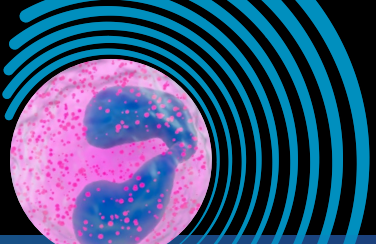
Payer Considerations for Off-Label Medical Treatment of

Eosinophilic ESOPHAGITIS

IMPLICATIONS FOR PAYER COVERAGE CRITERIA



DISEASE BACKGROUND

Eosinophilic esophagitis (EoE) is a chronic, antigen-mediated, eosinophilic inflammatory disease isolated to the esophagus. As a clinicopathologic disorder, a diagnosis of EoE requires a constellation of clinical symptoms of esophageal dysfunction and histologic findings (at least 15 eosinophils/high-powered microscope field [os/hpf]).

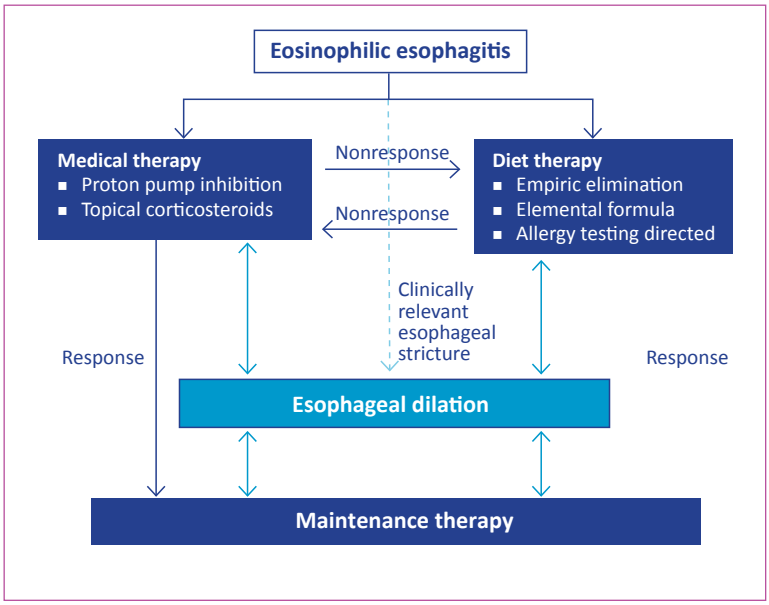
The treatment goals for EoE include improvements in clinical symptoms, quality of life, endoscopic features, and esophageal function as well as resolution of esophageal eosinophilia and other histologic abnormalities, minimized adverse effects of treatment, and prevention of disease progression and subsequent complications.

Currently, there is no cure for EoE, making long-term treatment necessary. Standard treatment modalities include dietary modifications, pharmacologic therapy, and esophageal dilation. Guideline recommended pharmacologic therapies include corticosteroids, proton pump inhibitors, and biological therapies. As of September 2023, one agent, dupilumab, is indicated by the FDA to treat EoE in patients aged 12 and older, and therefore most recommended treatments are used and dosed off-label. EoE is a relatively rare disease, and the off-label treatments are adapted from more common diseases (e.g., GERD, asthma) where dosing and routes of administration differ from EoE.

INTRODUCTION

AGA CLINICAL PRACTICE GUIDELINE CLINICAL DECISION SUPPORT TOOL[2]

To support managed care and payer professionals in the process of establishing coverage criteria grounded in published evidence and to tackle prevalent utilization management issues related to the non-standard dosing and off-label use of recommended treatment options in EoE, the following decision support scenarios are presented. Nothing in this payer support tool suggests or prohibits a health plan from requiring prior authorization or imposing other appropriate utilization controls in approving coverage for medical treatment of EoE.



