Timothy Grass Pollen Allergen Extract (GRASTEK®)

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

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 Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information (FDA approved April 2014)

Description/Mechanism of Action	Timothy Grass Pollen Extract (*Phleum pratense*) (T-GPAE) (GRASTEK®) is a sublingual allergen extract used for allergy immunotherapy (AIT). The precise mechanism of action of allergen immunotherapy is not known.
Indication(s) Under Review in this document (may include off label)	For the treatment of grass pollen-induced allergic rhinitis with or without allergic conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IqE antibodies for Timothy grass or cross-reactive grass pollens. T-GPAE has been approved for use in persons' aged 5 through 65 years.
Dosage Form(s) Under Review	Sublingual tablet, 2800 Bioequivalent Allergy Units (BAU) Treatment is initiated 12 weeks prior to the anticipated onset of grass allergy season as one sublingual (SL) tablet daily and continued throughout the allergy season. Alternatively, for sustained effectiveness after stopping immunotherapy, one SL tablet can be taken daily for 3 years.
REMS	☒ REMS ☐ No REMS ☒ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category B. *See section on special populations*

Executive Summary

Efficacy

The FDA approval of Timothy Grass Pollen Allergen Extract (T-GPAE) (GRASTEK®) is based upon the safety and efficacy from six phase 3 clinical trials conducted in Europe and the United States, in addition to phase 1 and 2 trials. Three of the phase 3 trials enrolled adult patients 18-65 years, two enrolled pediatric patients and one enrolled both adults and children. Approximately 2,000 adults were included in the studies. Since sublingual immunotherapy (SLIT) has been available outside of the U.S. for years, published systematic reviews and meta-analyses were relied upon primarily for the efficacy and safety assessment of T-GPAE.

Meta-analysis	Summary
Di Bona, *et al*[2]	Included 13 randomized, controlled trials of variable size, and patient populations in both Europe and North America. Efficacy was found to be greater in European vs. American studies, in studies using the 5-grass pollen allergen extract 5-GPAE) tablets vs. studies using T-GPAE, and in smaller studies. **Conclusion: SLIT provides marginal benefit over placebo.**
Dranitsaris, *et al.* [3]	Included 20 randomized controlled trials evaluating 5-GPAE, T-GPAE and SCIT. **Conclusion: T-GPAE, 5-GPAE, and SCIT were shown to have comparable benefit in reducing symptom score when compared with placebo. Benefit of therapy was small vs. placebo.** Patients receiving immunotherapy in general had higher rates of drug discontinuation when compared with placebo, but this did not differ significantly among the three therapies.
Devillier, *et al.*[5]	Included multicenter studies with at least 100 patients in each arm (treatment and control group) – all the SLIT tablet studies were large, multicenter trials.

	Conclusion: SLIT tablets provide a RCI similar to the intranasal steroid in indirect comparisons.

- There is one study in 634 adult patients (ages 18-65 years) in which T-GPAE was administered daily for three consecutive years vs. placebo and then patients were followed for two additional years after treatment cessation to determine sustained benefit. In the three years patients were taking T-GPAE SLIT daily, symptom and medication scores were statistically better than placebo. The effect of treatment was sustained in the first year after stopping treatment but not in the second year.
- There are no trials directly comparing SLIT, as sublingual tablets, to subcutaneous immunotherapy (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 T-GPAE contains a boxed warning regarding the potential for causing life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema. Boxed labeling includes the following:**
  - **Timothy Grass Pollen Extract (Grastek®) can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction.**
  - **Do not administer Timothy Grass Pollen Extract (Grastek®) to patients with severe, unstable or uncontrolled asthma.**
  - **Observe patients in the office for at least 30 minutes following the initial dose.**
  - **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.**
  - **Timothy Grass Pollen Extract (Grastek®) may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction (compromised lung function, unstable angina, arrhythmias, recent myocardial infarction or uncontrolled hypertension).**
  - **Timothy Grass Pollen Extract (Grastek®) may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.**
- T-GPAE was largely well tolerated in clinical trials with most adverse events rated as mild to moderate in severity. The most common adverse effects consisted of pruritus of the mouth and ear and minor oral and throat irritation and swelling.
- Withdrawal from clinical trials due to adverse events was reported in approximately 5-6% of patients receiving SLIT (T-GPAE or 5-grass pollen allergen extract [5-GPAE]).
- Serious adverse effects are rare with T-GPAE but can occur. Therefore, the initial dose of T-GPAE must be administered in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or local allergic reaction.

