Introduction

Treating allergies involves giving small doses of what a person is allergic to. This tends to increase a person’s immunity, or tolerance, to the source of the allergy. Allergy treatments often involve getting shots. But a newer method is to give drops under the tongue. This is called sublingual (which means under the tongue) immunotherapy. This treatment is also sometimes called allergy drops. This policy explains when sublingual immunotherapy is medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Sublingual Immunotherapy</th>
<th>Coverage Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oralair®</td>
<td>Sublingual immunotherapy (SLIT) using Oralair®, Grastek®, or</td>
</tr>
</tbody>
</table>
Ragwitek® may be considered medically necessary, when used according to FDA-labelling, for the treatment of pollen-induced allergic rhinitis when the following conditions are met:

- Patient has a history of rhinitis or rhinoconjunctivitis symptoms related to grass or short ragweed pollen exposure.
- Patient has a documented positive pollen-specific skin test or pollen-specific immunoglobulin E (IgE) test.
  - Allergy must be confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies to the species contained in the product or, for Grastek®, Timothy grass pollen extract, to cross-reactive species.
- Patient’s symptoms are not adequately controlled by appropriate pharmacotherapy (see Related Information).

Sublingual immunotherapy as a technique of allergy immunotherapy is considered investigational for all other uses.

Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<tr>
<td>95199</td>
<td>Unlisted allergy/clinical immunologic service or procedure</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
Use of Oralair®, Grastek®, and Ragwitek®

Documentation of Allergy

Allergy must be confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies to the species contained in the product or, for Grastek®, Timothy grass pollen extract, to cross-reactive species.

Contraindications

Contraindications include severe, unstable or uncontrolled asthma; history of any severe local reaction, or any severe systemic allergic reaction to SLIT or any severe local reaction to sublingual allergen immunotherapy; and history of eosinophilic esophagitis.

Administration and Dose

- Prescribing information includes a black box warning for severe allergic reactions including anaphylaxis and severe laryngopharyngeal edema. Patients must be prescribed an epinephrine auto-injector and be trained on how to use it.
- Oralair® is FDA-approved for patients 10 to 65 years of age. Grastek® is FDA-approved for patients 5 to 65 years of age. Ragwitek® is FDA-approved for patients 18 to 65 years of age.
- Treatment should begin 12 weeks (16 weeks for Oralair®) before the expected onset of the allergy-inducing pollen season. Each product is dosed once daily and continued throughout the pollen season (pre-seasonal dosing).
- The first dose is administered under the supervision of a physician experienced in diagnosing and treating severe allergic reactions. Subsequent doses may be taken at home.
- All 3 agents are dosed once daily.
- For Oralair®, dose titration is required in patients 10 to 17 years of age. Titration can be completed over 3 days at home (after the first dose) according to the schedule in Table 1. In patients between 18 to 65 years, no dose titration is needed; treatment is initiated at the maintenance dose of 300 IR (index of reactivity).
- Grastek® and Ragwitek® both are initiated at the maintenance dose (2800 BAU [bioequivalent allergy unit] and 12 Amb a 1 unit, respectively).
Pharmacotherapy of Pollen-Induced Allergic Rhinitis

Several clinical practice guidelines describe pharmacologic treatments of pollen-induced allergic rhinitis/rhinoconjunctivitis.4-8 There is general agreement that:

- Treatment should be individualized based on symptom severity and duration, comorbidities, and patient age, preference (e.g., route of administration, tolerance for adverse effects), and previous treatment history.

- Measures to increase treatment adherence (e.g., shared decision making, consideration of the patient’s school or work schedule, use of a medication calendar or check-off list) are encouraged.

- Goals of treatment are symptom reduction and improvements in functional capacity and quality of life.

- A “step-up” (if treatment is inadequate)/“step-down” (if symptom relief is achieved with other interventions, e.g., avoidance) approach to treatment is recommended.

- Allergen avoidance is the first step of treatment but may be unrealistic for some patients.

Six medication classes are used to treat allergic rhinitis:

1. H1-antihistamines (oral and intranasal)
2. Corticosteroids (oral [short-course for severe disease] and intranasal),
3. Leukotriene receptor antagonists (oral),
4. Sympathomimetic decongestants (oral and intranasal)
5. Chromones (intranasal),
6. Anticholinergic, ipratropium bromide (intranasal)

- Treatment should be symptom-specific, e.g., oral antihistamines may be less effective for prominent congestion than other treatments; prominent rhinorrhea may respond to intranasal ipratropium; rhinitis-only symptoms may be treated with local (intranasal) rather than systemic (oral) therapy.

- For mild or intermittent symptoms, oral or nasal antihistamine may be considered first-line treatment.
• Newer generation (selective) oral antihistamines generally are recommended over older (nonselective) antihistamines. Patients with insomnia and pregnant women may prefer older antihistamines because of their sedating effects and longer safety history, respectively.

