foam. Rectal glucocorticoid therapy is recommended as second-line treatment after rectal 5-ASA therapies and may be used concomitantly with systemic therapies for additional benefit.

References

[1] CORTENEMA – hydrocortisone enema (drug label information). ANI Pharmaceuticals, Inc. Baudette, MN, November 2011. Available at: http://www.anipharmaceuticals.com/products_view.php?i=3 .

[2] CORTIFOAM (hydrocortisone acetate rectal aerosol) 10% Rectal Foam (prescribing information). Meda Pharmaceuticals Inc., Somerset, NJ, May 2015. Available at: http://medapharma.us/products/pi/Cortifoam_PI.pdf

[3] MacDermott RP. Management of mild to moderate ulcerative colitis. In: UpToDate, Rutgeerts P, Grover S (Eds), UpToDate, Waltham, MA. (Accessed on 20 January 2016.)

[4] Proctofoam HC Aerosol Foam (hydrocortisone acetate 1% and pramoxine hydrochloride 1%) (prescribing information). Med Pharmaceuticals Inc., Somerset, NJ, September 2013. Available at: http://medapharma.us/products/pi/ProctofoamHC_PI.pdf .

[5] Sandborn WJ, Bosworth B, Zakko S, Gordon GL, Clemmons DR, Golden PL, Rolleri RL, Yu J, Barrett AC, Bortey E, Paterson C, Forbes WP. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. Gastroenterology. 2015 Apr;148(4):740-750

[6] Food and Drug Administration Medical Review of UCERIS (Budesonide Rectal Foam). 11 July 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205613Orig1s000MedR.pdf .

[7] Ghosh S, Daperno M. Topical therapy in ulcerative colitis: always a bridesmaid but never a bride? Gastroenterology. 2015 Apr;148(4):701-4

[8] Gross V, Bar-Meir S, Lavy A, et al. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther.* 2006;23(2):303-312

[9] Bar-Meir S, Fidder HH, Faszczyk M, et al. Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis. *Dis Colon Rectum.* 2003;46(7):929-936

[10] Hammond A, Andus T, Gierend M, Ecker KW, Scholmerich J, Herfarth H; German Budesonide Foam Study Group. Controlled, open, randomized multicenter trial comparing the effects of treatment on quality of life, safety and efficacy of budesonide foam and betamethasone enemas in patients with active distal ulcerative colitis. Hepatogastroenterology. 2004 Sep-Oct;51(59):1345-9

[11] Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut. 1997 Jun;40(6):775-81

[12] Naganuma M, Aoyama N, Suzuki Y, et al. Twice-daily Budesonide 2-mg Foam Induces Complete Mucosal Healing in Patients with Distal Ulcerative Colitis. J Crohns Colitis. 2015 Nov 16; pii: jjv208. [Epub ahead of print] PubMed PMID: 26577683

[13] Sambuelli A, Boerr L, Negreira S, Gil A, Camartino G, Huernos S, Kogan Z, Cabanne A, Graziano A, Peredo H, Doldán I, Gonzalez O, Sugai E, Lumi M, Bai JC. Budesonide enema in pouchitis--a double-blind, double-dummy, controlled trial. Aliment Pharmacol Ther. 2002 Jan;16(1):27-34

[14] UCERIS (budesonide) rectal foam (prescribing information). Salix Pharmaceuticals, Raleigh, NC, October 2014.

[15] Rubin DT, Sandborn WJ, Bosworth B, Zakko S, Gordon GL, Sale ME, Rolleri RL, Golden PL, Barrett AC, Bortey E, Forbes WP. Budesonide Foam Has a Favorable Safety Profile for Inducing Remission in Mild-to-Moderate Ulcerative Proctitis or Proctosigmoiditis. Dig Dis Sci. 2015 Nov;60(11):3408-17

[16] Lichtenstein GR, Hanauer SB, Sandborn WJ. Emerging Treatment Options in Mild to Moderate Ulcerative Colitis. Gastroenterol Hepatol (N Y). 2015 Mar;11(3 Suppl 1):1-16

[17] Swarbrick ET, Loose H, Lennard-Jones JE. Enema volume as an important factor in successful topical corticosteroid treatment of colitis. Proc Royal Soc Med 1974; 67: 753-4.

[18] Van Bodegraven AA, Boer RO, Lourens J, Tuynman HARE, Sindram JW. Distribution of mesalazine enemas in active and quiescent ulcerative colitis. Aliment Pharmacol Ther 1996; 10: 327-32

[19] Farthing MJG, Rutland MD, Clark ML. Retrograde spread of hydrocortisone containing foam given intrarectally in ulcerative colitis. BMJ 1979; 2: 822-4

[20] Wood E, Wilson CG, Hardy JG. The spreading of foam and solution enemas. Int J Pharmaceut 1985; 25: 191-7

[21] Campieri M, Corbelli C, Gionchetti P, Brignola C, Belluzzi A, Di Febo G, et al. Spread and distribution of 5-ASA colonic foam and 5-ASA enemas in patients with ulcerative colitis. Dig Dis SCi 1992; 37: 1890-7.

[22] Wilding IR, Kenyon CJ, Chauhan S, Hooper G, Marshall S, McCracken JS, et al. Colonic spreading of a non-chlorofluorocarbon mesalazine rectal foam enema in patients with quiescent ulcerative colitis. Aliment Pharmacol Ther 1995; 9: 161-6.

[23] Brunner M, Vogelsang H, Greinwald R, et al. Colonic spread and serum pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis. *Aliment Pharmacol Ther.* 2005;22(5):463-470

[24] Campieri M, Giochetti P, Corbelli C, et al. Colonic spread and distribution of budesonide foam in patients with ulcerative colitis. Gastroenterology 1995;108(4):A790.
[25] Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011 May;140(6):1785-94
[26] Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42
[27] AMCP Dossier for UCERIS (budesonide) rectal foam. Valeant Pharmaceuticals North America LLC. July 2015.
[28] Peppercorn MA, Kane SV. Clinical manifestations, diagnosis and prognosis of ulcerative colitis in adults. In: UpToDate, Rutgeerts P, Grover S (Eds), UpToDate, Waltham, MA. (Accessed on 20 January 2016.)
[29] Richter JM, Kushkuley S, Barrett JA, Oster G. Treatment of new-onset ulcerative colitis and ulcerative proctitis: a retrospective study. Aliment Pharmacol Ther. 2012 Aug;36(3):248-56
[30] Kornbluth A, Sachar DB, The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(5):501-523
[31] National Guideline Clearinghouse summary of: National Clinical Guideline Centre. Ulcerative colitis. Management in adults, children and young people. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jun. 37 p. (Clinical guideline; no. 166). Available at: http://www.guideline.gov/content.aspx?id=46936&search=ulcerative+colitis#Section420 .

Prepared March 2016. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, Pharmacy Benefits Management Services (10P4P)

Appendix A: GRADEing the Evidence

Quality of Evidence	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of theevidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.