5-Grass Pollen Allergen Extract (ORALAIR®)

National PBM Drug Monograph

March 2016

VHA 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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 (FDA approved October 2014)	
Description/Mechanism of Action	5-Grass Pollen Allergen Extract (5-GPAE) (Oralair®) is a mixed allergen extract composed of 5 pollens: Sweet Vernal (*Anthoxanthum odoratum L*), Orchard (*Dactylis glomerata L*), Perennial Rye (*Lolium perenne L*), Timothy (*Phleum pratense L*), and Kentucky Blue Grass (*Poa pratensis L*). The mechanism of action of 5-GPAE or other allergen immunotherapies is currently unknown.
Indication(s) Under Review in this document (may include off label)	5-Grass Pollen Allergen Extract (5-GPAE) (Oralair®) is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product. 5-GPAE is approved for use in persons 10 through 65 years of age.
Dosage Form(s) Under Review	5-GPAE is a sublingual tablet with dosage strength expressed in Index of Reactivity (IR). Currently, there are 2 tablet dosage strengths available: 100 IR and 300 IR. Adults ages 18 to 65 should use 300 IR daily starting 4 months prior to and continued throughout the grass pollen season.
REMS	☒ REMS ☐ No REMS ☒ Post-marketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy category B

Executive Summary	
Efficacy	The FDA approval of 5-GPAE was based on the results of 5 double-blind, placebo-controlled clinical trials (one study in pediatric patients is not reviewed in this document). Since sublingual immunotherapy (SLIT) has been available outside of the U.S. for many years, two meta-analyses of SLIT were included in this review. • The trials included in the two meta-analyses of sublingual immunotherapy (SLIT) were conducted primarily in patients with moderate to severe symptoms of seasonal allergic rhinoconjunctivitis (SARC). From the two meta-analyses, improvements in SARC symptoms with SLIT versus placebo were relatively small with a standardized mean difference (SMD) ranging from 0.24 to 0.47 (SMD 0.2 to <0.5 represent small differences). o Dranitsaris and colleagues (2014) included 20 randomized, placebo-controlled trials evaluating the effectiveness of 5-GPAE, TGPAE, and SCIT for the prevention of seasonal allergic rhinitis symptoms. An indirect comparison was then made between the 3 potential immunotherapies. Efficacy impact of 5-GPAE compared to placebo was found to be small. o Di Bona and colleagues (2015) included 13 randomized, placebo-controlled trials to compare SLIT (5-GPAE combined with TGPAE) versus placebo for seasonal allergic rhinoconjunctivitis (SARC). A reduction in symptoms of SARC as well as rescue medication use were

analyzed and compared with placebo. Efficacy impact of 5-GPAE compared to placebo was found to be small.

- In the individual trials examining the efficacy and safety of 5-GPAE, eligible patients with SARC were randomized to receive 5-GPAE vs. placebo. There are no studies comparing 5-GPAE to standard therapies or subcutaneous immunotherapy (SCIT) for SARC. Trials did not enroll patients over 65 years of age.
- Active treatment involved preseason intake 5-GPAE daily for two to four months and then treatment continued through the grass allergy season, generally two months. In each of the trials, patients treated with 5-GPAE experienced improved symptoms vs. those treated with placebo. In general, percent improvement vs. placebo ranged from 22.9% to <40%, depending upon the outcome measure used. In the trial by Cox, et al.[5] an improvement of 46.5% in use of rescue medications was reported for SLIT therapy vs. placebo but daily symptom score was improved by 22.9% and adjusted symptom score (based upon use of rescue medications) by 26.3%.
- In the same trial by Cox, et al., improvements in disease specific quality of life measures were reported vs. placebo. Although exact values were not provided, it appeared from the graphic data that the 95% CI overlap in many of the individual measures included in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Additionally, minimally important changes in RQLQ are changes of >0.5. Although the measures were more adversely impacted in the placebo group, activities, practical problems, nasal symptoms, eye symptoms and overall changes increased by >0.5 in the SLIT group (Higher numbers or increases in RQLQ indicate worse quality of life).
- In a study that utilized a two-month vs. four-month preseason treatment with 5-GPAE over three allergy seasons, no differences in measures of allergy symptoms were reported between the active treatment groups but both were superior to placebo.[7]
- Baseline allergy symptom scores were not provided in all of the trials and therefore the severity of disease of patients enrolled in those trials is unclear. The studies were not limited to patients with poor symptom control on standard therapies for SARC (e.g., antihistamines, nasal steroids, etc.). However, in most of the studies, these standard therapies were permitted as rescue therapy.
- There is one meta-analysis of SLIT and pharmacotherapy for pollen-induced SARC that showed a treatment effect for all drug classes including SLIT, oral antihistamines, nasal corticosteroids and montelukast vs. placebo. In an indirect comparison using the weighted mean relative clinical impact on symptoms scores for each therapy, the analysis showed the following: 5-GPAE -29.6% (95% CI -23% to -37%), TGPAE -19.2% (95% CI -6% to -29%), antihistamines -15% (95% CI -3% to -26%), nasal corticosteroids -23.5% (95% CI -7% to -54%) and montelukast -6.5% (95% CI -3% to -10%).[13]
- There are no trials directly comparing SLIT, as sublingual tablets, to SCIT. However, there is one meta-analysis that indirectly compared SLIT to SCIT and SLIT or SCIT to placebo. The authors concluded that both methods of immunotherapy are effective at reducing allergy symptoms versus placebo but conclusive results showing consistent advantages of SLIT vs. SCIT are lacking. Trends favoring SCIT vs. SLIT in improving symptom and medication scores were noted.
- Trials did not include patients older than 65 years so the efficacy and safety of SLIT in that population have not been established.
- The efficacy and safety of SLIT in perennial allergic rhinitis is less well established compared to seasonal allergic rhinitis.
- SLIT is not indicated for and should not be used for immediate control of allergy symptoms.