• Intranasal corticosteroids may be effective for more severe or persistent symptoms.

• Combination treatment (e.g., oral antihistamine plus intranasal corticosteroid, intranasal antihistamine and corticosteroid, antihistamine [oral or intranasal] plus sympathomimetic [oral or short-course (≤5 days to avoid rebound congestion) intranasal]) may be effective for symptoms nonresponsive to single medications.

• Oral sympathomimetics may cause insomnia; their use is limited in patients with certain comorbidities (e.g., diabetes mellitus, unstable hypertension).

• Oral leukotriene receptor antagonists may reduce asthma exacerbations in patients with comorbid asthma.

Benefit Application

Sublingual immunotherapy may be offered by specialized clinics.

Evidence Review

This policy is based on a 2003 TEC Assessment. This policy was updated regularly with literature reviews using MEDLINE; most recently, the literature was searched through August 11, 2016. Following is a summary of key literature to date.

Background

Sublingual immunotherapy (SLIT) is a potential alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy. SLIT is proposed as a more convenient alternative delivery route for treating a variety of allergic disorders.
Allergen-specific immunotherapy involves administering well-characterized allergen extracts, the potencies of which are measured and compared with a reference standard. An initial induction or build-up phase progressively increases the allergen dose; this is followed by multiple years of maintenance injections at the highest dose. Allergen-specific immunotherapy has been used to treat a variety of conditions including insect allergy, allergic rhinitis, and asthma. SCIT is the standard approach. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, SLIT is the most prominent. SLIT targets absorption to the sublingual and buccal mucosa. Allergen preparations used for SLIT are held under the tongue for one to several minutes and then swallowed or spit out.

**Allergic Rhinitis or Rhinoconjunctivitis**

**Systematic Reviews**

A 2003 TEC Assessment concluded that, due to the paucity of studies comparing sublingual immunotherapy (SLIT) with subcutaneous immunotherapy (SCIT) and the lack of U.S. Food and Drug Administration (FDA)–approved agents for use in SLIT, the evidence was insufficient on the use of SLIT for allergen immunotherapy.¹

In 2014, the FDA approved 3 sublingual allergen products for treatment of allergic rhinitis or rhinoconjunctivitis. A 2015 meta-analysis by Di Bona et al published a meta-analysis of studies on FDA-approved grass pollen SLIT tablets.² Thirteen studies met reviewers’ inclusion criteria, which were placebo-controlled RCTs on grass pollen SLIT in patients with a clinical history of seasonal allergic rhinoconjunctivitis and reported a symptom score or medication score. Most studies reported the same symptom score, which ranged from 0 to 18 points (higher scores indicate greater disease severity). In a pooled analysis of study data, SLIT was found to be more effective than placebo. The standardized mean difference (SMD) for the treatment effect was -0.28 (95% confidence interval [CI], -0.37 to -0.19; p<0.001). Findings were similar in an analysis excluding the 5 studies at high or moderate risk of bias.

**SLIT Compared With SCIT**

There are few head-to-head trials and thus SLIT and SCIT have been compared indirectly. Two indirect comparative effectiveness analyses published in 2014 and 2015 reached similar conclusions regarding relative efficacy of SLIT and SCIT for grass pollen allergies.³⁴ Both studies showed comparable reductions in allergic rhinitis symptoms with SLIT and SCIT, and 1 study showed comparable reductions in medication use.⁴ Both studies found evidence of publication bias.
In 2013, Dretzke et al published a systematic review that included an indirect comparison of SCIT and SLIT for seasonal allergic rhinitis using data from placebo-controlled trials. Several outcomes were examined. For symptom score, the overall standardized score difference (SSD) was 0.35 (95% CI, 0.13 to 0.59), a statistically significant result that favored SCIT. The overall SSD for medication score was 0.27 (95% CI, 0.03 to 0.53) which was statistically significant in favor of SCIT. The authors noted that heterogeneity among trials was substantial and that any conclusion about the clinical significance of the difference in outcomes between SCIT and SLIT was tentative.

**Randomized Controlled Trials**

The key RCTs that were performed as part of the FDA approval process for specific SLIT products are reviewed next.

Information about 3 SLIT products currently FDA-approved for the treatment of pollen-induced (i.e., seasonal) allergic rhinitis with or without conjunctivitis was obtained from FDA documents and prescribing information. Published RCTs are cited when these were identified. All RCTs were placebo-controlled and double-blinded. Patients had had a minimum 2-year history of allergic rhinitis or rhinoconjunctivitis and received treatment for their symptoms during the previous pollen season. Patients with mild intermittent asthma were included (16% across all trials); all other patients with asthma were excluded. Polysensitized people were included in some trials. Pre-seasonal dosing, i.e., commencing before the start of the allergen pollen season and continuing throughout the season, was used in all trials. The primary efficacy end point was the combined score (CS), defined as the mean of the Rhinoconjunctivitis Total Symptom Score (RTSS) and the Rescue Medication Score (RMS).