	○ Seven patients receiving T-GPAE experienced treatment related systemic allergic reactions, leading to cessation of therapy in 4 patients. Five patients had the allergic reaction on the first day of treatment and three were treated with epinephrine and antihistamines. One also received oral corticosteroids. Two other patients had reactions, one on day two and the other on day 42 of treatment. • Auto-injectable epinephrine should be prescribed to all patients receiving T-GPAE. Patients should be instructed on its proper use for emergency self-administration and instructed to seek immediate medical attention upon its use. • T-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 the effect of epinephrine including beta-blockers, alpha blockers or ergot alkaloids, tricyclic antidepressants, levothyroxine, monoamine oxidase inhibitors, chlorpheniramine or diphenhydramine, cardiac glycosides or diuretics. • The FDA has required the manufacturer to conduct an evaluation to further define the safety of T-GPAE using claims based and medical record based data. The studies are to last for three years or until information from10,000 patients has been collected from both the claims and medical records based study.
Place in Therapy	• Consistent with more recent U.S. guidelines in the management of allergic rhinitis and due to safety considerations, therapy with T-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.
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

Issues to be determined:

✔ Evidence of need

✔ Does T-GPAE offer advantages to currently available alternatives including subcutaneous immunotherapy?

✔ Does T-GPAE offer advantages over current VANF agents?

✔ What safety issues need to be considered?

✔ Does T-GPAE have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations	Restrictions
1st Generation Antihistamines ▪ Diphenhydramine ▪ Chlorpheniramine	Sedating Beers Criteria	None
2nd Generation Antihistamines ▪ Cetirizine		None

▪ Loratadine		
Intranasal Steroids		None
▪ Fluticasone		
Intranasal Anticholinergics		
▪ Ipratropium	Limited Efficacy	None
Mast Cell Stabilizers	Multiple times per day	
▪ Cromolyn		None
Decongestants, nasal		
▪ Oxymetazoline	Limited to 3 days of use	None
▪ Phenylephrine	Rebound nasal congestion	
▪ Sodium Chloride		
Decongestants, oral		
▪ Phenylephrine	Unsafe for use in patients	None
▪ Pseudoephedrine	with hypertension	
Leukotriene Receptor Antagonists		
▪ Montelukast	Limited Efficacy	None
Ophthalmic Agents		
▪ Ketotifen		None
▪ Cromolyn		
▪ Ketorolac		

Non-formulary Alternatives	**Other Considerations**
2nd Generation Antihistamines	
▪ Fexofenadine	
Intranasal Steroids	
▪ Beclomethasone	
▪ Budesonide	
▪ Flunisolide	
▪ Mometasone	
▪ Triamcinolone	
Intranasal Antihistamine	
▪ Azelastine	
Leukotriene Receptor Antagonists	
▪ Zafirlukast	
Ophthalmic Agents	
▪ Azelastine	
▪ Olopatadine	
▪ Epinastine	
Subcutaneous Immunotherapy	Requires once weekly injections/then monthly

Efficacy (FDA Approved Indications)[1,2,3,4]

Literature Search Summary

PubMed was systematically searched using the search terms “grass pollen sublingual immunotherapy”, “timothy grass pollen allergen extract,” “meta-analysis,” “rhinitis,” “allergic conjunctivitis,” “pollinosis,” allergen-specific immunotherapy,” “immunotherapy,” “grass allergen” and “Grastek” for randomized, controlled trials and meta-analyses published from January 1, 1966 to October 2015. Additionally, a literature search using the terms “pharmacokinetics AND sublingual immunotherapy” did not return any relevant results. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. Since sublingual immunotherapy (SLIT) has been available outside of the U.S. for years, published systematic reviews and meta-analyses were relied upon primarily for the efficacy and safety assessment of T-GPAE. However, clinical trials specifically evaluating the efficacy and safety of T-GPAE that were not included in any of the meta-analyses are discussed separately.

Review of Efficacy[1,2,3,4]

Introduction:

The clinical trial program for T-GPAE included six phase 3 trials evaluating efficacy and safety along with a number of phase 1 and 2 studies. Three of the trials were conducted in adults' ages 18-65 years, two were conducted in pediatric patients and one study involved both adults and children with allergic rhinitis. The pediatric studies will not be discussed in this document.

