Dupilumab (DUPIXENT) in Eosinophilic Esophagitis National Drug Monograph Addendum November 2022

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 if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.[1]
- Dupilumab is the first therapy approved for the treatment of eosinophilic esophagitis (EoE), a serious, chronic inflammatory condition with limited treatment options, for which safety and effectiveness have not been established.

Indication Under Review in This Document

- Treatment of adults with EoE.

Dosage Regimen Under Review

- 300 mg SC every week (QW).
- The dose of dupilumab for the treatment of EoE is higher (more frequent) than for other indications.

Clinical Evidence Summary

Efficacy Considerations

- No head-to-head trials have been conducted to inform the place in therapy of dupilumab in EoE.
- A 12-week phase 2 RCT involving 47 randomized patients with active EoE (2 episodes of dysphagia / week with peak esophageal eosinophil density of ≥ 15 eosinophils per high-power field [eos / hpf]), who had predominantly mild to moderate symptoms, showed that dupilumab 300 mg SC QW improved dysphagia frequency and intensity scores, histologic and endoscopic response measures, and esophageal distensibility.[2] Further studies were needed to confirm short-term efficacy and long-term efficacy and safety of dupilumab in the treatment of EoE.
- A single, unpublished, phase 3, placebo-controlled, randomized clinical trial (RCT; Study R668-EE-1774 / Study 1774) confirmed the efficacy of dupilumab in the treatment of patients with EoE.[1, 3] The approved dose was 300 mg QW; a less frequent dosage regimen of 300 mg Q2W did not provide additional dysphagia symptom benefits over placebo.[3]
- Histologic activity and clinical manifestations can vary independently; therefore, both histologic end points (reduction in eosinophilic inflammation) and clinical signs and symptoms are important outcome measures for assessing the efficacy of treatments for EoE. Histologic remission is defined as a change in peak esophageal eosinophil density from ≥ 15 eos/hpf to ≤ 6 eos/hpf.

Randomized Clinical Trials

Table 1 Methods of Phase 3 RCT

Topic	Study 1774
Study Design	MC DB PC RCT with two independent 24-wk treatment periods (Parts A and B) involving distinct study populations.
Major Entry Criteria	**Inclusions**. Adult and pediatric patients 12–17 y (weight ≥ 40 kg). ≥ 15 intraepithelia eosinophils per high-power field (eos/hpf) after ≥ 8 weeks of proton pump inhibitor therapy. Symptoms of dysphagia; baseline Dysphagia Symptom Questionnaire [DSQ] score ≥ 10; average ≥ 2 episodes of dysphagia with intake of solids per week in the 4 weeks before screening (considered a key inclusion criterion); ≥ 4 episodes of dysphagia in the 2 weeks before baseline, at least 2 of which require liquids, coughing, gagging, vomiting, or medical attention to obtain relief **Exclusions**: Initiation or change in food elimination diet in previous 6 weeks (those on such a diet had to remain on the same diet throughout the study); other causes of esophageal eosinophilia; hypereosinophilic syndrome; eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome); active *Helicobacter pylori* infection; history of achalasia, Crohn's disease, ulcerative colitis, celiac disease, and prior esophageal surgery; esophageal stricture unable to be passed with a 9- to 10-mm standard diagnostic endoscope; critical esophageal stricture requiring dilation; history of bleeding disorders or esophageal varices that would pose undue risk for complications from endoscopy; treatment with swallowed topical glucocorticoids in previous 8 weeks.
Interventions	Part A • Dupilumab 300 mg SC QW • Placebo Part B • Dupilumab 300 mg SC QW • Dupilumab 300 mg SC Q2W • Placebo
Maintenance Phase or Long-term Extension (Part C)	Part A/C and Part B/C: Ongoing 28-week open-label extended study involving patients who completed either Part A or Part B (total active treatment period of up to 52 weeks)
Co-primary Efficacy Measures	Achievement of histologic remission, defined as peak esophageal intraepithelial eosinophil count of ≤ 6 eos/hpf at Week 24 Absolute change from baseline to Week 24 in patient-reported DSQ score. The FDA determined that the range for a meaningful within-subject improvement from baseline in DSQ was between 20 and 24 points.[3]
Baseline Patient Characteristics	**Characteristic** / **Part A (N = 81)** / **Part B (N = 159)*** Adult: 61 / 107 Age, mean, y (range): 32 (13–62) / 28 (12–66) Male: 60% / 68% White: 96% / 90% History of esophageal dilation: 44% / 36% History of prior swallowed topical glucocorticoid use: 75% / 73% Proton pump inhibitor use at randomization: 68% / 73% Food elimination diet at screening: 40% / 37% *Excluding dupilumab Q2W group

Results

- Efficacy data for the approved dose of dupilumab in EoE (300 mg QW) are summarized in Table 2.