- **RTSS** is the sum of 6 symptom scores: sneezing, rhinorrhea, nasal itching, nasal congestion, itchy eyes, and watery eyes, each scored on a 0 (absent) to 3 (severe) scale (range, 0-18).

- **RMS** measures the potency of rescue medications used. For Oralair (Grastek and presumably Ragwitek), 1 point (6 points) was assigned to antihistamine, 2 points (8 points) to intranasal corticosteroid, 3 points (16 points) to oral corticosteroid, and 0 points (0 points) when no rescue medication was used. Maximum score was 3 for Oralair and 36 for Grastek (and presumably) Ragwitek.

- **CS** was calculated by combining RTSS and RMS. For Oralair, RTSS was divided by 6 and averaged with RMS (range, 0-3). For Grastek and Ragwitek, RTSS and RMS were summed (range, 0-54).
Although the CS is not validated, minimum clinically meaningful relative differences were prespecified. The relative difference (expressed as a percentage) was calculated by dividing the least squares mean difference by the within-group least squares mean of the placebo group. For Oralair (Grastek and Ragwitek), a minimum 15\(^{20}\) percentage point relative difference favoring the active agent, with a minimum 10\(^{10}\) percentage point lower bound of the 95% confidence interval, was required to demonstrate clinical efficacy. Analyses were intention-to-treat.

**Oralair**

Five pivotal trials were submitted to FDA in support of the biologics license application (BLA) for Oralair; 4 were natural field trials (3 European, 1 United States), and 1 was an environmental exposure chamber trial conducted in Europe. Trial participants had a history of seasonal rhinoconjunctivitis for at least 2 grass pollen seasons. Patients in European trials also had a positive skin prick test to 5-grass pollen extract and positive serum immunoglobulin E (IgE) to Timothy grass; patients in U.S. trials had a positive skin prick test to Timothy grass pollen extract. Polysensitive people exposed to additional allergens during grass pollen season (e.g., who lived in areas where grass pollen season overlapped with tree or ragweed pollen season) were excluded. The pregrass pollen season treatment duration was 4 months in most trials. As shown in Table 1, all studies satisfied the FDA requirement for efficacy.\(^6,7\) A sixth pivotal trial used a 2-month preseason treatment period and did not meet FDA criteria for efficacy.\(^8\)

**Table 1. Results of Five Pivotal Oralair Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Relative Difference In Combined Score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1: Phase 3, multicenter U.S. trial</td>
<td>473</td>
<td>28% (13% to 43%)</td>
</tr>
<tr>
<td>Trial 2: European dose-finding trial</td>
<td>284</td>
<td>30% (16% to 43%)</td>
</tr>
<tr>
<td>Trial 3: Phase 3, 3-year European trial</td>
<td>426</td>
<td>38% (22% to 55%)</td>
</tr>
<tr>
<td>Trial 4: Phase 3, European pediatric trial</td>
<td>278</td>
<td>30% (13% to 47%)</td>
</tr>
<tr>
<td>Trial 5: European EEC trial</td>
<td>89</td>
<td>29% (14% to 44%)(^a)</td>
</tr>
</tbody>
</table>

CI: confidence interval; EEC: environmental exposure chamber.

\(^a\) Rhinoconjunctivitis Total Symptom Score.
**Safety**

In the pooled FDA safety database, 1192 patients (13% children and adolescents) received Oralair 300 IR. Adverse events that occurred only at higher doses were noted as potential safety signals. In the pooled adult sample, the most common treatment-emergent adverse events (TEAEs) reported at higher frequencies with Oralair than with placebo were oral pruritus (33% vs 7%) and throat irritation (21% vs 4%). Other TEAEs reported in more than 2.5% of Oralair recipients and more commonly than in placebo recipients included tongue and ear pruritus; edema of the mouth, lip, tongue, or pharynx; oral paresthesia; and dyspepsia. Five percent of Oralair recipients and 1% of placebo recipients withdrew from trials due to TEAEs. Serious adverse events occurred in 13 (1.3%) Oralair recipients and 5 (0.6%) placebo recipients. Of those occurring in Oralair recipients, 1 episode of gastroenteritis requiring hospitalization was considered "possibly related" to Oralair, and 2 episodes of laryngopharyngeal disorders occurring within 5 minutes of receiving the first dose of Oralair were considered certainly related to Oralair. There were no reported deaths, cases of anaphylactic shock, or use of epinephrine in the pooled adult safety database.