It is beyond the scope of this tool to provide comprehensive recommendations for the treatment of EoE. Additional clinical guidance is available in the 2020 AGA institute and the Joint Task Force (AGA/JTF) on Allergy-Immunology Practice Parameters clinical guidelines for the management of eosinophilic esophagitis.[1,2] A 2023 Cochrane Review and the 2022 British Society of Gastroenterology (BSG) and Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) joint consensus guidelines are additional resources for the treatment of EoE.[3,4] And an international group of experts have published recommendations on monitoring patients with eosinophilic esophagitis in routine clinical practice.[5]

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi.

PROTON PUMP INHIBITORS (PPIs)

RECOMMENDATION	LEVEL OF RECOMMENDATION	GRADE OF EVIDENCE
AGA/JTF Suggests using proton pump inhibition over no treatment.	Conditional	Very low
BSG/BSPGHAN Proton pump inhibitor therapy is effective in inducing histological and clinical remission in patients with eosinophilic oesophagitis.	Strong	Moderate

EoE-SPECIFIC CONSIDERATIONS:

PPIs benefit patients with EoE by decreasing chemokine-mediated recruitment of eosinophils to the esophagus and improving esophageal barrier function. While the reduction in acid production in patients with coexistent GERD may also provide benefit, these other mechanisms appear to be acid independent. Notably, "high dose" or "double" dose PPI use (i.e., equivalent to 40 mg of omeprazole daily) is needed for initial treatment of EoE.

Patients are assessed for symptomatic improvement following an 8- to 12-week course of PPI treatment. Efficacy is also assessed by performing an upper endoscopy 8 to 12 weeks after initiating therapy to determine endoscopic and histologic improvement. For patients who respond, continue the PPI at the lowest dose successful at controlling symptoms, histologic findings, and endoscopic features.

COVERAGE ISSUES:

1. Prescription coverage for PPIs is often limited due to over-the-counter (OTC) status
2. The patient out-of-pocket cost for OTC PPIs is estimated to be $60 per 30-day supply
3. Access to a recommended dosage form (e.g., sprinkle capsule; dissolvable tablet) may be limited OTC
4. History of PPI use is often required as a preferred step in access to the FDA-approved treatment, but pharmacy claims data is not available for OTC use of PPIs

DOSING:

An initial treatment duration of 8 to 12 weeks is suggested. Recommended dosing is "high dose" or "double" dose PPI use (i.e., equivalent to 40 mg of omeprazole daily).

SUGGESTED COVERAGE CRITERIA OF PPIs FOR EoE:

- The patient has the diagnosis of EoE
- The request is for start of or continuation of therapy with a PPI (for continuation, the patient has been evaluated for improvement or relapse in symptoms or inflammation).

  Quantity: Approve 60 tablets/capsules per 30-day supply, to allow for twice-daily dosing.

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi.

TOPICAL (SWALLOWED) GLUCOCORTICOIDS

RECOMMENDATION	LEVEL OF RECOMMENDATION	GRADE OF EVIDENCE
AGA/JTF Recommend topical glucocorticosteroids over no treatment.	Strong	Moderate
BSG/BSPGHAN Topical steroids are effective for inducing histological and clinical remission in eosinophilic oesophagitis.	Strong	High

EoE SPECIFIC CONSIDERATIONS:

Topical steroids aim to coat the esophagus to provide a local anti-inflammatory effect in EoE. No formulation of topical glucocorticoids has been approved specifically for EoE in the U.S. Therefore, in the U.S., patients must adapt asthma formulations and swallow, rather than inhale, the medication to coat the esophagus. Of note, with this method, few asthma preparations are appropriate for EoE use. For example, combination steroid/beta agonist preparations cannot be used, and devices that require inhalation to dispense the medication cannot be used. The European Medicines Agency (EMA) and Health Canada approved budesonide in an orodispersible tablet formulation for adults with EoE, but this cannot be obtained in the U.S.