Table 2 Efficacy results from clinical trial

Outcome	Part A				Part B			
	DUP	PBO	Relative Risk (95% CI)	Difference (95% CI)	DUP	PBO	Relative Risk (95% CI)	Difference (95% CI)
Histologic remission at Wk 24, n/N (%)	25/42 (59.5)	2/39 (5.1)	11.6 (2.94, 45.80)	57.0 (40.9, 73.1)	47/80 (58.8)	5/79 (6.3)	9.28 (3.90, 22.11)	53.5 (41.2, 65.8)
CFB to Wk 24 in DSQ score (0–84), LSM (SE)	–21.9 (2.5)	–9.6 (2.8)	—	–12.3 (–19.1, –5.5)	–23.8 (1.9)	–13.9 (1.9)	—	–9.9 (–14.8, –5.0)

Source: 3
CFB, Change from baseline; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low)

- The anticipated absolute effects for achieving histologic remission in 24 weeks are presented in Table 3.

Table 3 Absolute Effects for Achieving Histologic Remission for Dupilumab vs Placebo at Week 24 (Pooled Results)

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
Histologic remission	530 (434 to 628) more	1.9 (1.6, 2.3)	I

AAE, Anticipated absolute effect for achieving the outcome (calculated using modified Scottish Intercollegiate Guidelines Network [SIGN] method); I, Insufficient data to assess risk of bias (would downgrade for imprecision because the optimal information size was not met, the confidence intervals were wide, and because of fragility due to total number of events and for indirectness since eos/hpf is a surrogate measure); **NNT**, Number needed to treat for one additional patient to benefit

- Secondary efficacy results:
  - The FDA did not consider secondary outcome measures to be pivotal in showing efficacy or likely to be informative to patients or prescribers.
- Subgroup Analyses
  - Subgroup analyses by age using pooled results for parts A and B showed that dupilumab was superior to placebo in the percentage of patients ≥ 18 years old achieving peak count < 6 eos/hpf: 53/85 (62.4%) vs 5/83 (6.0%), respectively; difference (95% CI) 57.6 (45.8, 69.4).[3]
  - Dupilumab was also superior to placebo in subgroups by sex (male / female), race (white / other), and history of esophageal dilation (yes / no) in terms of peak esophageal intraepithelial eosinophil count ≤ 6 eos/hpf and change in DSQ total score.
- Supplementary FDA Analyses
  - Percentage of patients who experienced meaningful change in DSQ score using thresholds of ≥ 24, ≥ 22, or ≥ 20 points to define meaningful change (dupilumab vs placebo, respectively): 38.1% to 47.6% vs 15.4% to 25.6% in Part A; 53.8% to 58.8% vs 21.8% to 32.1% in Part B.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) and duration of an adequate therapeutic trial are summarized by outcome measure in Table 4.

Table 4 Onset of Benefit and Adequate Therapeutic Trial in Adult Subgroups

Trial	Outcome Measure	Onset of Significant Treatment Benefit (Wks)	Duration of an Adequate Therapeutic Trial (Wks)
Part A / B	LSM CFB in 14-d DSQ Total Score	~ 2 / 4	20 / ≥ 24

Source: 3
CFB, Change from baseline; LSM, Least square mean

Durability of Response

- The interim results of the ongoing extension study (Part C) supported sustained histologic and symptomatic treatment effects with dupilumab QW therapy in parts A and C.[3] However, only 40 patients received dupilumab for 52 weeks at the time of data submission. Further data are required to fully assess the long-term safety and risk of loss of efficacy with dupilumab therapy in patients with EoE.

Evidence Gaps

- Hospitalization or readmission
- Health-related Quality of Life
- Functional ability / Disability
- Patient Satisfaction

Network Meta-analyses

- No network meta-analyses have included dupilumab trials.

Safety Considerations in EoE

- Safety results from the phase 2 and phase 3 trials showed that the adverse effect profile of dupilumab in EoE was consistent with those for previously approved indications (i.e., atopic dermatitis, chronic rhinosinusitis with nasal polyps, and asthma).[3]
- **Withdrawals Due to Adverse Events**: 2% in both dupilumab and placebo groups
- **Common Adverse Events (≥ 2%)**: In dupilumab (N = 122) and placebo (N = 117) groups, respectively: injection site reactions (38% vs 33%); upper respiratory tract infections (18% vs 10%); arthralgia (2% vs 1%); herpes viral infections (2% vs 1%).
- **Conjunctivitis**: In dupilumab and placebo groups, respectively: 0% vs 2%
- **Keratitis**: In dupilumab and groups, respectively: 0% vs 0%