The pooled child and adolescent safety database comprised 312 patients age 5 to 17 years; 45% of this sample was age 5 to 11 years (n=140). TEAEs reported at a higher frequency with Oralair than with placebo were oral pruritus (33% vs 4%), oral edema (13% vs 0%), and throat irritation (9% vs 5%). Other TEAEs reported in more than 2.5% of Oralair recipients were tongue, lip, and ear pruritus; tongue and lip edema; upper abdominal pain; and vomiting. As in the pooled adult sample, 5% of Oralair recipients and 1% of placebo recipients withdrew from trials due to TEAEs. No serious adverse event was considered related to Oralair. There were no reported deaths, cases of anaphylaxis, use of epinephrine, or severe laryngopharyngeal disorders in the pooled child and adolescent safety database.

A 2015 meta-analysis by Didier and Bons reviewed data on the safety of Oralair. The authors reported on 2 postmarketing safety studies. The 2008 study was conducted in 808 adults and 91 children and adolescents treated for a mean of 191 days. A total of 320 (36%) of patients experienced an adverse drug reaction (ADR). The 2009 study was conducted in 829 children and adolescents treated for a mean of 190 days and 218 (27%) patients experienced an ADR. ADRs led to discontinuation of the medication in 85 (9.5%) patients treated in 2008 and 72 (9.0%) patients treated in 2009. In the 2 studies combined, 9 serious ADRs possibly related to the medication were reported.
Grastek

Six phase 3 pivotal trials were submitted to FDA in support of the BLA for Grastek. All were natural field trials; 4 were conducted in North America and 2 in Europe. Trial participants had a history of grass pollen-induced rhinitis with or without conjunctivitis, positive serum IgE to Timothy grass pollen, and baseline forced expiratory volume in 1 second (FEV1) greater than 70% of predicted value. Polysensitized patients who required treatment for non-grass pollen allergies during grass pollen season were excluded. Patients were randomized 1:1 to daily Grastek 2800 BAU (bioequivalent allergy unit) or placebo. In 1 trial (trial 3), patients continued dosing for 3 years continuously. Three of 6 studies (2480/3501 [71%] of total patients) met the FDA criteria for efficacy, trials 1-3 (see Table 2). However, in trial 3, for the 241 (38%) of 634 patients who remained on-study for 2 years after discontinuing Grastek, the relative difference in the CS was 23% (95% CI, 6% to 37%), which no longer met the FDA criteria for efficacy.

Table 2. Results of Six Phase 3 Pivotal Grastek Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Relative Difference In Combined Score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1: U.S. and Canada adult and pediatric trial</td>
<td>1501</td>
<td>23% (13% to 36%)</td>
</tr>
<tr>
<td>Trial 2: U.S. and Canada pediatric trial</td>
<td>345</td>
<td>26% (10% to 38%)</td>
</tr>
<tr>
<td>Trial 3: European sustained effect trial</td>
<td>634</td>
<td>34% (26% to 42%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trial 4: German pediatric trial</td>
<td>253</td>
<td>24% (5% to 41%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trial 5: U.S. adult trial</td>
<td>329</td>
<td>10% (4% to 24%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trial 6: U.S. and Canada adult trial</td>
<td>439</td>
<td>21% (6% to 33%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pooled analysis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3094</td>
<td>20% (16% to 24%)</td>
</tr>
</tbody>
</table>

CI: confidence interval.  
<sup>a</sup> Year 1.  
<sup>b</sup> Did not meet Food and Drug Administration criteria for efficacy.  
<sup>c</sup> Does not account for 407 (12%) patients.

Safety

The pooled FDA safety database comprises 2389 patients who received Grastek (20% children and adolescents), 2116 (86%) of whom received Grastek 2800 BAU.(10) The most common TEAEs that led to trial discontinuation were oral pruritus (n=12), oral edema (n=7), and swollen tongue (n=6) among Grastek-treated adults, and throat irritation (n=6) and oral edema (n=5) among Grastek-treated children or adolescents. One adult patient who had severe swollen tongue required treatment with epinephrine. Systemic treatment-related allergic reactions (e.g., angioedema, dysphagia, cough) developed in 6 Grastek-treated adults and 1 Grastek-treated
adolescent. All were considered nonserious and not severe, although epinephrine was administered for 3 of the systemic reactions; onset ranged from immediate to day 42 of treatment. Among adults, 2 deaths were considered unrelated to Grastek. In pediatric studies, there were no reported deaths.\textsuperscript{11} Based on these data, FDA estimated a 0.1% to 0.5% risk of severe or serious laryngopharyngeal or systemic reactions with Grastek.\textsuperscript{12}

A 2015 article by Maloney et al analyzed safety data from 8 placebo-controlled trials on Grastek.\textsuperscript{13} There were 4195 patients in the pooled study population, 3314 adults and 881 children and adolescents. A total of 2115 were treated with grass SLIT tablets. Eight (0.4\%) SLIT-treated patients experienced a mild or moderate systemic allergic reaction, no serious systemic allergic reactions were reported. Sixteen (1.6\%) SLIT-treated patients reported treatment-related severe local allergic swellings. These comprised mouth edema, oropharyngeal swelling, palatal edema, pharyngeal edema, tongue edema, swollen tongue, throat tightness, and laryngeal edema.

