Policy Number	**MED206.006**
Policy Effective Date	**12/15/2024**

Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Sublingual immunotherapy using Oralair®, Grastek®, or Ragwitek® **may be considered medically necessary**, when used according to the U.S. Food and Drug Administration labeling, for the treatment of pollen-induced allergic rhinitis or rhinoconjunctivitis when the following conditions are met:

- Individual has a history of rhinitis or rhinoconjunctivitis symptoms related to grass or short ragweed pollen exposure; AND
- Individual 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); AND
- Individual's symptoms are not adequately controlled by appropriate pharmacotherapy or avoidance.

Sublingual immunotherapy using Odactra® **may be considered medically necessary**, when used according to the U.S. Food and Drug Administration labeling, for the treatment of house dust mite-induced allergic rhinitis or rhinoconjunctivitis when the following conditions are met:
- Individual has a history of rhinitis or rhinoconjunctivitis symptoms related to dust mite exposure; AND
- Individual has a documented positive house dust mite-specific skin test or house dust mite-specific IgE test (allergy must be confirmed by positive skin test, using licensed house dust mite allergen extracts or in vitro testing for house dust mite-specific IgE antibodies to the *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* species); AND
- Individual's symptoms are not adequately controlled by appropriate pharmacotherapy.

Sublingual immunotherapy as a technique of allergy immunotherapy **is considered experimental, investigational and/or unproven** for all other uses.

Policy Guidelines

Use of Oralair, Grastek, and Ragwitek

Documentation of Allergy

Allergy must be confirmed by positive skin test or in vitro testing for pollen-specific immunoglobulin E 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 sublingual immunotherapy 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. Individuals must be prescribed an epinephrine autoinjector and be trained on how to use it.
- Oralair, Grastek and Ragwitek have been FDA approved for individuals 5 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 (precoseasonal 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.

- For Oralair, dose titration is required in individuals 5 to 17 years of age. Titration can be completed over 3 days at home, 100 index of reactivity (IR) on day 1, 2 times 100 IR on day 2, and 3 times 100 IR on day 3. In individuals between 18 and 65 years, no dose titration is needed; treatment is initiated at the maintenance dose of 300 IR.
- Grastek and Ragwitek both are initiated at the maintenance dose (2800 bioequivalent allergy unit and 12 Amb a 1-unit, respectively).

Use of Odactra

Documentation of Allergy

Allergy must be confirmed by positive skin test, using licensed house dust mite allergen extracts or in vitro testing for house dust mite-specific immunoglobulin E antibodies to the *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* species.

Contraindications

Contraindications are as listed above for Oralair, Grastek, and Ragwitek.

Administration and Dose

- Prescribing information includes a black box warning for severe allergic reactions including anaphylaxis and severe laryngopharyngeal edema. Individuals must be prescribed an epinephrine autoinjector and be trained on how to use it.
- Odactra is approved by the FDA for individuals 12 to 65 years of age.
- Odactra is dosed at one 12 SQ-HDM tablet daily. Per the FDA, "SQ-HDM is the dose unit for ODACTRA. SQ is a method of standardization of biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite."
- 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.

Pharmacotherapy of Pollen-Induced Allergic Rhinitis

There is general agreement among clinical practice guidelines on the pharmacologic treatment of pollen-induced rhinitis or rhinoconjunctivitis:

- Treatment should be individualized based on symptom severity and duration, comorbidities and age, preference (e.g., route of administration, tolerance for adverse events), and previous treatment history.
- Measures to increase treatment adherence (e.g., shared decision making, consideration of the individual'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) or “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.

Medication classes commonly used to treat allergic rhinitis include: H_1 antihistamines (oral and intranasal), corticosteroids (oral [short-course for severe disease] and intranasal), leukotriene

receptor antagonists (oral), sympathomimetic decongestants (oral and intranasal), chromones (intranasal), and the 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, an oral or nasal antihistamine may be considered first-line treatment.
- Newer generation (selective) oral antihistamines are recommended over older (nonselective) antihistamines. Individuals with insomnia and pregnant individuals 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 individuals with certain comorbidities (e.g., diabetes, unstable hypertension).
- Oral leukotriene receptor antagonists may reduce asthma exacerbations in individuals with comorbid asthma.