Other Therapeutic Options

- The 2020 American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (JTF) recommendations on the management of EoE recommended using IL-5I therapy only in the context of a clinical trial, as the drug was not FDA approved at the time.[4]
- Dietary therapy can be a symptomatically and histologically effective first-line treatment option for EoE.[4] However, adherence with food restrictions and the prolonged process of reintroduction of foods can substantially limit the usefulness of it. The AGA / JTF guideline suggested two types of dietary therapy over no therapy.
    - One type of dietary therapy is an empirical six-food elimination diet to avoid allergen exposure from the most common foods associated with EoE: milk, wheat, soy, egg, nuts, and fish / seafood.[5] The elimination diet requires a motivated patient and entails multiple endoscopies to determine the problematic food. (Conditional recommendation, low quality evidence)
    - The other dietary therapy is an elemental, exclusively amino acid-based formula diet. The elemental diet is expensive, poorly palatable, and can increase IgE-mediated allergies when food groups are reintroduced.[5] (Conditional recommendation, moderate quality evidence)
- Drug therapies include proton pump inhibitors (PPIs) and swallowed topical glucocorticoids. The general steps in drug therapy of EoE are shown in Table 5.

Table 5 Alternative Systemic Pharmacotherapies for EoE Based on Society Guidelines

Step in Therapy	Treatment Alternatives	Dosage	SOR, QE	Issues for Consideration
PPI	**Omeprazole** Lansoprazole **Pantoprazole** Rabeprazole	20 mg BID 30 mg BID 40 mg BID 20 mg BID	Suggest use of PPI over no treatment: Conditional, very low	Effective, off-label, first-line treatment option with favorable long-term safety. Adequate trial: Dosed 1–2 times daily for 8 wks
Swallowed topical glucocorticoids (STGs)	Budesonide Oral Viscous Slurry	1–2 mg BID	Recommend use of STGs over no treatment: Strong, moderate Suggest STGs rather than oral glucocorticoids: Conditional, moderate	Similar in efficacy to fluticasone STG.[6] Studies suggest initial histologic response with STGs and potential loss of histologic response with long-term therapy.[3] Viscous budesonide can be compounded using the inhalational suspension mixed with sucralose[6,7] or other vehicles.[8] Off-label use in the US. Induction: 12 weeks
	Fluticasone MDI	440–880 µg BID	See budesonide	Off-label use. Spray and swallow without inhaling. Adequate trial: 4–8 wks Slowly taper off dose after achieving remission to avoid relapse.
Systemic glucocorticoids	**Prednisone** Others	Typically 1–2 mg/kg/d in divided doses up to 60 mg/d	Suggest STGs rather than oral glucocorticoids: Conditional, moderate	Limited role in treatment of EoE, for severe or recalcitrant disease when other treatments are not feasible. Risk of toxicity limits long-term use.

Sources: 4,5
Bolded drugs are on VA National Formulary.

- Long-term maintenance therapy is conditionally recommended based on very low quality evidence.[4] Symptomatic remission does not reliably correlate with histologic remission.
- Endoscopic dilation may be useful to relieve dysphagia in patients with esophageal strictures.

Projected Place in Therapy

- **Epidemiology and Prevalence of EoE**. EoE is a chronic, inflammatory, non–IgE-mediated allergic disease of the esophagus that is primarily caused by food antigens. Adults with EoE frequently present with dysphagia and food impactions, symptoms associated with esophageal fibrosis. For each year of untreated EoE symptoms, the risk of stricture was estimated to increase by 9%.[9] In adults the incidence of EoE has been estimated to be 7.7 per 100,000 per year and appears to be increasing, and the prevalence was estimated to be 42.2 per 100,000.[10]
- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials were available to inform place in therapy, uncertain-quality evidence from a single, short-term (24-week) placebo-controlled trial supports the use of dupilumab primarily in patients with EoE including histologic confirmation of eosinophilic inflammation (≥ 15 eos/hpf) who have an average of ≥ 2 episodes of

dysphagia with intake of solids per week in the previous 4 weeks and who had an inadequate response to proton pump inhibitor therapy. The majority of patients (73%–75%) had also received prior swallowed topical glucocorticoids, which were disallowed in the 8 weeks before start of the study. Overall, short-term histologic benefits were large and improvements in dysphagia symptoms were clinically meaningful. Final results of the extension study and clinical experience are needed to assess the long-term effectiveness of dupilumab in controlling EoE.

- **Potential Place in Therapy in VHA**. Dupilumab may be a third-line pharmacologic treatment alternative in patients with EoE who have histologic evidence of eosinophilic infiltration, significant symptoms and who have an inadequate response or intolerance to trials of proton pump inhibitors (twice daily for ≥ 8 weeks), swallowed topical glucocorticoids (≥ 8 weeks), and dietary therapy, taking into consideration that the diets are suitable for patients who are strongly motivated and adherent and have access to dietitian support. A prior trial of systemic glucocorticoids is not required. The safety and efficacy of dupilumab in EoE patients who were in complete symptomatic remission or who had prior esophageal surgery, esophageal stricture unable to be passed with a 9- to 10-mm standard diagnostic endoscope, or critical esophageal stricture requiring dilation have not been evaluated. Use of dupilumab in these cases should be adjudicated case by case.

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