- Most studies evaluated allergy symptoms over a single allergy season in patients residing in Europe or the United States.
- One study involved treatment with T-GPAE over three consecutive allergy seasons with a two-year follow up period to assess sustained effectiveness of treatment.
- Studies enrolled patients with primarily moderate to severe symptoms of allergic rhinitis to grass pollen allergens.
- Since sublingual immunotherapy (SLIT), including T-GPAE, has been available outside of the United States for years, the monograph focuses primarily on three meta-analyses that examined current allergen immunotherapies (AIT), including timothy grass pollen extract, 5-grass pollen allergen extract and subcutaneous immunotherapy (SCIT) for safety and efficacy. Since direct comparisons of AIT (SLIT vs. SCIT) or AIT in comparison to standard treatments for allergic rhinitis related to grass pollen allergens have not taken place, authors of two meta-analyses attempted indirect comparisons.
- In most trials, the use of "rescue" medications (antihistamines, decongestants, and steroids) was permitted and documented.
- The trials utilized:
    - 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. A 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.[16]
- 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.[13]
- The World Allergy Organization (WAO) recognizes a 20% difference as the standardization of efficacy for clinical trials with allergen-specific immunotherapy for respiratory allergy.[14-15]
- Cohen, et al. criteria for significance in clinical practice is not met for differences of <1 point.[16]

Evidence:

Di Bona, *et al.*[2] (2015)

This meta-analysis was published in June 2015 and served to review the efficacy and safety of SLIT (timothy grass pollen extract and 5-allergen grass pollen extract) compared with placebo. This meta-analysis included thirteen randomized, controlled trials (5 conducted in North America) featuring a total of 4,659 patients receiving SLIT. Randomized, controlled trials were included in the meta-analysis if (1) they compared grass pollen SLIT administered as tablets compared with a placebo control, (2) they involved patients having a clinical history of seasonal allergic rhinoconjunctivits (SARC) to grass pollen with or without mild allergic asthma with a positive grass pollen allergen-specific skin test and elevated serum grass pollen allergen-specific IgE levels, and (3) the symptom score (SS) and medication score (MS) were assessed as outcome measures of the treatment effect. The

patient populations included in the individual trials varied. Three studies only enrolled individuals 17 or younger, while 8 studies included adults up to 65 years of age. The severity of allergic rhinitis symptoms in the studies also varied, but most studies reported the severity of symptoms among the patient population as moderate to severe. Eight individual studies used the grass pollen allergen extract tablets at the same dosage (2800 bioequivalent allergy units) with comparable treatment durations. For details of the individual clinical trials see **Appendix A**.

Measurement of Efficacy
The most commonly used measurement of efficacy was the symptom score. Symptoms were composed of runny nose, blocked nose, sneezing, itchy nose, itchy eyes, and watery eyes. These six symptoms were scored based on severity (higher score indicating greater severity), with total symptom scores ranging from 18 to 21 points. Another frequently used measurement of efficacy was the medication score, which was a summed score for use of antihistamines, ocular antihistamines, nasal corticosteroids, and oral steroids. The score assigned to each medication varied among the individual studies.

Methods:
- The symptom score and medication score were assessed as outcome measures of the treatment effect.
- Efficacy analyses were performed using standardized mean differences (SMDs) vs. placebo since different scoring systems and scales were used for assessing symptoms and use of rescue medication between studies. A 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.[16]
- Since 11 of the 13 included randomized, controlled trials used the same symptom score scale, ranging from 0 to 18 (higher scores indicated worse disease severity), a sub-analysis of these trials was done using the mean difference in the original symptom score.

Results:
- Patients were treated for a mean length of preseason treatment of 14.3 weeks and seasonal treatment of 8.5 weeks.
- The results of studies on 5-GPAE vs. placebo and TGPAE vs. placebo for SARC were combined.
- The results of 13 studies of 4,659 patients were pooled and were used to calculate an average symptom score (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 pooled medication score (MS) was calculated from 4,558 patients in 12 trials. 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.
- Of the 11 studies that used a symptom score ranging from 0 to 18, the mean difference in symptom score between SLIT and placebo was -0.83 (95% CI, -1.03 to -0.63; P<0.001), without significant heterogeneity (I^2=16.4%); differences in 4 of the studies did not reach statistical significance.
- Subgroup analyses suggested a greater benefit in European vs. American studies, in studies using the 5-allergen grass pollen extract tablets (5-GPAE) vs. studies using the T-GPAE tablets, and in smaller studies.