Safety	• **Labeling for 5-GPAE contains a boxed warning regarding the potential for causing life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema. This was based on 6 safety trials that randomized 1038 subjects. Also included in the boxed warning:**
	  ○ **Do not administer to patients with severe, unstable or uncontrolled asthma**
	  ○ **Observe patients for at least 30 minutes after the initial sublingual dose (tablet).**
	  ○ **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.**
	  ○ **5-GPAE may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction.**
	  ○ **5-GPAE may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.**
	• The safety of 5-GPAE is from clinical trials in patients with seasonal grass pollen allergies in which 5-GPAE is initiated 2-4 months before the grass pollen allergy season and continued through the season. One trial evaluated 5-GPAE for 3 consecutive allergy seasons with two additional years of follow-up.
	• 5-GPAE is well tolerated with the most common adverse effects consisting of mouth and ear pruritus and minor oral irritation and swelling.
	• 5-GPAE is contraindicated in patients with severe, unstable or uncontrolled asthma, a history of eosinophilic esophagitis, and history of severe systemic or local reaction to SLIT and in patients with a hypersensitivity to any of the inactive ingredients.
	• The safety of initiating therapy with 5-GPAE during grass pollen season or after skipped doses has not been studied but the risk for adverse events may be increased.
	• Withdrawal due to adverse events was reported in approximately 5-6% of patients receiving 5-GPAE.
	• 5-GPAE may not be appropriate for patients with certain medical conditions that could reduce a patient's chance of survival in case of an allergic reaction and epinephrine administration. Compromised lung function, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension are examples of potential problematic medical conditions. Or in those patients receiving concomitant medications that may potentiate or inhibit epinephrine.
	• In post marketing safety studies with a total of 1728 individuals (808 adults and 920 kids 5-17) receiving 5-GPAE, the following adverse reactions were reported: anaphylactic reaction, oral allergy syndrome, flushing, dyspnea, laryngeal edema, and diarrhea
	• Spontaneous post-marketing reports reported after the approval of 5-GPAE include: autoimmune thyroiditis, eosinophilic myocarditis, eosinophilic esophagitis, palpitations, tachycardia, hypotension, loss of consciousness, circulatory collapse, malaise, pallor, peripheral vascular disorder, stridor, angioedema, face edema, weight decreased, wheezing, exacerbation of asthma, chest discomfort, oropharyngeal paresthesia, oropharyngeal blistering, headache, dizziness, tinnitus, asthenia, somnolence, anxiety, rash, pruritus, salivary gland enlargement and/or hypersecretion, dry mouth, dry eye, influenza-like syndrome, lymphadenopathy, eosinophil count increased. Since these reactions are reported from a population of uncertain size, it's not always possible to reliably estimate their frequency or establish causality.
	• Patients who have escalating or persistent local reactions associated with 5-GPAE should have their therapy reevaluated and consider discontinuation of

	therapy. • The FDA has required the manufacturer of 5-GPAE to conduct an observational post-marketing study in 6,000 patients ages 10-65 years to further evaluate safety.
Projected Place in Therapy	• Consistent with more recent U.S. guidelines in the management of allergic rhinitis and due to safety considerations, therapy with 5-GPAE or other SLIT therapies can be considered in those patients (18-65 years of age) with an inadequate response to a therapeutic trial of intranasal corticosteroids and oral antihistamines. • The decision to prescribe SLIT or SCIT should be limited to VA Allergy/Immunology and Ear Nose and Throat specialists or locally designated experts.
Potential Impact	• In patients who are identified as appropriate candidates for allergen immunotherapy, an advantage of SLIT over subcutaneous immunotherapy (SCIT) may be the ability for patients to self-administer the sublingual tablets at home, after the initial dose. A physician or provider must supervise the patient taking the first dose of 5-GPAE in a healthcare setting, in the event of a serious allergic or anaphylactic reaction. • All patients must be prescribed auto-injectable epinephrine and be instructed on its proper use for emergency self-administration.

Background

Purpose for review

5-GPAE is sublingual five-grass pollen allergen extract currently approved for the treatment of grass pollen-induced allergic rhinitis.

Issues to be determined:
- ✔ Evidence of need
- ✔ Does 5-GPAE offer advantages to currently available alternatives?
- ✔ Does 5-GPAE offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives	Other Considerations
1st generation H1 Antagonists • Diphenhydramine • Chlorpheniramine	1st generation antihistamines are known to be sedating and are medications on the Beers Criteria list
2nd generation H1 Antagonists • Cetirizine • Loratadine	Less sedating than 1st generation antihistamines
Intranasal Steroids • Fluticasone	
Nasal Decongestants • Oxymetazoline • Phenylephrine • Sodium Chloride	Oxymetazoline is limited to 3 days use due to rebound nasal congestion
Oral Decongestants • Phenylephrine • Pseudoephedrine	Patients should not use if they have uncontrolled hypertension, BPH/issues with urinary retention
Mast Cell Stabilizers • Cromolyn nasal solution	
Leukotriene Receptor Antagonist • Montelukast	Limited Efficacy
Intranasal Anticholinergics • Ipratropium	Limited Efficacy Multiple times per day
Non formulary Alternatives	**Other Considerations**

Oral Antihistamines • Fexofenadine • Levocetirizine • Desloratadine	
Intranasal Steroids • Beclomethasone • Budesonide • Flunisolide • Mometasone • Triamcinolone	
Intranasal Antihistamine • Azelastine	
Leukotriene Receptor Antagonist • Zafirlukast	
Subcutaneous Immunotherapy	Requires weekly/monthly injections

Efficacy (FDA Approved Indications)

Literature Search Summary
A literature search was performed on PubMed (1966 to August 2014) using the search terms <Oralair; grass pollen allergen; sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass; sublingual immunotherapy (SLIT); seasonal allergies; rhinoconjunctivitis >. 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. Since SLIT therapy has been available outside of the U.S. for years, published systematic reviews and meta-analyses were also included.

Review of Efficacy

Introduction[1]:
The FDA approval of 5-GPAE was based on the results of 5 double-blind, placebo-controlled clinical trials (one study in pediatric patients is not reviewed in this document).