Coding

CPT codes for allergen immunotherapy are specific to parenteral administration and should not be used for sublingual immunotherapy. The unlisted CPT code 95199 might be used.

Description

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.

Background

Allergen-specific immunotherapy involves administering well-characterized allergen extracts, the potencies of which are measured and compared with a reference standard. (1) An initial induction or build-up phase progressively increases the allergen dose; this is followed by years of maintenance injections at the highest dose. Allergen-specific immunotherapy has been used to treat various conditions, including insect allergy, allergic rhinitis, and asthma. Subcutaneous immunotherapy is the standard of care. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, sublingual immunotherapy is the most prominent. Sublingual immunotherapy targets absorption to the sublingual and buccal mucosa. Allergen preparations used for sublingual immunotherapy are held under the tongue for 1 to several minutes and then swallowed or spit out.

Regulatory Status

In April 2014, the first sublingual allergen extract tablets were approved by the U.S. Food and Drug Administration (FDA) through the biologics license application process for treatment of pollen-induced allergic rhinitis with or without conjunctivitis:

- On April 1, the FDA approved Oralair (Stallergenes) allergen extract for patients 10 to 65 years of age (product is now approved for patients 5 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, the FDA approved Grastek (Merck) Timothy grass pollen (*Phleum pretense*) allergen extract for patients 5 to 65 years of age (Grastek is marketed in Europe as Grazax®).
- On April 17, the FDA approved Ragwitek (Merck) short ragweed pollen allergen extract for patients 18 to 65 years of age. On April 16, 2021, Ragwitek received FDA approval for use in patients 5 to 17 years of age.

In March 2017, the FDA approved Odactra (Merck) allergan extract for patients 18 to 65 years of age (product is now approved for patients 12 to 65 years of age) who have house dust mite-induced allergic rhinitis with or without conjunctivitis. Odactra contains freeze-dried extracts of dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*).

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Pollen-Induced Allergic Rhinitis or Rhinoconjunctivitis

Clinical Context and Therapy Purpose

The purpose of sublingual immunotherapy (SLIT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with pollen-induced allergic rhinitis or rhinoconjunctivitis.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with pollen-induced allergic rhinitis or rhinoconjunctivitis.

Interventions

The therapy being considered is SLIT.

Comparators

The following therapies and practices are currently being used to treat pollen-induced allergic rhinitis or rhinoconjunctivitis: subcutaneous immunotherapy (SCIT) and standard care without allergen-specific immunotherapy.

Outcomes

The general outcomes of interest are symptoms, quality of life, hospitalizations, medication use, and treatment-related morbidity. Follow-up over months to years is of interest to monitor outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A meta-analysis by Meltzer et al. (2021) evaluated SLIT tablets and pharmacotherapy for allergic rhinitis in pediatric and adult patients. (2) Patients receiving SLIT were allowed rescue symptom-relieving pharmacotherapy in all trials. In adults and adolescents, the mean difference in total nasal symptom score (TNSS) between SLIT tablets and placebo was 0.57 (95% confidence interval [CI], 0.41 to 0.73) for patients with seasonal allergic rhinitis (n=4 trials) and 0.65 (95% CI, 0.42 to 0.88) for patients with perennial allergic rhinitis (n=3 trials). No trials for perennial allergic rhinitis in pediatric patients were found, but 2 trials in pediatric patients with seasonal allergic rhinitis found improved TNSS scores with SLIT tablets compared with placebo

(mean difference, 0.53; 95% CI, 0.19 to 0.87). Although not directly compared, the percentage improvement with SLIT was similar to that of intranasal corticosteroids.

The meta-analysis by Yang et al. (2018) evaluated the use of SLIT to treat allergic conjunctivitis or allergic rhinoconjunctivitis in patients aged 3 to 18 years, specifically looking for SLIT's effectiveness for relieving eye symptoms. (3) Thirteen RCTs were identified, which included a total of 1592 pediatric patients. Overall, the trials showed that allergic conjunctivitis symptoms were significantly reduced by SLIT (standardized mean difference [SMD], -0.21; 95% CI, -0.41 to -0.01; p=.04; I^2=55%). However, on a subgroup analysis of the different SLIT modalities, ocular symptoms improved with tablets (p<.001) but not drops (p=.47); in addition, SLIT significantly reduced pollen-induced allergic conjunctivitis (p<.001) but not mite-induced (p=.34). The investigators stated that the meta-analysis was limited by variations in the baseline severity of patients' allergic conjunctivitis or allergic rhinoconjunctivitis, the ocular scoring systems used, and in the SLIT therapeutic regimens, as well as the small sample sizes (n<30) of 46% of the studies. However, their results showed that SLIT effectively reduced conjunctivitis symptoms in pediatric patients with allergic conjunctivitis and allergic rhinoconjunctivitis.