Comments:
- Standardized mean differences 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.
- A statistically significant improvement in symptom control and/or medication use for allergic rhinitis was not shown in all studies.
- The authors discuss the small benefit of SLIT in reducing symptoms scores <1 point vs. placebo and note that while the effect was statistically significant, patients were allowed to use rescue medications during the treatment period making it is difficult to discern the true effect of SLIT on the symptom score alone.
- 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 subcutaneous immunotherapy (SCIT) for SARC.[3]

Dranitsaris, *et al.*[4] (2014)
This meta-analysis was published in 2014 and included 20 randomized, controlled trials (7 trials specific T-GPAE) completed in Europe and North America enrolling a total of 7,179 patients (2,745 receiving T-GPAE). The authors of the meta-analysis used two different methods to indirectly compare the efficacy and safety of T-GPAE immunotherapy to 5- grass pollen extract (5-GPAE), since trials directly comparing the agents are lacking. The meta-analysis also compared the efficacy of 5-GPAE to SCIT, but did not include a comparison of T-GPAE versus SCIT. Fifteen of the studies enrolled adults only, whereas 2 studies enrolled exclusively children, and the remaining included both adults and children. Approximately 17% of patients enrolled in all 20 trials were asthmatics.

Methods:
- Meta regression analysis was used to analyze primary clinical outcomes and adverse event rates reported in the selected trials for T-GPAE relative to both SCIT and 5-GPAE and results are expressed as a standardized mean difference (SMD) between the drugs.
- Univariate method of Butcher *et al*., was used to provide an indirect comparison of T-GPAE to 5-GPAE.
- An economic analysis was also conducted through the societal perspective that considered direct and indirect costs. The analysis included costs for drug acquisition, pharmacy dispensing fee, reimbursement for physician services, as well as secondary therapy when the primary agent had to be discontinued due to intolerance. In the economic analysis, assumptions included dosing (T-GPAE once daily continuously, 5-GPAE for four months before and two months during allergy season and SCIT as weekly injections for six months and then monthly for six months or weekly for three months and then monthly for four months) and the lack of need for auto-injectable epinephrine in the SLIT groups. Dosing was assumed for three consecutive years.

Results:
- Median duration of preseason treatment was 2.1 months and total duration of therapy of 5.3 months.
- Meta regression analysis: The reduction in the pooled SMD of T-GPAE to placebo was -0.34 (95% CI, -0.27 to 0.21, P < 0.001) with moderate heterogeneity (I^2= 57.5%), 5-GPAE was -0.47 (95% CI, -0.56 to -0.39, P<0.001) with no significant heterogeneity (I^2=0%), SCIT was -0.3 (95% CI, -0.39 to -0.2, P<0.001) without significant heterogeneity (I^2= 4.6%). These data are suggestive of a comparable benefit among therapies when compared to placebo.
- An indirect comparison of the three therapies revealed a difference of improved efficacy in symptom score reduction for 5-GPAE compared to T-GPAE (SMD -0.18 [-0.31 to -0.047], P = 0.033).
- 5-GPAE was reported to have significant cost savings when compared to year round and seasonal SCIT, as well as with T-GPAE.

Comments:
- Timothy grass pollen extract resulted in a statistically significant pooled mean reduction in symptom scores compared to placebo, representing a small effect (SMD= -0.34) as did 5-GPAE (SMD= -0.47) and SCIT (SMD= -0.3).
- Indirect comparison showed a trivial difference between 5-GPAE and T-GPAE (SMD= -0.13, NS) or SCIT (SMD= -0.18, p=0.033) in symptom score.
- 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.

Devillier, *et al.*[5] (2014)
This meta-analysis was published in 2014 and included 28 randomized, controlled trials completed in the United States and Europe evaluating medications used for allergic rhinitis. Eleven of the trials were specific for SLIT. Eight of the eleven studies were performed in adult patients (ages 18 or older) while the remaining three studies included pediatric patients. Data from the eleven studies (n=3,819 patients) were pooled for analysis of efficacy of SLIT.

Since there are no studies directly comparing SLIT to standard treatments for allergic rhinitis, an indirect analysis was used to compare the efficacy of T-GPAE and 5-GPAE to other standard treatments (antihistamines, leukotriene receptor antagonists, intranasal corticosteroids) for allergic rhinitis.

Measurement of Efficacy
The most frequently utilized criterion for symptom severity, and subsequent calculation in reduction of symptom severity for efficacy analysis, was the rhinoconjunctivitis total symptom score (RTSS). Some trials additionally adjusted the RTSS for the use of "rescue" medications in the Average-Adjusted Symptom Score (AAdSS).

Methods:
- Degree of symptom relief was determined through the calculation of relative clinical impact (RCI) scores, defined as the percentage difference between the total symptoms score obtained for active treatment versus placebo. RCI scores were calculated for all six randomized, controlled trials of T-GPAE.
- The RCI can be interpreted as the percent difference in symptom score between the treatment and placebo group and allows for an estimate of clinical efficacy that is more comparable to the measurements found in clinical trials as compared to mean differences.