- Study participants had at least a two-year history of rhinoconjunctivitis symptoms triggered by grass pollen allergies. For European studies, subjects had a positive skin prick test to 5-grass pollen extract and positive in vitro test for tomography grass-specific serum IgE. In the U.S. studies, subjects had a positive skin prick test to Timothy grass pollen extract.
- Patients were excluded from trials if their asthma symptoms were classified as more than mild intermittent asthma and those likely to have allergic rhinoconjunctivitis symptoms from sensitization to allergens other than grass pollens during the allergy season.
- The trials utilized:[2-7]
    - The daily Rhinoconjunctivitis Total Symptom Score (RTSS, range 0-18): The total of the six individual symptom scores (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) each graded by participants on a 0 (no symptoms) to 3 (severe symptoms) point scale (0-18 possible points, higher scores indicate more severe symptoms).
    - The daily Rescue Medication Score (RMS, range 0-3): Grades the intake of rescue medication as 0 = absent, 1 = antihistamine, 2 = nasal corticosteroid, 3 = oral corticosteroid. In case of multiple rescue medications being administered, the higher score was retained.
    - The daily Combined Score (CS, range: 0-3): Considers the total symptom score as well as the daily use of rescue medications score.
    - Meta-analyses by Dranitsaris et al (2014) and Di Bona et al (2015) used standardized mean differences (SMD), which measures the effect size between the experimental and placebo groups. An SMD of < 0.2 was considered trivial, > 0.2-0.5 as small, >0.5-0.8 as moderate, and >0.8-1.2 as important.
- The Agency for Health Research and Quality (AHRQ) has indicated that: 1) a 30% improvement vs. placebo is clinically meaningful; 2) in a trial assessing TNSS on a scale from 0-12, authors considered a change of 0.52 as a minimally important clinical change (The trial by Didier used a RTSS 0-18 point scale). When experts from AHRQ were questioned regarding minimally clinically important reductions in TNSS, two experts suggested a

reduction in 4 points was clinically relevant while one expert felt that a 2 point reduction in TNSS was relevant.[8]
- The World Allergy Organization (WAO) recognizes a 20% difference as the standardization of efficacy for clinical trials with allergen-specific immunotherapy for respiratory allergy.[9-10]
- Cohen, et al. criteria for significance in clinical practice is not met for differences of <1 point.[11]

TABLE 1: SYSTEMATIC REVIEWS AND META-ANALYSES

Dranitsaris et al. (2014)[2]

Methods:
- Of the 258 citations reviewed for eligibility, 20 trials were included. Trials were excluded for a number of reasons including the lack of a placebo control group, less than 25 patients per treatment group, enrollment of only asthmatics, duplicate publication, evaluation of treatment for allergic conditions other than AR and a lack of an assessment of AR symptom control.
- The objective of the meta-analysis was to compare symptom control in patients with allergic rhinitis (AR) and discontinuation of 5-GPAE, Timothy Grass Pollen Allergen Extract (Grastek® in the U.S.; Grazax® in Europe) (TGPAE), and subcutaneous immunotherapy (SCIT) due to adverse events. A cost analysis was also completed and assumed no rescue epinephrine injections would be provided to patients on SLIT. The use of rescue medications to control allergy symptoms was not included as an outcome measure since trials did not consistently report standard deviation or standard error associated with this outcome.
- Since there were no trials that directly compared these therapies, the method of comparison was indirect using placebo as the control, active drug as the independent variable, and use of a meta regression analysis.
- The following data were extracted: baseline patient characteristics, data collection methods, definition of primary and secondary outcomes, duration of immunotherapy, trial duration, use of rescue medication, changes in patient quality of life, patient compliance, trial setting, geographic region, and overall withdrawal and withdrawal due to adverse events.
- 15 of 20 studies enrolled adults, 2 studies were conducted exclusively in children and 3 studies had mixed populations. 15 of 20 studies were conducted in Europe, 3 were in North America and 2 were global trials.
- 5-GPAE was administered for 4 months prior to grass pollen season and for approximately 2 months during the pollen season. Grazax was administered once daily for the year and SCIT was administered weekly for 6 months and then monthly for the remaining 6 months OR weekly for 3 months prior to allergy season and then monthly for 4 months. These dosing schedules were assumed for years 2 and 3 for the economic analysis.

Results:
- Median duration of pre-seasonal therapy was 2.1 months and total duration of therapy was 5.3 months.
- 5-GPAE had an SMD = -0.47 (-0.56 to -0.38), P <0.001 (I^2 = 0%); TGPAE had an SMD = -0.34 (-0.47 to -0.21), P <0.001 (I^2 = 57.5%); SCIT had an SMD = -0.3 (-0.39 to -0.2), P <0.001 (I^2 = 4.6%) compared to placebo.
- The indirect comparison suggested 5-GPAE had improved efficacy compared to TGPAE (-0.18 [-0.32 to -0.035], P = 0.018) and placebo (-0.21 [-0.36 to -0.066], P = 0.007) in terms of AR symptom relief in the meta regression model.
- 5-GPAE demonstrated improved efficacy compared to SCIT for AR symptom relief using the univariate method of Bucher and colleagues (-0.18 [-0.31 to -0.047], P = 0.033) but not to TGPAE (non-inferior).
- Adjusted by duration of therapy, treatment discontinuation rate due to adverse events for 5-GPAE was 5.6% (RR 4.86, 95% CI 2.41 to 9.79, P <0.001); TGPAE was 3.5% (RR1.90, 95% CI 1.21-7.10, P=0.006); and SCIT was 2.7% (RR 3.16, 95% CI 1.4-7.10, P=0.005). All comparisons vs. placebo. There were no differences when active agents were compared to each other (5-GPAE vs. TGPAE p>0.058 and 5-GPAE vs. SCIT p=0.39).
- Quality of Evidence – Moderate quality (indirect comparison)

Comments:
- Indirect evidence cannot be used to claim superiority of one agent over another when they are not studied directly in the same clinical trial and same population, etc. To determine superiority of one active treatment over another, the agents must be studied directly in a prospective, randomized and controlled clinical trial.
- A possibility of publication bias was reported, noting asymmetry in the funnel plot and a significant p-value using the Egger test (p=0.035). Smaller studies appeared to have larger effect sizes.

- The economic analysis did not include the cost of a rescue epinephrine auto-injection for the oral grass pollen therapies. In the US, both oral SLIT agents contain boxed labeling directing providers to prescribe a rescue epinephrine auto-injection device for home use.
- The authors refer to two other indirect analyses comparing SLIT to SCIT which both found SCIT superior to SLIT in controlling symptoms of allergic rhinitis.[12-13] These analyses were not limited to sublingual tablet immunotherapy (approved in the US) but also included drops which are not available in the US.

