Budesonide Oral Suspension (EOHILIA) in Eosinophilic Esophagitis
National Drug Mini-Monograph

May 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; BIS, budesonide inhalation suspension; BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; CO, crossover; CS, corticosteroid; DB, double-blind; DSQ, Dysphagia Symptom Questionnaire; eos/hpf, eosinophils per high-powered field; GC, glucocorticoid; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MDQ, Mayo Dysphagia Questionnaire; MN, multinational; NMA, network meta-analysis; PBO, placebo; PC, placebo-controlled; PEM, primary efficacy measure; Q, GRADE quality of evidence; RCT, randomized clinical trial; SAF, swallowed aerosolized fluticasone; SB, single-blind; SEM, secondary efficacy measure; SNB, swallowed nebulized budesonide; STG, swallowed topical glucocorticoid

FDA APPROVAL INFORMATION

Description / MOA	Budesonide is a glucocorticoid with limited systemic activity due to a high first-pass effect when taken orally. Budesonide oral suspension (BOS) is the second treatment FDA approved for eosinophilic esophagitis (EoE). It is a thixotropic, mucoadherent formulation that becomes temporarily more fluid when shaken then reverts to a viscous state after being swallowed.
Indication Under Review[1]	For 12 weeks of treatment in adult and pediatric patients 11 years of age and older who have EoE. *Limitations of Use*: Has not been shown to be safe and effective for treatment of EoE for longer than 12 weeks.
Dosage Regimen	2 mg orally twice daily for 12 weeks. Not to be taken with or mixed with food or liquid. After administration at least 30 minutes should elapse before eating or drinking and before rinsing the mouth with water. When the mouth is rinsed, the patient should spit out (and not swallow) the water.
Dosage Forms Under Review	Oral suspension: 2 mg/10 mL single-dose stick packs

EFFICACY CONSIDERATIONS

Trial	ORBIT1/SHP621-301 by Hirano (2022)[2]
Design	Phase 3 MC DB PC RCT with a 4-wk, SB PBO-lead-in period; conducted in the US
Population	Histologic evidence of EoE (≥ 15 eosinophils/high-power field [eos/hpf] at screening and Dysphagia Symptom Questionnaire (DSQ)-measured dysphagia on ≥ 4 d in any 2 consecutive wks during screening and in the 2 wks before randomization. Excluded patients who completed < 70% days' worth of the DSQ and who had < 4 days of dysphagia in the last 2 wks of the PBO lead-in period. Prior therapies: Diet therapy 25%, budesonide slurry 20%, fluticasone aerosol 34%, oral CS 8%, any of the 3 previous CS therapies 54%, esophageal dilation 43%, inhaled / nasal CS 19%, PPIs 85%
Interventions	BOS 2 mg BID x 12 wks Placebo (PBO)
Efficacy Measures	PEMs: (1) stringent histologic responders (≤ 6 eos/hpf across all available esophageal levels) and (2) dysphagia symptom responders (≥ 30% reduction in DSQ score from BL to Wk 12 [DSQ-30]) SEMs: Full responders (combined stringent histologic response and dysphagia symptom response (≤ 6 eos/hpf and DSQ-30)
Results	**Efficacy Results at Wk 12**

Measure	BOS N = 213	PBO N = 105	RR (95% CI)	ARD (95% CI)	Q
Stringent Histologic Response	114 (53.5)	1 (1.0)	56.2 (8.0, 396.8)	53 (43.8, 59.5)	L[α]
Dysphagia Symptom Responders	112 (52.6)	41 (39.1)	1.4 (1.0, 1.8)	13 (1.6, 24.3)	L[α]
Full Response	64 (30.0)	0 (0.0)	∞	30 (23.7, 36.0)	M[β]

[α] Downgraded for indirectness and imprecision (suboptimal information size; wide CI)
[β] Downgraded for imprecision (suboptimal information size)

Trial	ORBIT1/SHP621-302 by Dellon (2022)[3]

Design

36-wk phase 3 MC DB randomized withdrawal study in US, extension of ORBIT1/SHPY21-301 study (total 52 wks: 12 wks induction + up to 4 wks screening + up to 36 wks extension)

Population

(1) Fully responded (≤ 6 eos/hpf and ≥ 30% reduction in DSQ score) to induction — 36-wk DB PC withdrawal RCT

(2) Partial or no response to BOS — additional 36 wks of DB BOS (up to 52 wks)

(3) Received PBO induction — 36 wks of DB BOS. PBO induction full responders who relapsed could reinitiate DB BOS 2 mg BID.