**Ragwitek**

Two pivotal trials on Ragwitek are included in the prescribing information.\textsuperscript{13} Both natural field trials that enrolled adults ages 18 to 50 years who had ragweed pollen-induced allergic rhinitis with or without conjunctivitis, positive serum IgE to ragweed pollen, and baseline FEV1 at least 70\% of predicted. As shown in Table 3, both trials met FDA criteria for efficacy.

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Relative Difference In Combined Score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1: Phase 2/3 U.S. and Canada dose-finding trial</td>
<td>375</td>
<td>26% (14% to 38%)</td>
</tr>
<tr>
<td>Trial 2: Phase 3 U.S., Canada, and Eastern Europe dose-finding trial</td>
<td>394</td>
<td>27% (14% to 39%)</td>
</tr>
</tbody>
</table>

CI: confidence interval.

**Safety**

The pooled FDA safety database comprises 1057 adults who received at least 1 dose of Ragwitek. The most common TEAEs in this group were throat irritation (17\% vs 3\% in the placebo group), oral pruritus (11\% vs 2\%), ear pruritus (10\% vs 1\%), and oral paresthesia (10\% vs 4\%). Four percent and 0.8\% of Ragwitek-treated and placebo-treated patients, respectively,
discontinued treatment due to adverse reactions. Among Ragwitek-treated patients, the most common adverse reactions that led to study discontinuation were oral edema, swollen tongue, and dysphagia.

In trial 1 and trial 2 (total N=962 Ragwitek-treated patients), no deaths, systemic allergic reactions, or life-threatening events occurred. TEAEs tended to occur early in the treatment course (within the first week or weeks). Most (82% in trial 1, 96% in trial 2) TEAEs were mild to moderate in severity. In trial 2, the most frequently reported adverse event leading to discontinuation was swollen tongue (n=10), all assessed as mild or moderate in severity. One patient required epinephrine for what was considered a progression of treatment-related local reactions.

Section Summary

Three sublingual pollen extracts (1 multiple-allergen product [Oralair], 2 single-allergen products [Grastek and Ragwitek]) were FDA-approved for treatment of pollen-induced allergic rhinitis with or without conjunctivitis. Large, well-designed, randomized controlled trials supporting the marketing applications for these products provide consistent evidence of efficacy and safety. Although trials were placebo-controlled, rather than SCIT-controlled, minimum clinically important criteria for demonstrating efficacy were prespecified and were met in most studies. Moreover, a 2015 meta-analysis of the placebo controlled trials on FDA-approved grass pollen SLIT tablets found significantly greater efficacy in the treatment versus the control group.

House Dust Mite Specific Allergy

Systematic Reviews

In 2015, Liao et al published a systematic review and meta-analysis of studies on dust mite SLIT for treating children with asthma. The authors identified 11 RCTs and prospective controlled studies evaluating SLIT in children (i.e. <18 years old) with asthma and reporting clinical outcomes. Studies compared SLIT to placebo and/or pharmacotherapy. Findings of the meta-analysis were mixed. A pooled analysis of 8 studies reporting an asthma symptom score found that the score decreased significantly more in the SLIT groups than the control groups (SSD = -1.20; 95% CI, -2.07 to -0.33; p=0.007). A pooled analysis of 3 studies reporting medication scores did not find significant differences between groups in change in medication usage (SSD = -0.52; 95% CI, -1.753 to 0.713; p=0.408). Group also did not differ significantly in an analysis of change in specific Dermatophagoides pteronyssinus IgE levels before and after treatment (SSD=0.430;
95% CI, -0.045 to 0.905; p=0.076). In all analyses, there were high levels of heterogeneity among studies.

In 2014, Gendelman and Lang published a systematic review of house dust mite SLIT in atopic dermatitis.\textsuperscript{16} Five studies (total N=344 patients) were identified, but low methodologic quality limited conclusions that could be drawn. In 2013, Bae et al published a systematic review and meta-analysis of house dust mite immunotherapy for children and adults with house dust mite-induced atopic dermatitis.\textsuperscript{17} Literature was searched through November 2012, and 8 placebo-controlled RCTs were included (6 SCIT [N=307], 2 SLIT [N=90]). Using a dichotomous variable for treatment success, defined as the proportion of patients whose condition improved as assessed by investigators or patients, regardless of evaluation method used, the odds ratio was 5.35 (95% CI, 1.61 to 17.77). The significance of this finding is uncertain given the heterogeneity of treatments administered and use of a nonstandard outcome measure.