Di Bona et al. (2015)[3]

Methods:

- In order to be included, trials must have compared grass pollen immunotherapy tablets to placebo, conducted in patients with or without mild allergic asthma to grass pollen assessed by specific tests (skin test and grass pollen specific IgE levels) and reported the symptom and medication score.
- The results of 13 randomized, placebo-controlled trials (n=4659 patients) were used to assess the efficacy and safety of SLIT for SARC to grass pollen vs. placebo.
- The symptom score (SS) and medication score (MS) were assessed as outcome measures for the trials, regardless of whether they were primary endpoints in the original trial. The SS and MS quantified patients' symptoms of SARC and use of rescue medications for symptomatic relief while taking SLIT, respectively.
- Since 11/13 studies measured the SS using a scale of 0-18 (higher number indicates worse symptoms), these studies were used to find the mean difference vs. placebo.

Efficacy Results:

- Data were available for symptom score in all 13 included trials and medication score was available in 12/13 of the studies. Severity of SARC symptoms was rated as moderate to severe in most of the trials.
- Duration of treatment exposure: 5-GPAE: preseason=16.7 weeks and 5.7 weeks during grass pollen season. TGPAE: preseason=14.3 weeks and 8.5 weeks during grass pollen season. The results of studies on 5-GPAE vs. placebo and TGPAE vs. placebo for SARC were combined.
- The pooled results indicated that of 4,659 patients used to calculate an average SS, the SMD was -0.28 (-0.37 to -0.19), $P < 0.001$(heterogeneity: $I^2 = 54.2\%$, $\tau^2 = 0.0142$) vs. placebo; 6 of 13 studies did not reach statistical significance for improved SS of SLIT vs. placebo. Exclusion of a single study reduced heterogeneity: I^2=28% and SMD of -0.24 (-0.32 to -0.16, $p<0.001$).
- The mean difference in symptom score vs. placebo: -0.83 (-1.03 to -0.63, $p<0.001$); 4 of the studies did not reach statistical significance.
- The pooled MS was calculated from 4,558 patients and the SMD was -0.24 (-0.31 to -0.17), $P < 0.001$ (heterogeneity: $I^2 = 21.7\%$, $\tau^2 = 0.0031$); 5 of 12 studies did not reach statistical significance for MS for SLIT vs placebo.
- A sub-group analysis suggested a greater benefit of SLIT in European vs. American studies and in 5-GPAE vs. TGPAE and in smaller studies.
- Quality of Evidence – Moderate

Comments:

- SMD for both symptom and medication score was -0.28 and -0.24, respectively, suggesting a small benefit of SLIT therapy vs. placebo in patients with moderate to severe SARC.
- The authors discuss the small benefit of SLIT in reducing symptoms scores <1 point vs. placebo and note that rescue therapy with standard medications for allergy symptoms were likely responsible for symptom relief seen in both groups.
- The accompanying editorial emphasizes the small effect of SLIT therapy on reducing SARC symptoms and medication use; with even a smaller effect in American vs. European populations. The high incidence of adverse events is also noted in patients receiving SLIT (70% SLIT vs. 44% placebo) and the author questions the place in therapy of these agents in patients suffering from seasonal grass pollen allergies in comparison to standard therapies or SCIT for SARC.[14]

I^2=test for statistical heterogeneity (>50% may represent significant heterogeneity), SARC-seasonal allergic rhinoconjunctivitis, SCIT=subcutaneous immunotherapy, SLIT=sublingual immunotherapy, SMD=Standardized mean difference.

TABLE 2. RANDOMIZED, CONTROLLED TRIALS OF FIVE-GRASS POLLEN ALLERGEN EXTRACT

Didier et al. (2007)[4]

Methods:

- Double-blind, placebo-controlled European study designed to evaluate the efficacy, safety, and optimal dosage of 5-GPAE in patients 18-45 years of age.
- Enrolled 628 patients with moderate-to-severe seasonal grass pollen-related allergic rhinoconjunctivitis in 10 European countries.
- Excluded patients likely to have allergic rhinoconjunctivitis symptoms from sensitization to allergens other than grass pollens during the allergy season and patients who have received immunotherapy for grass allergens in the past.
- Patients were given 5-GPAE 100 IR, 300 IR, 500 IR, or placebo sublingually once daily 4 months before the expected start of grass pollen season and continued through one entire season.
- Primary efficacy endpoint was the impact of 5-GPAE on the RTSS; the score ranked symptoms of sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes from 0 to 3 (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms).

Efficacy Results:

- Patients receiving the 300 IR and 500 IR 5-GPAE tablets had a statistically significant mean decrease in RTSS vs. placebo: 300IR -1.39 [-2.09, -0.69], P=0.0001; 500 IR -1.22 [-1.91, -0.53], P =0.0006
- Patients receiving the 100 IR dose did not have a statistically significant decrease in RTSS: -0.26 [-0.95, 0.43] vs. placebo, P=0.46
- There was a 37% improvement in the 300 IR and 35.1% improvement in the 500 IR groups.
- Median percent days using rescue medications: 300 IR=10.62% (95% CI 0-29.77, p=0.0194 vs. placebo [NS]), 500 IR: 10.53% (95% CI 0-40.63, p=0.1611 vs. placebo [NS]), Placebo: 19.72% (95% CI 0-46.67)
- Quality of Evidence – Moderate

Comments:

- Median percentage of days using rescue medications did not differ between active groups and placebo, 95% CI were wide for each group and overlapped.

Cox et al. (2012)[8]

Methods:

- Double-blind, placebo-controlled, parallel group, randomized, per-protocol, multicenter study at 51 sites in the U.S.
- Enrolled 473 adult men and women 18-65 years of age with documented grass pollen-related allergic rhinitis for at least the 2 previous grass pollen seasons, a positive skin prick test response to timothy grass, a Retrospective RTSS of ≥ 12 during the previous grass pollen season and an FEV1 ≥ 80%. Most participants (78%) were polysensitized to ragweed, trees (oak, ash, maple, and mountain cedar), house dust mites, animal dander, and molds and 25% had intermittent asthma.
- Treatment started 4 months before the expected start of the grass pollen period at each study center and patients received either a 300 IR or placebo tablet taken sublingually at the same time every day. The first 3 doses were taken at the study site so that patients could be monitored, but the remaining doses were taken at home with rescue medications permitted (antihistamines and nasal corticosteroids) for intolerable symptoms.
- The primary efficacy endpoint was determined by a combined score (CS), which combines symptom (RTSS) and rescue medication (RMS) scores. CS=[(RTSS/6)+RMS]/2
- The secondary efficacy criteria included RTSS, RMS, and daily adjusted symptom score (AdSS; which adjusts the RTSS if patient used rescue medications).