Interventions

BOS–BOS (2 mg BID) for induction full responders (intervention arm of randomized withdrawal) (n = 25)

BOS–PBO (comparator arm of randomized withdrawal) (n = 23)

BOS 2 mg BID for induction partial and nonresponders (n = 106)

Induction PBO BID (n = 65)

PEM

Patients from the randomized withdrawal period who relapsed

Results

Efficacy Results in Full Responders, Full Analysis Set

Measure	BOS–BOS N = 25	BOS–PBO N = 23	RR (95% CI)	ARD (95% CI)	Q
Histologic and Dysphagia Symptom Relapse at Wk 36	6 (24.0)	10 (43.5)	0.55 (0.24, 1.28)	19.5% (–45.2, 8.2)	Low[α]
Maintained Full Response at Wk 12	16 (64.0)	1 (4.5)	14.7 (2.1, 102.4)	59.6 (39.1, 80.2)	Low[α]
Histologic Relapse (≥ 15 eos/hpf)	3 (12.0)	15 (65.2)	18.4 (6, 55)	53.2 (30.0, 76.5)	Low[α]

α Double downgraded for inconsistency and imprecision (suboptimal information size; wide CI)

Onset

Wk 12 – based on the time of the first significant treatment difference (BOS 2 mg BID vs PBO) in change from baseline in DSQ score.[6]

NETWORK META-ANALYSIS

Rokkas (2021)[4]

Design

NMA of direct and indirect treatment comparisons from English-language RCTs

Population

K = 17 (11 in adults), N = 1011

Interventions

Total, 15 treatments (11 in adults):

- BOS (K = 4; dosage range, 1 mg/d to 2 mg BID)
- Budesonide 1 mg orodispersible tablet BID (BOT1)
- Budesonide 2 mg orodispersible table BID (BOT2)
- Esomeprazole
- Fluticasone (K = 6; 440–880 mcg/d in 2–4 divided doses)
- Nebulized steroid
- PBO
- Prednisone
- Mepolizumab
- Reslizumab 1 mg/kg
- Reslizumab 2 mg/kg
- Reslizumab 3 mg/kg
- 3 investigational agents

Efficacy Measures

PEM: Significant decrease in histologic esophageal eosinophil load

SEM: Resolution of EoE-related symptoms without need for additional treatment

Results

Comparative effect sizes from direct and indirect comparisons were consistent.

Summary of League Matrix for All Possible Pair-wise Comparisons

Ranked Best	Ranked Worst	BOS better than	BOS similar to	BOS worse than
BOT1	Mepolizumab Placebo	Reslizumab 2 mg/kg Reslizumab 3 mg/kg Reslizumab 1 mg/kg Mepolizumab Placebo	BOT2 Esomeprazole Prednisone Fluticasone Nebulized steroid	BOT1

	Other Relevant Studies	• 12-wk Ph2 MC DB PC RCT: Showed significant treatment benefits in DSQ scores, histologic response, and endoscopic severity scores[5,6] • Ph2 24-wk MC OLE[7]
	Evidence Gaps	Trials comparing BOS with patient-mixed STGs. Long-term safety and efficacy.

SAFETY CONSIDERATIONS	**Boxed Warnings**	None
	Contraindications	Hypersensitivity
	Other Warnings	Hypercorticism and adrenal axis suppression; immunosuppression and increased risk of infection; erosive esophagitis; reduction in growth velocity (pediatrics); symptoms of steroid withdrawal in patients transferred from other systemic glucocorticoids; other glucocorticoid effects; Kaposi's sarcoma
	Top 5 AEs (≥ 3%)	Respiratory tract infection, gastrointestinal mucosal candidiasis, headache, gastroenteritis, throat irritation
	Drug Interactions	CYP3A4 inhibitors (e.g., ketoconazole, grapefruit juice): Avoid concomitant use (increased systemic budesonide concentrations)
	Hepatic Impairment	Severe hepatic impairment (Child-Pugh Class C): Use is not recommended (increased risk of hypercorticism and adrenal axis suppression). Moderate hepatic impairment (Child-Pugh Class B): Monitor for hypercorticism.
	Pregnancy	May cause fetal harm.
	Lactation	Insufficient studies in humans; weigh risks vs benefits.