**Randomized Controlled Trials**

Focusing on trials comparing SLIT and SCIT, 3 were published in 2010 and 2011.\textsuperscript{18-20} None of these found statistically significant differences between treatment with SLIT and SCIT in overall reduction of symptoms or medication use. For example, Eifan et al published findings on 48 children who had asthma or rhinitis and had been sensitized to house dust mites.\textsuperscript{18} Participants were randomized to receive treatment with SLIT (n=16), SCIT (n=16), or usual pharmacotherapy alone (n=16). There was no significant difference in efficacy between the SLIT and SCIT groups. Compared with pharmacotherapy alone, both immunotherapy groups demonstrated significant reduction in rhinitis and asthma symptom scores and medication use scores. A small 2013 RCT compared house dust mite SCIT and SLIT in children with rhinitis and asthma who were monosensitized to house dust mites.\textsuperscript{21} Thirty children were randomized to receive 1 or 2 years of SCIT or SLIT. Symptom scores were improved after 1 year of SCIT and after 2 years of SLIT. The significance of this finding is uncertain given the small sample size.

**Section Summary**

A number of RCTs have been published evaluating SLIT for patients with dust mite allergies, mainly placebo-controlled. Meta-analyses of these studies found high levels of heterogeneity among studies. The most recent meta-analysis, published in 2015, had mixed findings; some outcomes but not others favored SLIT over placebo or pharmacological treatment. Trials comparing SLIT and SCIT tended not to find differences in efficacy, but conclusions are limited due to small sample sizes.
Food Allergy

Systematic Reviews

A 2014 systematic review of the literature identified 5 randomized trials of SLIT in patients with food allergies (fruit, peanut), 4 of which showed symptom improvement compared with placebo. However, all trials were considered low quality; for example, most did not include symptom assessments off treatment.

Also in 2014, Romantsik et al reported on a Cochrane review of oral immunotherapy and SLIT for egg allergy. No RCTs of SLIT were identified through in their literature search (through November 2013).

Randomized Controlled Trials

Several RCTs have been published after the systematic reviews. In 2015, Narisety published a double-blind RCT comparing oral immunotherapy and SCIT in 21 children with peanut allergies. Five (24%) children dropped out. Among the remaining 16 patients, those in the oral immunotherapy group had a significantly greater challenge threshold at 12 months than the SCIT group (p=0.01). However, only 4 patients had sustained unresponsiveness. Adverse events, generally mild, were significantly more common in the oral immunotherapy group. A 2015 RCT by Burks et al reported on a placebo-controlled SLIT study in 40 patients (20 per group) with peanut allergy. At week 44, 14 (70%) in the SLIT group were considered responders compared with 3 (15%) in the placebo group. Seventeen patients in the placebo group crossed over to receive high-dose SLIT and 7 (44%) were considered responders after 44 weeks.

No trials comparing SLIT and SCIT for treatment of food allergies were identified.

Section Summary

There are few RCTs evaluating SLIT for treatment of food allergies and these studies had small sample sizes and tended to be rated as low quality by systematic reviewers. The available RCTs did not consistently find that SLIT was more effective than placebo or oral immunotherapy. No RCTs were identified that compared SLIT and SCIT.
Summary of Evidence

For individuals who have pollen-induced allergic rhinitis or rhinoconjunctivitis who receive sublingual immunotherapy, the evidence includes randomized controlled trials (RCTs) and systematic reviews.

Relevant outcomes are symptoms, quality of life, hospitalizations, medication use, and treatment-related morbidity. Three sublingual pollen extracts are U.S. Food and Drug Administration (FDA) approved for treatment of pollen-induced allergic rhinitis with or without conjunctivitis. Large, well-designed RCTs supporting the marketing applications for these products have provided consistent evidence of efficacy and safety. Although trials were placebo-controlled, rather than SCIT-controlled, minimum clinically important criteria for demonstrating efficacy were prespecified and were met in most studies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have house dust mite-specific allergy who receive sublingual immunotherapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, quality of life, hospitalizations, medication use, and treatment-related morbidity. Most RCTs evaluating SLIT for patients with dust mite allergies have been placebo-controlled. Meta-analyses of these studies have found high levels of heterogeneity among studies. The most recent meta-analysis, published in 2015, had mixed findings; some outcomes but not others favored SLIT over placebo or pharmacologic treatment. Trials comparing SLIT and SCIT have tended not to find differences in efficacy, but conclusions are limited due to small sample sizes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have food allergy who receive sublingual immunotherapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, quality of life, hospitalizations, medication use, and treatment-related morbidity. A few RCTs have evaluated SLIT for treatment of food allergies and these studies have had small sample sizes and have tended to be rated as low quality by systematic reviewers. The available RCTs have not consistently found that SLIT is more effective than placebo or oral immunotherapy. No RCTs were identified that compared SLIT and SCIT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Consideration of Age

The ages stated in this policy for which Grastek®, Ragwitek®, and Oralair®, are considered medically necessary is based on the ages approved in the FDA labeling.
Practice Guidelines and Position Statements

*American Academy of Otolaryngology - Head and Neck Surgery Foundation*

In 2015, they published a clinical practice guideline on allergic rhinitis that contained the following statement\(^{26}\): “Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls. Recommendation based on RCTs and systematic reviews, with a preponderance of benefit over harm.”