Efficacy Results:

- Treatment duration averaged 126.6 days before pollen period and 42.8 days during the pollen period.
- Retrospective RTSS was 14.9 in both groups.
- Statistically significant difference between the 2 treatment groups with difference in least-squares (LS) means of -0.13 (95% CI, -0.19 to -0.06) of daily CS scores corresponds to a relative LS mean difference from placebo of -28.2%.

- On the basis of previous study results, a daily CS LS mean of 0.65 in the placebo group was assumed. The expected mean difference between the 300 IR and placebo groups during the pollen period was defined as -0.14 with a common SD of 0.50 to correspond to a relative difference of more than 20%. The study had 80% power to detect these differences. The 28.2% relative LS mean difference vs placebo in daily CS exceeded the 20% value recommended by the World Allergy Organization as the standardization of efficacy for clinical trials with allergen-specific immunotherapy for respiratory allergy.
- Daily RTSS (22.9%), RMS (46.5%), and AdSS (26.3%) were also significantly lower in treatment group vs placebo; all individual symptom scores were statistically significant except "itchy nose" vs. placebo but the "20% improvement threshold" was not reached for sneezing, itchy nose, or nasal congestion vs. placebo.
- Sensitization status and asthma status were not significant covariates, meaning they did not affect the primary efficacy endpoint.
- Significant relative mean difference in overall rhinoconjunctivitis quality of life questionnaire (RQLQ) score was observed in the 300 IR treatment group as compared to placebo. Although exact values are not provided, it appears from the graphic data that the 95% CI overlap in many of the individual measures included in the RQLQ. Additionally, minimally important changes in RQLQ are changes of >0.5. Although the measures were more adversely impacted in the placebo group, activities, practical problems, nasal symptoms, eye symptoms and overall changes increased by >0.5 in the SLIT group. (Higher numbers or increases in RQLQ indicate worse quality of life)
- Quality of Evidence – Moderate

Horak et al. (2009)[5]

Methods:

- Randomized, double-blind, placebo-controlled trial that took place in Europe (Austria) and utilized an allergen challenge chamber (ACC).
- Enrolled 89 men and women between 18 and 50 years old with a documented history of moderate-to-severe seasonal grass pollen-related allergic rhinoconjunctivitis for at least the previous 2 pollen seasons.
- Patients had to display a baseline symptomatic reaction to an allergen challenge test (an RTSS of at least 7 out of 18) within 2 hours of being challenged.
- Patients were treated with 5-GPAE 300 IR or placebo tablets sublingually once daily for 4 months; allergen challenges took place at baseline and after 1 week and 1, 2, and 4 months of treatment.
- Allergen challenges were carried out in in the Vienna Challenge Chamber (VCC); patients scored the 6 allergic rhinoconjunctivitis symptoms (as a part of the RTSS) every 15 minutes during the 4-hour challenges and nasal secretions and nasal airflow were measured every 30 minutes.
- Rescue medications were not allowed (antihistamines, decongestants, antileukotrienes, cromones, corticosteroids, and topical nasal or ocular treatments); this was possible because the study took place outside of grass pollen allergy season.
- The primary endpoint was the Average Rhinoconjunctivitis Total Symptom Score (ARTSS). Patients score 6 individual rhinitis symptoms on a 4-point scale, range of scores: 0-18, higher scores indicate more severe allergy symptoms.

Efficacy Results:

- In the intention-to-treat population (N = 89), a significant difference in ARTSS vs. placebo was observed for patients at 1 month (P= 0.0042), 2 months (P= 0.0203) and 4 months (P= 0.0007) after starting 5-GPAE.
- In the 5-GPAE group, the ARTSS went from 7.4 at week 1 to 5.89 at month 1 to 5.09 at month 2 to 4.85 at month 4. ARTSS for placebo was 7.26 at baseline and mean of 6.87 at 4 months. ARTSS for other months are not specifically reported for placebo except at 2 months in which the ARTSS was lowest=6.21.
- The relative mean improvement of ARTSS of the 5-GPAE group vs. placebo was 29.3% (median = 33.3%) at the end of treatment (month 4).
- No significant difference was found between the 5-GPAE group vs. placebo in nasal airflow or nasal secretion weight after 4 months of treatment.
- Quality of Evidence - Moderate

Randomized Long-Term Study
Didier et al. (2011)[6]
Methods:

- Double-blind, placebo-controlled, multinational (mostly European countries, Canada, and Russia) study that evaluated the long-term efficacy and safety of 5-GPAE.
- Enrolled 633 adult men and women 18-50 years of age who had demonstrated sensitization to 5-grass-pollen allergens and reported the previous pollen season's most severe rhinoconjunctivitis symptoms to calculate a retrospective RTSS.
- Treatment was initiated 4 months before the start of the pollen season and patients received either placebo, 2 months of 5-GPAE 300 IR (and 2 months of placebo) once daily, or 4 months of 5-GPAE 300 IR once daily.
- Treatment continued through the pollen season every year and was given for a total of 3 years (2007-2009); patients were followed for 2 additional non-treatment years.
- The six symptoms of rhinoconjunctivitis were assessed daily to get a RTSS score.
- The daily adjusted symptom score (AdSS) was used to adjust for symptom bias caused by use of rescue medications—using rescue medications on a certain day could impact patients' rankings or assessment of symptoms.