OTHER CONSIDERATIONS	**BOS**	Bioavailability after oral administration is 14% in fasting healthy subjects. High (80%–90%) first-pass metabolism to metabolites with negligible glucocorticoid activity.
	OVB Slurry	Half-life of OVB in the esophagus was shown to be < 2 minutes.[13] Longer mucosal contact time correlated with improvement in eosinophil counts.[8] No placebo-controlled RCTs.
	SAF	Three placebo-controlled trials of SAF consistently showed significant benefits in histologic endpoints but no significant treatment differences in dysphagia improvement.[9,10,11] Vomiting or heartburn were improved on SAF relative to baseline.

PLACE IN THERAPY

INTERVENTION	VANF	CFU	FDA	2020 AGA/JTFAI EoE GUIDELINES[12]	ACTIVE COMPARATOR STUDIES
Swallowed Topical Glucocorticoids					
Budesonide Oral Suspension (BOS)	TBD	TBD	12 wks of treatment for EoE	Recommends swallowed topical glucocorticoids (STGs) over no treatment (strong recommendation, moderate QE; includes only one trial of BOS[5]).	None for BOS. Two RCTs compared OVB with other STGs. In one RCT, OVB (N = 11) was nonsignificantly better than SNB (N = 11), each dosed at 1 mg twice daily for 8 weeks, in achieving complete (< 1 eos/hpf) and near complete (< 7 eos/hpf) histologic response: 7 (64%) vs 3 (27%) (RR 2.3, 95% CI 0.8, 6.8; ARD 37, 95% CI 2, 75) and 8 (73%) vs 4 (36%) (RR 2.0, 95% CI 0.8, 4.7; ARD 37, 95% CI –2.4, 75.1), respectively.[8] Posttreatment Mayo Dysphagia Questionnaire (MDQ) scores were not significantly different (changes from baseline were not analyzed). In the other RCT, OVB (1 mg BID) and SAF (880 mcg BID) were NSD in achieving histologic response (< 15, < 5, and < 1 eos/hpf) and improving DSQ scores.[13] After treatment discontinuation, the rate of histologic recurrence (≥ 15 eos/hpf) at the time of symptom recurrence or 1-year follow-up was 88% (22/25) in the OVB group and 68% (17/25) in the SAF group (RR 1.3, 95% CI 0.95, 1.76); ARD 20, 95% CI 2, 42).[14] An NMA of 1 RCT[13] and 2 retrospective comparative studies showed no significant difference between budesonide and fluticasone in rates of histologic response (< 15 eos/hpf).[15]
Oral Viscous Budesonide (OVB) Using Budesonide Inhaled Suspension (BIS)†	No	NA	Off-label use		
Swallowed Nebulized Budesonide (SNB) Using BIS	No	NA	Off-label use		
Swallowed Aerosolized Fluticasone (SAF) via Metered Dose Inhaler	No	NA	Off-label use		
Interleukin-4/13 Inhibitor					
Dupilumab	No	Requires prior trials of STG (e.g., OVB or SAF for ≥ 8 wks) and dietary therapy	Treatment of adult and pediatric patients aged ≥ 1 year, weighing at least 15 kg, with EoE	Approved in May 2022	—
Systemic Glucocorticoids					
Prednisone (or Other GCs), oral	Yes	NA	Off-label use	Suggests STGs rather than oral GCs (conditional recommendation, moderate QE).	—
Proton Pump Inhibitors					
Omeprazole Pantoprazole	Yes	NA	Off-label	Suggests PPIs over no treatment for symptomatic EoE (conditional recommendation, very low QE).	Two RCTs have compared SAF with esomeprazole. One (N = 30 enrolled, 24 analyzed) showed that esomeprazole 40 mg QD and SAF 440 mcg BID x 8 wks were NSD in improvements in dysphagia scores and eosinophil infiltration counts in patients with EoE.[16] The other (N = 42) showed NSD in histologic response (< 7 eos/hpf).[17] Esomeprazole, but not SAF, significantly improved Mayo Dysphagia Questionnaire (MDQ) scores from baseline. Treatment differences in CFB in MDQ scores were not reported.
Dexlansoprazole Esomeprazole Rabeprazole	No	NA			
Dietary Treatment Options					