In 2014, the U.S. Food and Drug Administration (FDA) approved 3 sublingual allergen products for the treatment of allergic rhinitis or rhinoconjunctivitis. Di Bona et al. (2015) conducted a meta-analysis of studies on FDA approved grass pollen SLIT tablets. (4) Thirteen studies met reviewers' inclusion criteria, which were placebo-controlled randomized trials on grass pollen SLIT in patients with a clinical history of seasonal allergic rhinoconjunctivitis and data on symptom scores or medication scores. Most studies reported the same symptom score, which ranged from 0 to 18 points (higher scores indicating greater disease severity). In a pooled analysis, SLIT was more effective than placebo. The SMD for the treatment effect was -0.28 (95% CI, -0.37 to -0.19; p<.001). Findings were similar in an analysis that excluded the 5 studies at high or moderate risk of bias.

Sublingual Immunotherapy versus Subcutaneous Immunotherapy

Dretzke et al. (2013) published a systematic review that included an indirect comparison of SLIT and SCIT for seasonal allergic rhinitis, using data from placebo-controlled trials. (5) 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. Reviewers noted that heterogeneity among trials was substantial and that any conclusions about the clinical significance of the differences in outcomes between SCIT and SLIT would be tentative. An updated systematic review of 7 RCTs in patients with allergic rhinitis by Tie et al. (2022) failed to find a difference between SLIT or SCIT. (6) The authors also conducted an indirect comparison of trials evaluating SCIT versus placebo (n=13) or SLIT versus placebo (n=33) and found no significant differences between SCIT and SLIT.

Two indirect comparative effectiveness analyses, Nelson et al. (2015) and Dranitsaris et al. (2014), reached similar conclusions on the relative efficacy of SLIT and SCIT for grass pollen allergies. (7, 8) Both studies showed comparable reductions in allergic rhinitis symptoms with

SLIT and SCIT, and 1 showed comparable reductions in medication use. (7) Both reviews found evidence of publication bias.

Randomized Controlled Trials

The key RCTs performed as part of the FDA approval process for specific SLIT products are reviewed next, followed by recent RCTs and meta-analyses.

Information about 3 SLIT products approved by the FDA for the treatment of pollen-induced (i.e., seasonal) allergic rhinitis with or without conjunctivitis was obtained from the FDA documentation and prescribing information. Published RCTs are cited when identified. All randomized trials 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. Precoseasonal 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 endpoint was the combined score, 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 to 18).
- RMS measures the potency of rescue medications used. For Oralair (and for Grastek and presumably Ragwitek), 1 point (up to 6 points) was assigned to antihistamine, 2 points (up to 8 points) to intranasal corticosteroid, 3 points (up to 16 points) to oral corticosteroid, and 0 points (0 points) when no rescue medication was used. The maximum score was 3 for Oralair and 36 for Grastek (and presumably Ragwitek).
- The combined score was calculated by combining RTSS and RMS. For Oralair, RTSS was divided by 6 and averaged with RMS (range, 0 to 3). For Grastek and Ragwitek, RTSS and RMS were summed (range, 0 to 54).

Although the combined score is not validated, the 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 (and for 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% CI, was required to demonstrate clinical efficacy. Analyses were intention-to-treat.

Oralair

Five pivotal trials were submitted to the FDA in support of the biologics license application for Oralair; 4 were natural field trials (3 European, 1 U.S.) and 1 was an environmental exposure chamber trial (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 a 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. A sixth pivotal trial used a 2-month preseason treatment period and did not meet the FDA criteria for efficacy. (9)

Table 1. Results of 5 Pivotal Oralair Trials

Trial	N	Relative Difference in Combined Score % (95% CI)
Trial 1: Phase 3, multicenter U.S. trial	473	28 (13 to 43)
Trial 2: European dose-finding trial	284	30 (16 to 43)
Trial 3: Phase 3, 3-year European trial	426	38 (22 to 55)
Trial 4: Phase 3, European pediatric trial	278	30 (13 to 47)
Trial 5: European EEC trial	89	29 (14 to 44)[a]

CI: confidence interval; EEC: environmental exposure chamber; N: number; U.S.: United States.
[a] Rhinoconjunctivitis Total Symptom Score.