Efficacy Results:

- The primary endpoint found that the mean average adjusted symptom score (AAdSS) over the 3rd pollen season was reduced by 34.8% in the 5-GPAE 4-month group and 37.7% in the 5-GPAE 2-month group, respectively, compared to placebo.
- Absolute differences in the AAdSS during the 3rd pollen season compared to placebo were -1.81 (-2.61 to -1.02) for the 5-GPAE 4-month group and -1.96 (-2.79 to -1.16) for the 5-GPAE 2-month group ($P < 0.0001$ for both).
- No differences were noted between the 2 month and 4 month preseason treatment with 5-GPAE.
- Quality of Evidence – moderate

AdSS=daily adjusted symptom score, LS=least-squares mean, RMS=rescue medication score, RQLQ=rhinoconjunctivitis quality of life questionnaire, RTSS=rhinoconjunctivitis total symptom score

Summary of Findings[2-7]

- The trials included in the two meta-analyses of sublingual immunotherapy (SLIT) were conducted primarily in patients with moderate to severe symptoms of seasonal allergic rhinoconjunctivitis (SARC). From the two meta-analyses, improvements in SARC symptoms with SLIT versus placebo were relatively small with a standardized mean difference (SMD) ranging from 0.24 to 0.47 (SMD 0.2 to <0.5 represent small differences).
    - Dranitsaris and colleagues (2014) included 20 randomized, placebo-controlled trials evaluating the effectiveness of 5-GPAE, TGPAE, and SCIT for the prevention of seasonal allergic rhinitis symptoms. An indirect comparison was then made between the 3 potential immunotherapies. Efficacy impact of 5-GPAE compared to placebo was found to be small.
    - Di Bona and colleagues (2015) included 13 randomized, placebo-controlled trials to compare SLIT (5-GPAE combined with TGPAE) versus placebo for seasonal allergic rhinoconjunctivitis (SARC). A reduction in symptoms of SARC as well as rescue medication use were analyzed and compared with placebo. Efficacy impact of 5-GPAE compared to placebo was found to be small.
- In the individual trials examining the efficacy and safety of 5-GPAE, eligible patients with SARC were randomized to receive 5-GPAE vs. placebo. There are no studies comparing 5-GPAE to standard therapies or subcutaneous immunotherapy (SCIT) for SARC. Trials did not enroll patients over 65 years of age.
- Active treatment involved preseason intake 5-GPAE daily for two to four months and then treatment continued through the grass allergy season, generally two months. In each of the trials, patients treated with 5-GPAE experienced improved symptoms vs. those treated with placebo. In general, percent improvement vs. placebo ranged from 22.9% to <40%, depending upon the outcome measure used. In the trial by Cox, et al.[8] an improvement of 46.5% in use of rescue medications was reported for SLIT therapy vs. placebo but daily symptom score was improved by 22.9% and adjusted symptom score (based upon use of rescue medications) by 26.3%.
- In the same trial by Cox, et al., improvements in disease specific quality of life measures were reported vs. placebo. Although exact values were not provided, it appeared from the graphic data that the 95% CI overlap in many of the individual measures included in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Additionally, minimally important changes in RQLQ are changes of >0.5. Although the measures were more

adversely impacted in the placebo group, activities, practical problems, nasal symptoms, eye symptoms and overall changes increased by >0.5 in the SLIT group (Higher numbers or increases in RQLQ indicate worse quality of life).

- In a study that utilized a two-month vs. four-month preseason treatment with 5-GPAE over three allergy seasons, no differences in measures of allergy symptoms were reported between the active treatment groups but both were superior to placebo.[7]
- Baseline allergy symptom scores were not provided in all of the trials and therefore the severity of disease of patients enrolled in those trials is unclear. The studies were not limited to patients with poor symptom control on standard therapies for SARC (e.g., antihistamines, nasal steroids, etc.). However, in most of the studies, these standard therapies were permitted as rescue therapy.
- There is one meta-analysis of SLIT and pharmacotherapy for pollen-induced SARC that showed a treatment effect for all drug classes including SLIT, oral antihistamines, nasal corticosteroids and montelukast vs. placebo. In an indirect comparison using the weighted mean relative clinical impact on symptoms scores for each therapy, the analysis showed the following: 5-GPAE -29.6% (95% CI -23% to -37%), TGPAE -19.2% (95% CI -6% to -29%), antihistamines -15% (95% CI -3% to -26%), nasal corticosteroids -23.5% (95% CI -7% to -54%) and montelukast -6.5% (95% CI -3% to -10%).[15]
- There are no trials directly comparing SLIT, as sublingual tablets, to SCIT. However, there is one meta-analysis that indirectly compared SLIT to SCIT and SLIT or SCIT to placebo. The authors concluded that both methods of immunotherapy are effective at reducing allergy symptoms versus placebo but conclusive results showing consistent advantages of SLIT vs. SCIT are lacking. However, trends were noted which favored SCIT vs. SLIT in improving symptom and medication scores.[13]
- Trials did not include patients older than 65 years so the efficacy and safety of SLIT in that population have not been established.
- The efficacy and safety of SLIT in perennial allergic rhinitis is less well established compared to seasonal allergic rhinitis.
- SLIT is not indicated for and should not be used for immediate control of allergy symptoms.

Potential Off-Label Use

- None noted.

Safety[1]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• **5-GPAE can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema.** • **Do not administer to patients with severe, unstable or uncontrolled asthma.** • **Observe patients in the office for at least 30 minutes after the initial sublingual dose (tablet).** • **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.** • **5-GPAE may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction.** • **5-GPAE may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.**
Contraindications	• Severe, unstable or uncontrolled asthma • History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy • A history of eosinophilic esophagitis • Hypersensitivity to any of the inactive ingredients contained in this product
Warnings/Precautions	• Patients with escalating or persistent local reactions to 5-GPAE should be re-

evaluated for its use and consider discontinuing therapy.

- The initial dose should be administered in a healthcare setting under the supervision of a physician. Patients should be observed in the office for at least 30 minutes after taking 5-GPAE.
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.
- Educate patients on signs and symptoms of a severe allergic reaction.
- If patients experience oral inflammation or have oral wounds, such as those following oral surgery or dental extraction, patients should stop treatment with 5-GPAE to allow complete healing of the oral cavity.
- 5-GPAE may not be suitable for patients who will not be compliant with treatment for 4 months prior to and throughout the grass-pollen season.
- 5-GPAE may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction or increase the possibility for an adverse event after epinephrine administration (e.g. Acute or chronic compromised lung function, unstable angina, arrhythmias, recent myocardial infarction or uncontrolled hypertension).
- 5-GPAE may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include:
    - Beta-adrenergic blockers
    - Alpha-adrenergic blockers
    - Ergot alkaloids
    - Tricyclic antidepressants
    - Levothyroxine
    - Monoamine oxidase inhibitors
    - Certain antihistamines such as chlorpheniramine and diphenhydramine
    - Cardiac glycosides
    - Diuretics
- Eosinophilic esophagitis has been reported with SLIT. In patients who experience severe or persistent gastro-esophageal symptoms (e.g., dysphagia or chest pain), therapy with 5-GPAE should be stopped and a diagnosis of eosinophilic esophagitis should be considered.
- 5-GPAE has not been evaluated in patients with moderate to severe asthma or in those asthmatics that require daily medications.
- The concomitant use of other allergen immunotherapy with 5-GPAE has not been studied but may result in a greater risk for local or systemic reactions to SCIT or SLIT.
- The risk of allergic type reactions may increase if 5-GPAE is initiated during grass pollen season.