Among topical glucocorticoids, fluticasone (typically swallowed from a multidose inhaler, or swallowed from powder obtained from opening a disk device) and budesonide (typically mixed into a slurry from the aqueous respule formulation for nebulizers) have been best studied, with multiple randomized, placebo-controlled studies consistently showing a benefit for these medications. Small studies and case series have examined other topical glucocorticoids for treating EoE. Systemic glucocorticoids have a limited role in EoE, except possibly in patients with severe disease in whom other approaches are not feasible.

Topical steroid induction therapy is given for 8 to 12 weeks, followed by assessment of symptomatic response (e.g., dysphagia) and performance of upper endoscopy to assess for endoscopic and histologic improvement.

COVERAGE ISSUES:

1. Prescription coverage for glucocorticoids may be limited or denied based on asthma indication and dosing.
2. Coverage limits may include specific age groups based on asthma indication, which can trigger new coverage rejections as patients age (e.g., budesonide, when used for asthma, is indicated for 12 months to 8 years of age and fluticasone is indicated for patients 4 years and older. If grandfathering for history of budesonide is not in place, plans may require a trial of fluticasone for members 4 years and older before continuing budesonide.)
3. The history of glucocorticoid use is often required as a preferred step in access to the FDA-approved treatment, but topical steroids may not be a covered option for EoE.

Possible Additional Coverage Issue: Both FLOVENT HFA and DISKUS will be discontinued on December 31, 2023. Authorized generics for FLOVENT HFA and FLOVENT DISKUS are currently available. A generic version of fluticasone propionate (ArmonAir Digihaler) is available.

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi.

DOSING

Fluticasone

- Fluticasone propionate metered dose inhaler (MDI) without a spacer: The medication is sprayed into the patient's mouth and then swallowed. Patients should not inhale when the medication is being delivered and they should not eat or drink for 30 minutes following administration. Instruct patients to divide the total daily dose as 2 to 4 times daily. The general approach for fluticasone propionate MDI dosing in EoE is based upon patient age:
    - Children ages 1 to 11 years – 110 mcg/spray, 8 sprays daily in divided doses (880 mcg daily)
    - Children ages ≥ 12 years and adults – 220 mcg/spray, 8 sprays daily in divided doses (1,760 mcg daily)

- **Fluticasone propionate Diskus**: Diskus can be opened to access fluticasone powder, which can then be directly placed onto the tongue and swallowed. The general approach for fluticasone propionate Diskus dosing in EoE is based upon patient age:
    - Children ages 1 to 11 years – 250 mcg device is used, dosed as 1 mg (4 blisters) daily
    - Children ages ≥ 12 years and adults – 250 mcg device is used, dosed as 2 mg (8 blisters) daily

Budesonide

- Pulmicort Respules are used to make "oral viscous budesonide." Patients mix a budesonide slurry by combining the Respules with sucralose (e.g., Splenda; 10 1-gram packets per 1 mg of budesonide, creating a volume of approximately 8 mL) or another carrier vehicle (i.e., honey or maple syrup) that is viscous. Patients should swallow the budesonide and should not eat or drink for 30 minutes after taking it. The total daily dose is often divided into twice daily. The general approach for budesonide dosing for EoE is based upon patient age:
    - Children < 10 years: 1 mg daily
    - Children ages ≥ 10 years and adults: 2 mg twice daily

SUGGESTED COVERAGE CRITERIA OF TOPICAL STEROIDS FOR EoE:

Fluticasone MDI or Diskus

- The patient has the diagnosis of eosinophilic esophagitis (EoE)
- The request is for start of or continuation of therapy with fluticasone at an age-appropriate, product-specific dose as outlined above
- For continuation, the patient has been evaluated for improvement or relapse in symptoms or inflammation

Quantity:

Fluticasone MDI: Approve for 2 inhalers (120 actuations) per month (240 inhalations) to support up to 1,760 mcg/day, with divided dosing

Fluticasone Diskus: Approve for 4 disk devices (60 blisters) per month, for a total of 240 blisters to support dosing of up to 2 mg/day, with divided dosing

Budesonide (Pulmicort Respules):

- The patient has the diagnosis of eosinophilic esophagitis (EoE)
- The request is for start of or continuation of therapy with Pulmicort (budesonide) Respules at a dose of 1 mg twice daily (2 mg daily)
- For continuation, the patient has been evaluated for improvement or relapse in symptoms or inflammation

Quantity:

Approve for 2 packages (60 respules) of the Pulmicort Respules 1 mg/2 mL strength per month to accommodate higher dosages of 2 mg daily, with divided dosing. Alternatively, approve for 4 packages (60 respules) of the 0.5 mg/2 mL strength per month to accommodate higher dosages of 2 mg daily, with divided dosing.