[redacted]	Elemental Diet	NA	NA	NA	Suggests an elemental diet over no treatment (conditional recommendation, moderate QE). Patients may reasonably decline this treatment option because adherence to elimination of common foods and the long food reintroduction process can be difficult.	None vs drug therapy
	Empiric Food Elimination Diet	NA	NA	NA	Suggests using an empiric six-food elimination diet over no treatment (conditional recommendation, low quality evidence). Patients may reasonably decline this treatment option because adherence to elimination of common foods and the long food reintroduction process can be difficult.	None vs drug therapy

† Prepared by mixing budesonide inhalation suspension with a sweetener such as powdered sucralose to form a thick paste or viscous liquid; other vehicles may be used. [18, 19]

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. From Q2CY2023 to Q1CY2024, VHA had 8524 patients with a diagnosis of EoE and of those, 1175 (14%) were treated with budesonide, fluticasone, or dupilumab. 2. There is low to moderate certainty evidence that BOS produces large histologic effects and moderate full (histologic and symptomatic) response in patients with EoE. There have been no active-controlled trials of BOS—in particular, no trials comparing BOS with patient-mixed STGs / OVB or SAF—to inform its relative efficacy, safety, and mucosal contact time and place in therapy. The main potential advantages of BOS over other STGs are standardized formulation and reduced time, effort, and cost burdens on patients related to self-preparing STGs or obtaining them from compounding pharmacies. SAF and budesonide inhalation suspension (for mixing OVB) are less costly than BOS. 3. BOS offers a standardized, convenient product that should be preferred over OVB. BOS may be considered for 12-week treatment of EoE as an alternative to SAF.

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References

1 EOHILIA (budesonide oral suspension) [prescribing information online]. Lexington, MA: Takeda Pharmaceuticals America. February 2024. Available at: content.takeda.com/?contenttype=PI&product=EOH&language=ENG&country=USA&documentnumber=1. Accessed 28 February 2024.

2 Hirano I, Collins MH, Katzka DA, Mukkada VA, Falk GW, Morey R, Desai NK, Lan L, Williams J, Dellon ES; ORBIT1/SHP621-301 Investigators. Budesonide Oral Suspension Improves Outcomes in Patients With Eosinophilic Esophagitis: Results from a Phase 3 Trial. Clin Gastroenterol Hepatol. 2022 Mar;20(3):525-534.e10. doi: 10.1016/j.cgh.2021.04.022. Erratum in: Clin Gastroenterol Hepatol. 2022 Oct;20(10):2418

3 Dellon ES, Collins MH, Katzka DA, Mukkada VA, Falk GW, Morey R, Goodwin B, Eisner JD, Lan L, Desai NK, Williams J, Hirano I; ORBIT2/SHP621-302 Investigators. Long-Term Treatment of Eosinophilic Esophagitis With Budesonide Oral Suspension. Clin Gastroenterol Hepatol. 2022 Jul;20(7):1488-1498.e11. doi: 10.1016/j.cgh.2021.06.020

4 Rokkas T, Niv Y, Malfertheiner P. A Network Meta-Analysis of Randomized Controlled Trials on the Treatment of Eosinophilic Esophagitis in Adults and Children. J Clin Gastroenterol. 2021 May-Jun 01;55(5):400-410. doi: 10.1097/MCG.0000000000001356

5 Dellon ES, Katzka DA, Collins MH, Hamdani M, Gupta SK, Hirano I; MP-101-06 Investigators. Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis. Gastroenterology. 2017 Mar;152(4):776-786.e5. doi: 10.1053/j.gastro.2016.11.021