Results:
- The RCI score for T-GPAE was -19.2 (-6.1, -28.7). (See the table below for comparison of RCI scores).
- There was no heterogeneity noted in the T-GPAE trials; limited heterogeneity for 5-GPAE and intranasal steroid trials and moderate heterogeneity in trials of montelukast and antihistamines.

Drug Class	Weighted Mean RCI (Range)	Number of Studies included in Studies used for RCI calculation
Five-grass pollen extract (5-GPAE) (Oralair)	-29.6 (-22.8, -37.7)	5
Intranasal Corticosteroids	-23.5 (-6.5, -54.2)	9
Timothy grass pollen extract (T-GPAE) (Grastek)	-19.2 (-6.1, -28.7)	6
H1 Antihistamines	-15 (-3.0, -28.1)	23
Montelukast	-6.5 (-3.1, -9.7)	4

Comments:
- The meta-analysis confirms the presence of an effect of treatment for all agents including SLIT. Indirect comparison shows an advantage of treatment in the following order: 5-GPAE > intranasal steroids > T-GPAE > antihistamines > montelukast on improving symptoms in seasonal allergic rhinitis.

Summary of Evidence		
Meta-analysis	**Quality of Evidence**	**Comments**
Di Bona, *et al*[2]	Moderate	Included 13 randomized, controlled trials of variable size, and patient populations in both Europe and North America. Efficacy measured by standardized mean differences (SMD). Efficacy was found to be greater in European vs. American studies, in studies using the 5-GPAE tablets vs. studies using the 1-allergen grass pollen extract tablets, and in smaller studies. **Conclusion:** SLIT provides marginal benefit over placebo.
Dranitsaris, *et al.* [3]	Moderate	Included 20 randomized controlled trials evaluating 5-GPAE, T-GPAE and SCIT. Included an indirect analysis of efficacy, safety, and cost. **Conclusion:** T-GPAE, 5-GPAE, and SCIT were shown to have comparable benefit in reducing symptom score when compared with placebo. Patients receiving immunotherapy in general had higher rated of drug discontinuation when compared with placebo, but this did not differ significantly among the three therapies.

Devillier, *et al*.[5]	Moderate	Included multicenter studies with at least 100 patients in each arm (treatment and control group) – all the SLIT tablet studies were large, multicenter trials. Relative clinical impact (RCI) defined as the percentage difference between the total symptom score or total nasal symptom score for active treatment versus placebo. **Conclusion:** SLIT tablets provide a RCI similar to the intranasal steroid in indirect comparisons.

- There is one study in 634 adult patients (ages 18-65 years) in which T-GPAE was administered daily for three consecutive years vs. placebo and then patients were followed for two additional years after treatment cessation to determine sustained benefit. In the three years patients were taking T-GPAE SLIT tablets daily, symptom and medication scores were statistically better than placebo and the effect of treatment was sustained in the first year after stopping treatment but not in the second year.[1]
- 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.[17]
- 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

- Potential off-label use has not been identified in the literature at this time.

Safety[1]

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

	Comments
Boxed Warning[1]	• **Timothy Grass Pollen Extract (Grastek®) can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction.** • **Do not administer Timothy Grass Pollen Extract (Grastek®) to patients with severe, unstable or uncontrolled asthma.** • **Observe patients in the office for at least 30 minutes following the initial dose.** • **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.** • **Timothy Grass Pollen Extract (Grastek®) may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction (compromised lung function, unstable angina, arrhythmias, recent myocardial infarction or uncontrolled hypertension).** • **Timothy Grass Pollen Extract (Grastek®) may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.**
Contraindications[1]	• 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[1]	• Patients with escalating or persistent local reactions to T-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 T-GPAE.
- Educate patients on signs and symptoms of a severe allergic reaction and instruct them to seek immediate medical care and discontinue therapy if these occur.
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.
- If patients experience oral inflammation or have oral wounds, such as those following oral surgery or dental extraction, patients should stop treatment with T-GPAE to allow complete healing of the oral cavity.
- T-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).
- T-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 T-GPAE should be stopped and a diagnosis of eosinophilic esophagitis should be considered.
- T-GPAE has not been evaluated in patients with moderate to severe asthma or in those asthmatics who require daily medications.
- The concomitant use of other allergen immunotherapy with T-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 T-GPAE is initiated during grass pollen season. Evidence for restarting treatment during allergy season after missed doses is unknown. In clinical trials, interruptions in treatment were permitted for up to seven days.