*American Academy of Allergy, Asthma and Immunology et al*

In 2013, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the European Academy of Allergy and Clinical Immunology (EAACI) published a consensus report on allergy immunotherapy.\(^{27}\) The report summarized the literature and current practices in the United States and Europe; it did not include clinical recommendations. The authors concluded: “AIT (allergy immunotherapy) is effective in reducing symptoms of allergic asthma and rhinitis, as well as venom-induced anaphylaxis. In addition, AIT modifies the underlying course of disease. However, AIT remains a niche treatment secondary to symptomatic drugs because of its cost, long duration of treatment and concerns regarding safety and effectiveness....”

In 2011, a joint task force of AAAAI, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology issued updated practice parameters for allergen immunotherapy.\(^{28}\) The document stated that RCTs of SLIT in patients with allergic rhinitis and asthma have demonstrated significant improvement in symptoms. The authors noted that there were no FDA-approved extract formulations for a noninjection route of immunotherapy.

*European Academy of Allergy and Clinical Immunology*

In 2014, EAACI published evidence-based guidelines on the diagnosis and management of food allergy.\(^{29}\) Based on single-arm studies (level III evidence), guideline authors concluded: “Food allergen-specific immunotherapy for primary food allergy is a promising immunomodulatory
treatment approach, but it is associated with risk of adverse reactions, including anaphylaxis; it is therefore not currently recommended for routine clinical use.” Based on expert opinion (level IV evidence), guideline authors stated: “For patients with respiratory or other allergy symptoms to inhalant allergens that may also cause cross-reactive food allergy, specific immunotherapy is only recommended for the treatment of the respiratory symptoms, not for cross-reactive food allergy.”

American Academy of Otolaryngology – Head and Neck Surgery Foundation

In 2015, the American Academy of Otolaryngology – Head and Neck Surgery Foundation published evidence-based consensus guidelines on allergic rhinitis. Based on RCTs and systematic reviews showing greater benefit than harm, guideline developers recommended SLIT or SCIT “for patients with allergic rhinitis who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls.” The purpose of the statement was “to increase the awareness of immunotherapy as a treatment for allergic rhinitis, promote its appropriate use, and reduce unnecessary or harmful variation in care.”

World Allergy Organization

In 2013, the World Allergy Organization updated its position paper on SLIT. Evidence-based conclusions included:

- Grass-pollen SLIT is effective in seasonal allergic rhinitis in children 5 years of age or older and probably effective in children as young as 4 years of age.

- Grass or house dust mite SLIT may be used for allergic rhinitis in children with asthma, although more large randomized trials are needed.

- Although SLIT for latex allergy, atopic dermatitis, food allergy, and hymenoptera venom is under investigation, more evidence is needed to support the use of SLIT for these indications.

- Patients eligible for SLIT should have a history of symptoms related to allergen exposure and a documented positive allergen-specific IgE test.

- SLIT may be considered as initial treatment, particularly for patients whose allergy is uncontrolled with optimal pharmacotherapy (i.e., those who have severe chronic upper
airway disease); patients intolerant of injections or adverse effects of pharmacotherapy; or patients who do not want to be on constant or long-term pharmacotherapy.

- Failure of pharmacotherapy is not an essential prerequisite for SLIT.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Trial Name</th>
<th>Planned Enrollent</th>
<th>Primary Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02277483</td>
<td>Efficacy and Safety of LAIS® Mites Sublingual Tablets in Patients Aged Over 60 Years Suffering From House Dust Mite-induced Allergic Rhinconjunctivitis With/Without Asthma</td>
<td>45</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>NCT02443805</td>
<td>Efficacy and Safety of STG320 Sublingual Tablets of House Dust Mite (HDM) Allergen Extracts in Adults and Adolescents With HDM-associated Allergic Rhinitis</td>
<td>990</td>
<td>Feb 2017</td>
</tr>
<tr>
<td>NCT02005627</td>
<td>Randomized Placebo-controlled Study of Grass Pollen Allergen Immunotherapy Tablet (AIT) for Seasonal Rhinitis: Time Course of Nasal, Cutaneous and Immunological Outcomes</td>
<td>44</td>
<td>Mar 2017</td>
</tr>
<tr>
<td>NCT02216175</td>
<td>Phase 2/3 Clinical Trial to Assess the Effect of a Sublingual Treatment Phase Prior to Oral Immunotherapy in Children With Cow’s Milk Allergy</td>
<td>53</td>
<td>May 2017</td>
</tr>
<tr>
<td>NCT02304991</td>
<td>Peanut Sublingual Immunotherapy Induction of Clinical Tolerance of Newly Diagnosed Peanut Allergic 12 to 48 Month Old Children</td>
<td>50</td>
<td>April 2020</td>
</tr>
<tr>
<td>NCT01373242</td>
<td>Peanut Sublingual Immunotherapy and Induction of Clinical Tolerance in Peanut Allergic Children</td>
<td>50</td>
<td>Jun 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