Safety Considerations

Meta-Analyses and Clinical Trials

Clinical Trial	Adverse Events
Dranitsaris, et al.[2] Meta-analysis	Safety was measured in relative risk (RR) for discontinuing treatment vs. placebo: 5-GPAE: RR 4.88 (95% CI 2.49-9.58) TGPAE: RR 1.90 (95% CI 1.21-3) SCIT: RR 3.16 (95% CI 1.4-7.10) Discontinue therapy due to adverse events: 5-GPAE: 5.6% TGPAE: 3.5%

	SCIT: 2.7%
Di Bona, et al.[3] Meta-analysis	Overall adverse events reported: SLIT: 70% Placebo: 44.5% **Most events were reported as moderate in severity* Treatment related adverse events: SLIT: 61.3% Placebo: 20.9% Withdrawal due to adverse events: SLIT: 6% Placebo: 2.2% *No anaphylactic reactions were reported, however there were events that required epinephrine SLIT: n=9 Placebo: n=3 Treatment related events that required epinephrine: SLIT: n=7 Placebo: n=0
Didier, et al.[4] Clinical trial	Overall adverse events reported: SLIT (300 IR): 62.6% Placebo: 48.7% **Most events were reported as mild to moderate in severity* Withdrawal due to adverse events: SLIT (300 IR): 5.2% Placebo: 0% *No serious adverse events were considered to be related to treatment*
Cox, et al.[5] Clinical trial	Overall adverse events reported: SLIT (300 IR): 82% Placebo: 76.7% Treatment related adverse events: SLIT: 54.9% Placebo: 22.5% Withdrawal due to adverse events: SLIT (300 IR): 6.4% Placebo: 0.8%;
Horak, et al.[6] Clinical trial (Allergen challenge chamber)	Treatment related adverse events: SLIT: 60% Placebo: 31.8% **All events were reported as mild in severity* Withdrawal due to adverse events: SLIT (300 IR): n=1 Placebo: n=2
Didier, et al.[7] Clinical trial	Treatment related adverse events: YEAR 1: SLIT (300 IR): 71% (4 month group); 57% (2 month group) Placebo: 25.1% YEAR 2: SLIT (300 IR): 58.7% (4 month group); 47.2% (2 month group) Placebo: 9.3% YEAR 3: SLIT (300 IR): 45% (4 month group); 37.2% (2 month group) Placebo: 3.6% **Serious ADEs occurred in 11 pts in 1st year: 1 placebo, 3 in 2 month group and 7 in 4 month group (3 of the 4-month group related to treatment: n=1 severe local reaction, n=1 angioedema, n=1 diarrhea)* Withdrawal due to adverse events: YEAR 1: SLIT (300 IR): 6.3% (4 month group); 5.8% (2 month group) Placebo: 0.9% YEAR 2: SLIT (300 IR): 3% (4 month group); 0.6% (2 month group) Placebo: 0.5%

	YEAR 3: SLIT (300 IR): 0% (4 month group); 0% (2 month group) Placebo: 0% *Oral pruritis, throat irritation and mouth edema were most commonly reported.*

- 5-GPAE was largely well tolerated in clinical trials. The most common adverse effects consist of pruritus in the mouth and ear and minor oral irritation and swelling.
- Serious adverse effects are rare with 5-GPAE but can occur. Therefore, the initial dose of 5-GPAE must be administered in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or local allergic reaction.
- Auto-injectable epinephrine should be prescribed to all patients receiving 5-GPAE.
- Withdrawal due to adverse events was reported in approximately 5-6% of patients receiving 5-GPAE.
- 5-GPAE may not be appropriate for patients with certain medical conditions that could reduce a patient's chance of survival in case of an allergic reaction and epinephrine administration. Compromised lung function, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension are examples of potential problematic medical conditions. Or in those patients receiving concomitant medications that may potentiate or inhibit epinephrine.

Adverse Reactions

Common adverse reactions	Incidence ≥ 5%: oral pruritus, throat irritation, ear pruritus, mouth edema, tongue pruritus, cough, oropharyngeal pain Incidence < 2%: dysphagia, nausea, vomiting, esophageal pain, gastritis, and gastro-esophageal reflux
Death/Serious adverse reactions	• Allergic reactions and anaphylaxis, angioedema, laryngeal edema, severe diarrhea, eosinophilic esophagitis; no death reports.
Discontinuations due to adverse reactions[2,4]	• 300 IR 5.2% vs placebo 0% • 5.6%; RR vs placebo = 4.86 (2.41 to 9.79), P <0.001)

Drug Interactions

Drug-Drug Interactions[1]:

- No direct drug-drug interactions
- 5-GPAE may not be suitable for patients taking drugs that can potentiate or inhibit the effects of epinephrine. Potential examples include beta-adrenergic blockers, alpha-adrenergic blockers, ergot alkaloids, tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, certain antihistamines, cardiac glycosides, and diuretics.

Drug-food Interactions: None

Drug-Lab Interactions: None

Risk Evaluation

As of October 4, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Grass Pollen Allergen Extract (5 Grass Extract): Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass 100IR, 300IR SL tab	Grass Pollen Allergen Extract (Timothy Grass)	None	None	None
Oralair	Singulair	None	None	Pentolair Orapred

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[1]

- Of note, studies were not conducted in patients older than 65 years of age and were conducted in patients with seasonal allergic rhinoconjunctivitis. Based on the National Center for Veterans Analysis and Statistics, 45.82% of veterans are aged 65 and older as of September 2015.[16] Thus, caution should be used if 5-GPAE is used in patients older than 65 years since safety has not been evaluated in this patient population. Use of SLIT in patients with perennial allergic rhinitis is less established.