Safety Considerations[1-3, 5]

Di Bona, *et al*.[2]

Methods:

- Adverse event data was combined for all studies reporting data on safety and treatment related adverse events.

Results:

- Of patients receiving SLIT, 1,817 of 2,597 (70.0%) vs. 1,137 of 2,555 (44.5%) patients receiving placebo reported adverse events.
- Probable treatment-related adverse events were reported in 9 of 13 studies, with 3 times as many adverse events in patients receiving SLIT, 1,384 of 2,259 (61.3%) compared with those receiving placebo, 477 of

2,279 (20.9%).

- Seven treatment-related adverse events requiring epinephrine were reported in patients receiving SLIT vs. 0 in patients receiving placebo.
- However, most adverse events were mild to moderate in severity, including oral pruritus, throat irritation, ear pruritus, mouth edema, and mouth inflammation.
- No events of anaphylaxis were reported in patients receiving SLIT or in patients receiving placebo.
- Six percent of patients receiving SLIT discontinued therapy due to adverse events compared to 2.2% of patients receiving placebo.

Comments:

- While adverse events appear to be common in patients receiving SLIT, they are primarily local reactions, mild to moderate in severity, and contributed to a higher percentage of patients discontinuing therapy versus placebo.
- Treatment benefit and adherence could be limited by the higher frequency of side effects.

Dranitsaris, *et al*.[3]

Methods:

- Adverse event rates for 5-GPAE, T-GPAE, and SCIT were combined for all randomized, controlled trials reporting this data.
- Relative Risks (RR) were used to express the safety results of the pooled data. The RR of drug discontinuation compared to placebo for all three therapies was reported. The rate of drug discontinuation due to adverse events was then determined for each of the three treatments.

Results:

- Overall, patients receiving treatment with any immunotherapy were more likely to have their treatment discontinued compared to placebo, RR 2.64, P<0.001.
- The pooled RR for treatment discontinuation compared to placebo was: T-GPAE (pooled estimate from eight trial arms): RR 1.90 (95% CI, 1.21 to 3.00), 5-GPAE (pooled estimate from six trial arms) RR 4.88 (95% CI, 2.49 to 9.58), and SCIT (pooled estimate from seven trial arms): RR 3.16 (95% CI, 1.40 to 7.10).
- The risk of drug discontinuation rates due to adverse reaction for T-GPAE 1.90 (95% CI, 1.21 to 3.00), 5-GPAE 4.86 (95% CI, 2.41 to 9.79), and SCIT 3.16 (95% CI, 1.4 to 7.10). There was no statistically significant difference between active treatment groups using meta-regression analysis.

Comments:

- While patients receiving treatment with immunotherapy were more likely to discontinue treatment when compared with placebo, the risk of drug discontinuation between therapies due to adverse events did not differ significantly.

Devillier, *et al*.[5]

Safety analysis was not performed in this meta-analysis.

Safety Summary:

- T-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.
- Seven patients receiving T-GPAE experienced treatment related systemic allergic reactions, leading to cessation of therapy in 4 patients. Five patients had the allergic reaction on the first day of treatment and three were treated with epinephrine and antihistamines. One also received oral corticosteroids. Two other patients had reactions, one on day two and the other on day 42 of treatment.
- Serious adverse effects are rare with T-GPAE but can occur. Therefore, the initial dose of T-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 T-GPAE.
- Withdrawal due to adverse events was reported in approximately 5-6% of patients receiving SLIT (T-GPAE or 5-GPAE).
- T-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[1]

Common adverse reactions	Incidence ≥10%: ear pruritus, oral pruritus, tongue pruritus, mouth edema, throat irritation
Death/Serious adverse reactions	Angioedema, anaphylaxis, anaphylactic shock, status asthmaticus, respiratory distress; No deaths reported
Discontinuations due to adverse reactions	4.9% vs. 0.9% placebo Most common reasons for stopping therapy were pharyngeal edema and oral pruritis.

Drug Interactions[1]

Drug-Drug Interactions[1]

- There are no known significant interactions.
- T-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 (chlorpheniramine or diphenhydramine, cardiac glycosides, and diuretics.

Drug-food Interactions[1]

- There are no known significant interactions.

Drug-Lab Interactions[1]

- There are no known significant interactions.