DIET THERAPY

EMPIRIC ELIMINATION

RECOMMENDATION	LEVEL OF RECOMMENDATION	GRADE OF EVIDENCE
AGA/JTF Suggests using an empiric six-food elimination diet over no treatment.	Conditional	Low
BSG/BSPGHAN Elimination diets are effective in achieving clinico-histological remission in both adults and paediatric patients with eosinophilic oesophagitis.	Strong	Moderate

AGA/JTF
Patients who put a higher value on avoiding the challenges of adherence to diet involving elimination of multiple common food staples and the prolonged process of dietary reintroduction may reasonably decline this treatment option.

BSG/BSPGHAN
When undertaking a dietary restriction therapy for eosinophilic oesophagitis, support from an experienced dietitian throughout both the elimination and reintroduction process is strongly recommended.

EoE SPECIFIC CONSIDERATIONS:

Empiric elimination diet recommendation is based on published experience with the six-food elimination diet (SFED). This diet involves removing specific food groups from the individual's diet based on the most common allergens associated with EoE, aiming to identify and eliminate trigger foods. Emerging data on less restrictive diets (4 food, milk elimination, 2-4-6 step up diet) may increase both provider and patient preference for diet therapy. After the elimination phase and once symptoms have improved, foods are gradually reintroduced one at a time in a systematic manner. This is typically done under the guidance of a health care professional, such as a registered dietitian or gastroenterologist. The registered dietitian provides nutritional assessment at the beginning of treatment to estimate the caloric intake needed to maintain adequate growth. The dietitian can also advise on which food choices are available and appropriate for the patient and can be helpful if the patient gets to a phase of food reintroduction.

COVERAGE ISSUES:

1. The Affordable Care Act mandates that health insurance covers nutrition counseling.
2. Medicaid covers nutrition counseling, but coverage varies by state.
3. Coverage can vary by provider and by plan and often depends on medical necessity.
4. Special diets are often costly for the patient which can be a treatment barrier, and it's challenging for patients to adhere to them.

SUGGESTED COVERAGE OF DIETARY SERVICES:

Include eosinophilic esophagitis in list of medical conditions deemed medically necessary for dietitian-covered services.

This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc. and Sanofi.

ELEMENTAL FORMULA

RECOMMENDATION	LEVEL OF RECOMMENDATION	GRADE OF EVIDENCE
AGA/JTF Suggests using elemental diet over no treatment. *Patients who put a higher value on avoiding the challenges of adherence to an elemental diet and the prolonged process of dietary reintroduction may reasonably decline this treatment option.*	Conditional	Moderate
BSG/BSPGHAN Exclusive elemental diets have a limited role in eosinophilic oesophagitis, with high efficacy but low compliance rates and should be reserved for patients refractory to other treatments.	Strong	Low

EoE SPECIFIC CONSIDERATIONS:

In this diet, all sources of protein are removed from a patient's diet. An elemental diet includes only an amino acid formula with no whole or partial proteins. Complete resolution of disease activity is generally achieved with an amino acid-based elemental diet. An elemental diet requires the use of a nutritionally balanced, complete formula to replace or supplement solid food. Since individuals who require an elemental diet cannot get their nutrition though a regular diet, elemental formulas use individual amino acids as the protein source. The cellular components of the immune system cannot recognize these proteins, so they do not create an immune response. Most elemental formulas are nutritionally complete, providing adequate amounts of calories and nutrients such as essential fats, amino acids, vitamins and minerals for normal growth. Elemental formulas are classified by the FDA as medical foods rather than pharmaceuticals.[6] The FDA defines medical foods in section 5(b) of the Orphan Drug Act as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the dietary management of a specific disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