Safety

In the pooled FDA safety database, 1192 patients (13% children and adolescents) received Oralair 300 index of reactivity (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 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 ages 5 to 17 years; 45% (n=140) of this sample was age 5 to 11 years. The 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%), respectively. 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 meta-analysis by Didier and Bons (2015) reviewed safety data on Oralair. (10) Reviewers reported on 2 postmarketing safety studies. A 2008 study was conducted in 808 adults and 91 children and adolescents treated for a mean of 191 days. A total of 320 (36%) patients experienced an adverse drug reaction (ADR). A 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 medication discontinuation in 85 (9.5%) patients treated in the 2008 study and 72 (9.0%) patients treated in the 2009 study. In both studies combined, 9 serious ADRs possibly related to the medication were reported.

Grastek

On April 11, 2014, Grastek was approved in the U.S. for use in individuals 5 to 65 years of age. Grastek is indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis as confirmed by positive skin tests or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. The product was first approved under the trade name Grazax in Sweden and has subsequently received marketing authorizations in 31 countries.

Six phase 3 pivotal trials were submitted to the FDA in support of the biologics license application 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 greater than 70% of the predicted value. Polysensitized patients who required treatment for nongrass pollen allergies during grass pollen season were excluded. Patients were randomized 1:1 to daily Grastek 2800 bioequivalent allergy unit or placebo. In 1 trial (trial 3), patients continued dosing for 3 years continuously. Three (trials 1 through 3) of 6 studies (2480/3501 [71%] of total patients) met the FDA criteria for efficacy (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 combined score was 23% (95% CI, 6% to 37%), which no longer met the FDA criteria for efficacy.

Table 2. Results of 6 Phase 3 Pivotal Grastek Trials

Trial	N	Relative Difference in Combined Score % (95% CI)
Trial 1: U.S. and Canada adult and pediatric trial	1501	23 (13 to 36)
Trial 2: U.S. and Canada pediatric trial	345	26 (10 to 38)
Trial 3: European sustained effect trial	634	34 (26 to 42)[a]
Trial 4: German pediatric trial	253	24 (5 to 41)[b]
Trial 5: U.S. adult trial	329	10 (4 to 24)[b]
Trial 6: U.S. and Canada adult trial	439	21 (6 to 33)[b]
Pooled analysis (11)	3094[c]	20 (16 to 24)

CI: confidence interval. N=number; U.S.: United States.

[a] Year 1.

[b] Did not meet U.S. Food and Drug Administration criteria for efficacy.

[c] Does not account for 407 (12%) patients.

Safety

The pooled FDA safety database comprised 2389 patients who received Grastek (20% children and adolescents), 2116 (86%) of whom received Grastek 2800 bioequivalent allergy unit. (11) 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 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, 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, no deaths were reported. (12) Based on these data, the FDA estimated a 0.1% to 0.5% risk of severe or serious laryngopharyngeal or systemic reactions with Grastek. (13)

Maloney et al. (2015) analyzed safety data from 8 placebo-controlled trials on Grastek. (14) There were 4195 patients in the pooled study population, 3314 adults and 881 children and adolescents. A total of 2115 was 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.

Grastek is the U.S. version of Grazax, which is marketed in Europe. However, the 2 drugs are essentially the same, and studies on the efficacy and safety of Grazax are relevant to this medical policy as described below.

Grazax

Systematic Reviews

A meta-analysis of placebo-controlled randomized trials by Feng et al. (2017) evaluated the efficacy and safety of SLIT use in pollen-induced allergic rhinitis in children ages 3 to 18 years. (15) Of the 26 eligible RCTs (published 1990 to 2016), 14 (1475 patients) studied symptom reduction, and 12 (1196 patients) examined medication use. Only the subgroup analysis evaluated the use of SLIT for the population of interest, thereby rendering the overall results of the meta-analysis beyond the scope of this medical policy. Nasal symptom and medication scores were assessed using mean differences and SMD (see Table 3).