In April 2014, FDA approved the first sublingual allergen extract tablets for treatment of pollen-induced allergic rhinitis with or without conjunctivitis.

- On April 1, FDA approved Oralair® allergen extract (Stallergenes S.A., Antony, France) for patients 10 to 65 years of age. Oralair® contains freeze-dried pollen allergen extracts of 5 grasses: Kentucky Blue Grass, Orchard, Perennial Rye, Sweet Vernal, and Timothy.

- On April 11, FDA approved Grastek® Timothy grass pollen (Phleum pretense) allergen extract (Merck, Whitehouse Station, NJ) for patients 5 to 65 years of age. Grastek® is marketed in Europe as Grazax®.

- On April 17, FDA approved Ragwitek® short ragweed pollen allergen extract (Merck, Whitehouse Station, NJ) for patients 18 to 65 years of age.

References


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**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>11/05/97</td>
<td>Add to Medicine Section - New Policy</td>
</tr>
<tr>
<td>11/03/98</td>
<td>Replace Policy - Scheduled review, no criteria changes.</td>
</tr>
<tr>
<td>08/12/03</td>
<td>Replace Policy - Policy regarding sublingual immunotherapy and SET-guided immunotherapy reviewed; policy statement unchanged.</td>
</tr>
<tr>
<td>08/09/05</td>
<td>Replace Policy - Policy revised with literature search; policy retitled, now focuses solely on sublingual immunotherapy; other forms of immunotherapy no longer addressed.</td>
</tr>
<tr>
<td>06/16/06</td>
<td>Update Scope and Disclaimer - No other changes.</td>
</tr>
<tr>
<td>11/14/06</td>
<td>Replace Policy - Policy updated with literature review; policy statement unchanged. References added.</td>
</tr>
<tr>
<td>05/13/08</td>
<td>Replace Policy - Policy updated with literature search; no change to the policy statement. References added.</td>
</tr>
<tr>
<td>05/12/09</td>
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<td>References 8 and 11 added; other references renumbered/removed. ICD-10 codes added to policy.</td>
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<td>07/25/12</td>
<td>Related Policies Update – Title to 2.01.01 has been changed to include: (i.e., Multiple Chemical Sensitivities)</td>
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<td>08/24/12</td>
<td>Update Coding Section – ICD-10 codes are now effective 10/01/2014.</td>
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<tr>
<td>05/28/13</td>
<td>Replace policy. Policy updated with literature review through January 22, 2013; no change in policy statement. References 4, 8 and 14 added; other references renumbered/removed.</td>
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<td>Replace policy. Policy updated with literature review through April 20, 2013. No change in policy statement. References 2, 3, 14, 17 and 18 added; other references renumbered/removed.</td>
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<tr>
<td>07/14/14</td>
<td>Annual Review. Policy statement changed to medically necessary for Oralair®, Grastek®, and Ragwitek® to treat grass or short ragweed pollen allergies when criteria are met. These medications are investigational for all other uses. Policy updated with literature review through April, 2014. References 1-8, 14-16, 20-42, 47, 52, and 55 added, 10 and 54 updated; 22 deleted; others renumbered/removed. Policy statement changed as noted. Coding update: CPT codes 95144-95165 and ICD-9 and ICD-10 diagnosis and procedure codes removed from policy.</td>
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<td>08/28/15</td>
<td>Update Related Policies. Remove 2.01.01 as it was archived.</td>
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<tr>
<td>11/08/16</td>
<td>Annual Review. Policy updated with literature review through August 11, 2016; references 2, 9, 13, 15, and 24-26 added. Policy statements unchanged. Language added to the Rationale section to indicate that the age application of the policy is based on FDA-labeling.</td>
</tr>
<tr>
<td>03/03/17</td>
<td>Policy moved to new format. No change to policy statement.</td>
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  Email AppealsDepartmentInquiries@Premera.com

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You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
- U.S. Department of Health and Human Services
  200 Independence Avenue SW, Room 509F, HHH Building
  Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
  Complaint forms are available at

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