Risk Evaluation

As of September 8, 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 (Timothy Grass) 2800 BAU SL tab	Grass Pollen Allergen Extract (5 Grass Extract)	None	None	None
Grastek	None	None	None	Gattex Gentak Ketek Rilutek Elitek Granix

- 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

- Of note, studies were not conducted in patients older than 65 years of age and were limited to 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.[18] Thus, caution should be used if T-GPAE is used in patients older than 65 years since safety has not been evaluated in this patient population. Also, use of SLIT in patients with perennial allergic rhinitis is less well 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.

- Serious adverse reactions reported in post-marketing surveillance, which included European studies in 1,666 patients receiving T-GPAE, include anaphylactic reaction, asthma exacerbation, hoarseness, laryngitis, oral ulceration and ulcerative colitis exacerbation.[1]

- Spontaneous post-marketing reports reported after the approval of T-GPAE include: altered state of consciousness, anaphylactic shock, angioedema, exercise induced asthma, chest pressure, diarrhea, difficulty speaking, dizziness, drowsiness, eosinophilic esophagitis, erythema facial, face edema, forced expiratory volume decreased, increased heart rate, irregular heart rate, etc. (see manufacturers labeling for the comprehensive list of reports). There was one case in which a male with asthma experienced anaphylactic shock within minutes of receiving T-GPAE.[1] 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 to conduct an evaluation to further define the safety of T-GPAE using claims based and medical record based data. The studies are to last for three years or until information from10,000 patients has been collected from both the claims and medical records based study.[19]

- Patients should read the T-GPAE (GRASTEK®) medication guide before starting the medication and at each refill. All patients should be prescribed auto-injectable epinephrine and be instructed on its proper use in the event of an allergic reaction.

Dosing and Administration

- One 2800 Bioequivalent Allergy Unit (BAU) tablet daily.
- Treatment should be initiated at least 12 weeks before the expected onset of grass pollen season and treatment should be continued throughout the remainder of the allergy season. T-GPAE may also be taken daily for up to three consecutive years for sustained effectiveness. However, in a single clinical trial, sustained effectiveness during grass pollen season was evidence in the first year after stopping treatment but not in the second year vs. placebo.
- The first dose of Timothy Grass Pollen Extract (Grastek®) must be administered in a healthcare setting and supervised by a physician with experience in the diagnosis and treatment of severe allergic reactions.
- After administration of the first dose, the patient must be observed for 30 minutes in the office to monitor for signs and symptoms of a severe allergic reaction, local or systemic. If the patient tolerates the first dose, the remainder of the doses may be administered at home.
- The dose is administered as a sublingual tablet. After removing the tablet from the blister pack, place the tablet immediately under the tongue and allow to completely dissolve. Do not take with food or beverages. Do not swallow for at least one minute and avoid food and beverages for at least 5 minutes. Hands should be washed after touching the tablet.
- Prescribe auto-injectable epinephrine to patients initiating therapy with T-GPAE. Patients should be instructed on the proper use of this agent for emergency self-injection and to seek medical attention upon its use.
- The safety and efficacy of initiating treatment with T-GPAE during grass pollen season is unknown. Evidence in patients with missed doses is lacking. However, interruption in therapy of up to seven days was permitted in clinical trials without medical supervision to restart treatment.
- Refer to the package insert for full dosing information.

Special Populations (Adults)[1]

	Comments
Elderly	• No data identified.
Pregnancy	• Pregnancy Category B. • Reproductive and developmental toxicity studies performed in female mice have revealed no evidence of harm to the fetus due to Timothy Grass Pollen Extract (Grastek®). • There are no adequate and well-controlled studies in pregnant women. • T-GPAE should only be used if clearly indicated in pregnant women.
Lactation	• It is not known if Timothy Grass Pollen Extract (Grastek®) is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when Timothy Grass Pollen Extract (Grastek®) is administered in a nursing woman.
Renal Impairment	• No data identified.
Hepatic Impairment	• No data identified.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy (this section may be edited prior to final approval of document)

Allergic rhinitis (AR) is an inflammatory, IgE-mediated disease characterized by nasal congestion, rhinorrhea (nasal drainage), sneezing, and/or nasal itching. Examples of the symptoms of AR are sneezing, stuffy nose, runny nose, postnasal drip, and itchy eyes, ears and soft palate. Allergic rhinitis can be classified by temporal pattern of exposure triggering allergen: seasonal, perennial/year-round, or episodic (environmental from exposures not normally encountered in the patient's environment). Allergic rhinitis can also be classified by frequency: intermittent or persistent and severity of symptoms: mild or more severe.