COVERAGE ISSUES:

1. Coverage for medical foods such as elemental (amino-based acid) formula is commonly denied because medical necessity is not established, or medical food is not included in the plan coverage, or because a feeding tube is not in place.
2. Many insurance companies will not cover the cost if the formula is delivered orally.
3. Typically, medical food is provided to the patient through durable medical equipment benefit, not the pharmacy benefit.
4. Many families have trouble paying out-of-pocket for elemental formulas that can cost up to $3,600 per month
5. There is no federal legislation that facilitates consistent coverage of elemental formula throughout the U.S. The result is that legislation is state-dependent, and state mandates are applicable to the state in which the insurance policy is underwritten, not the state in which the patient lives. Fully insured plans are subject to state and federal law, including state law insurance mandates.
   In a self-funded plan, the employer has sole discretion as to which services will be covered and is only subject to federal law.

EVIDENCE-BASED COVERAGE OF ELEMENTAL FORMULA FOR EoE:

For health plans in states that do not have state insurance mandates for elemental formula and self-funded plans, provide coverage and reimbursement, preferably under the pharmacy benefit, for amino acid-based elemental formulas, for the diagnosis and treatment of eosinophilic disorders when the prescribing physician has issued a written order stating that the amino acid-based elemental formula is medically necessary.

For additional information on state insurance mandates for elemental formula see:
https://apfed.org/advocacy/medical-foods-legislation/

REFERENCES

1. 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. *Ann Allergy Asthma Immunol*. 2020 May;124(5):416-423. doi: 10.1016/j.anai.2020.03.020. PMID: 32336462; PMCID: PMC8135034.

2. Treatment of eosinophilic esophagitis(Eoe). *Gastroenterology*. 2020;158(6):1787. doi: 10.1053/j.gastro.2020.03.070

3. Franciosi JP, Gordon M, Sinopoulou V, Dellon ES, Gupta SK, Reed CC, Gutiérrez-Junquera C, Venkatesh RD, Erwin EA, Egiz A, Elleithy A, Mougey EB. Medical treatment of eosinophilic esophagitis. Cochrane Database Syst Rev. 2023 Jul 20;7(7):CD004065. doi: 10.1002/14651858.CD004065.pub4. PMID: 37470293.

4. Dhar A, Haboubi HN, Attwood SE, Auth MKH, Dunn JM, Sweis R, Morris D, Epstein J, Novelli MR, Hunter H, Cordell A, Hall S, Hayat JO, Kapur K, Moore AR, Read C, Sami SS, Turner PJ, Trudgill NJ. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. *Gut*. 2022 Aug;71(8):1459-1487. doi: 10.1136/gutjnl-2022-327326. Epub 2022 May 23. PMID: 35606089.

5. Arnim UV, Biedermann L, Aceves SS, Bonis PA, Collins MH, Dellon ES, Furuta GT, Gonsalves N, Gupta S, Hirano I, Lucendo AJ, Miehlke S, Oliva S, Schlag C, Schoepfer A, Straumann A, Vieth M, Bredenoord AJ; EUREOS and TIGERs. Monitoring Patients With Eosinophilic Esophagitis in Routine Clinical Practice - International Expert Recommendations. *Clin Gastroenterol Hepatol*. 2023 Sep;21(10):2526-2533. doi: 10.1016/j.cgh.2022.12.018. Epub 2022 Dec 24. PMID: 36572109.

6. U.S. Food and Drug Administration. Medical Foods Guidance Documents & Regulatory Information. Available at: https://www.fda.gov/food/guidance-documents-regulatory-information-topic-food-and-dietary-supplements/medical-foods-guidance-documents-regulatory-information