6 Dellon ES, Collins MH, Katzka DA, Hudgens S, Lan L, Williams J, Vera-Llonch M, Hirano I. Improvements in Dysphagia and Pain With Swallowing in Patients With Eosinophilic Esophagitis Receiving Budesonide Oral Suspension. Clin Gastroenterol Hepatol. 2021 Apr;19(4):699-706.e4. doi: 10.1016/j.cgh.2020.03.060

7 Dellon ES, Katzka DA, Collins MH, Gupta SK, Lan L, Williams J, Hirano I. Safety and Efficacy of Budesonide Oral Suspension Maintenance Therapy in Patients With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol. 2019 Mar;17(4):666-673.e8. doi: 10.1016/j.cgh.2018.05.051

8 Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology 2012; 143:321–324.e1.

9 Alexander JA, Jung KW, Arora AS, Enders F, Katzka DA, Kephardt GM, Kita H, Kryzer LA, Romero Y, Smyrk TC, Talley NJ. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2012 Jul;10(7):742-749.e1. doi: 10.1016/j.cgh.2012.03.018.

10 Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, Akers R, Cohen MB, Collins MH, Assa'ad AH, Aceves SS, Putnam PE, Rothenberg ME. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. Gastroenterology. 2006 Nov;131(5):1381-91. doi: 10.1053/j.gastro.2006.08.033.

11 Butz BK, Wen T, Gleich GJ, Furuta GT, Spergel J, King E, Kramer RE, Collins MH, Stucke E, Mangeot C, Jackson WD, O'Gorman M, Abonia JP, Pentiuk S, Putnam PE, Rothenberg ME. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. Gastroenterology. 2014 Aug;147(2):324-33.e5. doi: 10.1053/j.gastro.2014.04.019.

12 Hirano I, Chan ES, Rank MA, Sharaf RN, Stollman NH, Stukus DR, Wang K, Greenhawt M, Falck-Ytter YT; AGA Institute Clinical Guidelines Committee; Joint Task Force on Allergy-Immunology Practice Parameters. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. Gastroenterology. 2020 May;158(6):1776-1786. doi: 10.1053/j.gastro.2020.02.038

13 Dellon ES, Woosley JT, Arrington A, McGee SJ, Covington J, Moist SE, Gebhart JH, Tylicki AE, Shoyoye SO, Martin CF, Galanko JA, Baron JA, Shaheen NJ. Efficacy of Budesonide vs Fluticasone for Initial Treatment of Eosinophilic Esophagitis in a Randomized Controlled Trial. Gastroenterology. 2019 Jul;157(1):65-73.e5. doi: 10.1053/j.gastro.2019.03.014

14 Dellon ES, Woosley JT, Arrington A, McGee SJ, Covington J, Moist SE, Gebhart JH, Galanko JA, Baron JA, Shaheen NJ. Rapid Recurrence of Eosinophilic Esophagitis Activity After Successful Treatment in the Observation Phase of a Randomized, Double-Blind, Double-Dummy Trial. Clin Gastroenterol Hepatol. 2020 Jun;18(7):1483-1492.e2. doi: 10.1016/j.cgh.2019.08.050

15 Numan L, Kalot MA, Brotherton T, Tarakji A, Hamdeh S. Comparison of viscous budesonide and fluticasone in the treatment of patients with eosinophilic esophagitis: a systematic review and meta-analysis. Ann Gastroenterol. 2023 Sep-Oct;36(5):511-516. doi: 10.20524/aog.2023.0822

16 Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. Dig Dis Sci. 2010 May;55(5):1313-9. doi: 10.1007/s10620-009-0859-4.

17 Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. Am J Gastroenterol. 2013 Mar;108(3):366-72. doi: 10.1038/ajg.2012.443

18 Zur E. Eosinophilic esophagitis: treatment with oral viscous budesonide. Int J Pharm Compd. 2012 Jul-Aug;16(4):288-93

19 Hefner JN, Howard RS, Massey R, Valencia M, Stocker DJ, Philla KQ, Goldman MD, Nylund CM, Min SB. A Randomized Controlled Comparison of Esophageal Clearance Times of Oral Budesonide Preparations. Dig Dis Sci. 2016 Jun;61(6):1582-90. doi: 10.1007/s10620-015-3990-4.