Allergic rhinitis is one of the most common diseases affecting adults, is the most common chronic disease in children in the United States today, and is the fifth most common chronic disease in the United States overall.[6-8] Allergic rhinitis is estimated to affect nearly 1 in every 6 Americans and generates $2 to $5 billion in direct health expenditures annually. It can impair quality of life and, through loss of work and school attendance, is responsible for as much as $2 to $4 billion in lost productivity annually. [9,10,11]

In February of 2015, the American Academy of Otolaryngology (AAO) – Head and Neck Surgery Foundation released updated clinical practice guidelines for allergic rhinitis.[11] There are no VA DoD guidelines on the treatment of allergic rhinitis. Per the AAO guidelines, clinicians can offer to refer outpatients with allergic rhinitis for immunotherapy (SLIT or SCIT) for those patients who failed to have an adequate response to traditional pharmacotherapies.[10] Allergen-specific immunotherapy modifies the disease process through repetitive dosing of allergen(s) to increase the immune tolerance of the allergen(s). Traditionally, this has been achieved through subcutaneous injection of allergen-specific serums. Subcutaneous immunotherapy (SCIT) has proven efficacy in treating allergic rhinitis, but requires regular injections at a physician's office and serious local or systemic allergic reactions are a recognized risk.

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. 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: Randomized Clinical Trials Evaluated in Di Bona et al.[2]

Source	Treatment vs. Placebo (N)	Severity of SARC	Type of Treatment	Treatment Duration (Preseason + Grass Pollen Season) (wk)	Reduction in symptom score (mean difference, 95% CI)*	Reduction in medication score (SMD, 95% CI)	Dropout or withdrawal rate (Due to ADE) (%)
Pradalier 1999	62 vs. 61	NR	5- grass (variable dosage)	8 + 12	SMD -0.18 (-0.53 to 0.18)	-0.14 (0.50 to 0.21)	5.6 (3.2)
Smith 2004	50 vs. 51	Severe	5- grass (variable dosage)	12 + 12	SMD -0.32 (-0.72 to 0.07)	NR	28 (NR)
Dahl 2006	282 vs. 286	Moderate or severe	Phleum p5 extracts (15mcg)	25 + 8	-1.00 (-1.32 to -0.68)	-0.40 (-0.57 to -0.24)	14 (4)
Dahl 2006	61 vs. 32	Moderate or severe	Phleum p5 extracts (15mcg)	12 + 8	-1.20 (-2.07 to -0.33)	-0.45 (-0.88 to -0.02)	18.4 (2.6)
Durham 2006	131 vs. 129	Mild to severe	Phleum p5 extracts (15mcg)	8 + 10	-0.48 (-0.99 to 0.03)	-0.28 (-0.52 to -0.03)	4 (2)
Didier 2007	136 vs. 148	Moderate or severe	5- grass (variable dosage)	16 + 4	-1.35 (-2.07 to -0.63)	-0.35 (-0.58 to -0.12)	9 (2.3)
Bufe 2009	117 vs. 121	Mild to severe	Phleum p5 extracts (15mcg)	17 + 11	-0.50 (-1.08 to 0.08)	-0.12 (-0.38 to 0.13)	7.5 (2.4)
Wahn 2009	131 vs. 135	Moderate or severe	5- grass (variable dosage)	16 + 6	-1.26 (-1.96 to -0.56)	-0.30 (-0.54 to -0.06)	4.4
Blaiss 2011	149 vs. 158	Moderate or severe	Phleum p5 extracts (15mcg)	16 + 7	-1.20 (-2.32 to -0.08)	-0.13 (-0.36 to 0.09)	18.8
Nelson 2011	184 vs. 207	Moderate or severe	Phleum p5 extracts (15mcg)	16 + 7	-0.86 (-1.73 to 0.01)	-0.15 (-0.35 to 0.05)	16.2 (4.3)
Cox 2012	210 vs. 228	Severe	5- grass (variable dosage)	18 + 6	-0.92 (-1.57 to -0.27)	-0.36 (0.55 to -0.17)	19
Murphy 2013	139 vs. 150	Moderate or severe	Phleum p5 extracts (15mcg)	16 + 7	-0.37 (-1.54 to 0.80)	-0.15 (-0.38 to 0.08)	16.2 (5)
Maloney 2014	629 vs. 672	NR	Phleum p5 extracts (15mcg)	≥12 + 8	-0.47 (-0.91 to -0.03)	-0.14 (-0.24 to 0.03)	16.4 (7)

*Mean difference was reported where available, SMD was reported in trials where this information was not available and correlates to effect size as determined by Cohen et al.
NR = Not reported
Phleum p5 extracts (15mcg) = timothy grass pollen extract 2800 BAU

Appendix C: 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.