- Because there are regional differences in grass pollen allergens across the U.S., it would be up to the prescribing physician to know which seasonal grass pollens and allergens are prevalent in the local regions.

- In post marketing safety studies with a total of 1728 individuals (808 adults and 920 kids 5-17) receiving 5-GPAE, the following adverse reactions were reported: anaphylactic reaction, oral allergy syndrome, flushing, dyspnea, laryngeal edema, and diarrhea.

- Spontaneous post-marketing reports reported after the approval of 5-GPAE include: autoimmune thyroiditis, eosinophilic myocarditis, eosinophilic esophagitis, palpitations, tachycardia, hypotension, loss of consciousness, circulatory collapse, malaise, pallor, peripheral vascular disorder, stridor, angioedema, face edema, weight decreased, wheezing, exacerbation of asthma, chest discomfort, oropharyngeal paresthesia, oropharyngeal blistering, headache, dizziness, tinnitus, asthenia, somnolence, anxiety, rash, pruritus, salivary gland enlargement and/or hypersecretion, dry mouth, dry eye, influenza-like syndrome, lymphadenopathy, eosinophil count increased. Since these reactions are reported from a population of uncertain size, it's not always possible to reliably estimate their frequency or establish causality.

- The FDA has required the manufacturer of 5-GPAE to conduct an observational post-marketing study in 6,000 patients ages 10-65 years to further evaluate safety.[17]

- Patients should read the 5-GPAE (ORALAIR®) medication guide before starting the medication and at each refill needed.

Dosing and Administration[1]

- 300IR sublingual tablet daily for patients ages 18-65 years.
- Administer the first dose of 5-GPAE in a healthcare setting in which acute allergic reactions can be treated under the supervision of a physician with experience in the diagnosis and treatment of severe allergic reactions.
- After receiving the first dose of 5-GPAE, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction.
- If the patient tolerates the first dose, the patient may take subsequent doses at home.
- To administer:
    - Remove the 5-GPAE tablet from the blister just prior to dosing.
    - Place the tablet immediately under the tongue until complete dissolution for at least 1 minute before swallowing.
    - Wash hands after handling the tablet.
- Do not take 5-GPAE with food or beverage. To avoid swallowing allergen extract, food or beverage should not be taken for 5 minutes following dissolution of the tablet.
- Initiate treatment 4 months before the expected onset of each grass pollen season and maintain it throughout the grass pollen season.
- Data regarding the safety of initiating treatment during the pollen season or restarting 5-GPAE treatment after missing a dose are not available.
- An auto-injectable epinephrine pen should be prescribed for all patients who are prescribed 5-GPAE. Patients should be instructed and trained on the proper use of self-injection and to immediately seek medical attention upon its use.

Special Populations (Adults)[1]

	Comments
Elderly	• 5-GPAE has not been studied in patients over 65 years of age
Pregnancy	• Pregnancy Category B. Reproductive and developmental toxicity studies were performed on rats and rabbits with no evidence of harm. However, no well-controlled studies were performed in pregnant women. Use during pregnancy should only be considered if 5-GPAE is clearly needed.
Lactation	• It is not known if 5-GPAE is excreted in human milk. Use with caution in women who are breastfeeding.
Renal Impairment	• No data identified
Hepatic Impairment	• No data identified
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

Allergic rhinitis is a condition characterized by inflammation of nasal tissue, which results in nasal congestion, watery eyes, sneezing, and itching of the eyes, nose, and throat areas. According to the American Academy of Allergy Asthma and Immunology, in 2010, 11.1 million visits to physician offices resulted with a primary diagnosis of allergic rhinitis.[18] This common condition has a significant impact on quality of life and is often associated with a high socioeconomic burden.[19]

The American Academy of Otolaryngology (AAO)—Head and Neck Surgery Foundation's clinical practice guidelines recommend first line therapy with intranasal steroids in patients whose symptoms are adversely impacting their quality of life or treatment with oral second-generation antihistamines in patients whose symptoms are primarily sneezing and itching. Other therapies that may be offered include intranasal antihistamines or use of combination therapy in those patients inadequately controlled with single drug therapy. The guideline authors recommend that practitioners should consider immunotherapy if patients have failed to achieve an adequate

response to traditional therapies first.[20] The British Society for Allergy and Immunology Guideline for Immunotherapy for Allergic Rhinitis also recommend reserving immunotherapy for patient failing to achieve adequate relief of symptoms despite treatment with intranasal corticosteroids and/or antihistamines.[21] Currently, there is conflicting guidance on the use of sublingual immunotherapy. According to the position statement by the World Allergy Organization, sublingual immunotherapy may be considered as an initial treatment for allergic rhinitis.[22] There are no VA/DoD guidelines for managing allergic rhinitis.

Identification of appropriates candidates for immunotherapy is necessary for the safe and effective use of such therapy and involves determining the causal allergen or trigger by considering a combination of factors including clinical history and skin and/or blood testing for allergen specific IgE. Specific allergen immunotherapy is the only treatment that can induce tolerance to specific allergens when the body is exposed to a high allergen dose for prolonged periods of time (e.g., 3 or more years).[23-24] Routes of administration for this type of treatment include subcutaneous and sublingual allergy immunotherapy. Since clinical trials directly comparing SCIT to SLIT (as sublingual tablets) are not available, the comparative effectiveness is unknown. One advantage of SLIT over SCIT is the ability for patients to self-administer the sublingual tablets at home, after the initial dose. A physician or provider must supervise the patient taking the first dose of 5-GPAE in a healthcare setting, in the event of a serious allergic or anaphylactic reaction.

Consistent with more recent U.S. guidelines in the management of allergic rhinitis and due to safety considerations, therapy with 5-GPAE or other SLIT therapies can be considered in those patients (18-65 years of age) with an inadequate response to a therapeutic trial of intranasal corticosteroids and oral antihistamines. The decision to prescribe SLIT or SCIT should be limited to VA Allergy/Immunology, Ear Nose and Throat specialists or locally designated experts.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	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 > 100 participants; 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 the evidence.
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.