Table 3. Subgroup Analysis of Efficacy for Pollen-Induced Allergic Rhinitis

Outcomes	No. of Studies	No. of Patients	SMD	95% CI	p
Symptom score	14	1475	-0.43	-0.69 to -0.17	.001

Medication score	12	1196	-0.26	-0.44 to -0.08	.005

CI: confidence interval, No: number; SMD: standard mean difference.

Although the meta-analysis overall demonstrated a significant reduction in symptoms and medication use for pediatric patients, the subgroup analysis found that that SLIT was effective for grass pollen-induced allergic rhinitis only. Overall, oral pruritus was the most common adverse event in children who were receiving SLIT. Although the trial addressed heterogeneity and potential of bias overall, neither was specifically reported for the studies included in the subgroup analysis.

Randomized Controlled Trials

A double-blinded, placebo-controlled randomized trial by Scadding et al. (2017) enrolled 106 adults with moderate-to-severe seasonal allergic rhinitis at a single-center to determine whether 2 years of SLIT improved symptoms at the 3-year follow-up,1 year after discontinuation of treatment. (16) Patients were randomized to SLIT with placebo, SCIT with placebo, or double-placebo; 92 patients completed the study overall. The primary endpoint was the measurement of the TNSS (range 0 [best] to 12 [worst] within 10 hours of the challenge) after a nasal response challenge at 3-year follow-up. Although the intention-to-treat population included all randomized patients, only those with an evaluable endpoint were included in the analysis (modified intention-to-treat [ITT]) (see Table 4).

Table 4. Imputed TNSS Scores for the Modified ITT Population

Treatment Groups	**Pretreatment**			**3 Years**		
	N	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**
Sublingual immunotherapy	34	6.36	5.76 to 6.96	30	4.55	3.67 to 5.43
Placebo	33	6.06	5.23 to 6.88	31	4.82	3.90 to 5.74
Subcutaneous immunotherapy	33	6.10	5.32 to 6.89	31	3.96	3.21 to 4.71

CI: confidence interval; ITT intention to treat; N: number(s); TNSS: Total Nasal Symptom Score.

The reported between-group difference was -0.18 (95% CI, -1.25 to 0.90; p=.75), adjusted for baseline, demonstrating no statistically significant improvement in the primary outcome compared with placebo.

Secondary endpoints included a change in peak nasal inspiratory flow after challenge, seasonal weekly visual analog scale score, seasonal weekly rhinitis quality of life, end-of-season global rhinitis severity score, seasonal medication use, and early and late skin responses to intradermal allergen. There was no benefit from SLIT or SCIT compared with placebo for peak nasal inspiratory flow, visual analog scale scores, seasonal weekly rhinitis quality of life, or global rhinitis severity score. Throughout the 3 years, approximately 90% of participants returned some medication, and 47% to 70% returned all medication. At year 3, however, there were no significant between-group differences in medication use. Both SLIT and SCIT had lower early and late skin responses to allergen than placebo. Although there were no serious adverse events from treatment, the SCIT group had a greater number of adverse events overall.

Statistically significant differences between SLIT and placebo included hypersensitivity (p=.19) and dyspepsia (p=.03).

Researchers reported several limitations. To avoid seasonal variability in natural pollen exposure, the trial used the nasal allergen challenge in a controlled environment rather than daily symptom diaries. The trial focused on intervention effects for 2 years only and was not designed to compare 2 with 3 years of SLIT. Though the trial was not powered to compare SLIT with SCIT, and dropout rates were similar among the 3 groups, adherence was greater in the SLIT group (>90%) compared with the SCIT group (82%). Because blinding may have been compromised in patients in the placebo groups who experienced adverse events, an individual who was not involved in seasonal assessments or the clinical immunotherapy protocol performed all nasal challenges and skin tests.

The largest pediatric trial to date by Valvorita et al. (2018) assessed the impact of SLIT on grass pollen allergic rhinoconjunctivitis symptoms, medication use, immunologic markers, and notably, the onset of asthma. (17) The 5-year, double-blind, placebo-controlled trial with 2 years of follow-up was conducted at 101 sites in 11 European countries and enrolled 812 children ages 5 to 12 years with a history of allergic rhinoconjunctivitis (mean, 3.4 years). Of those randomized, 608 (75%) completed the trial.

There was no difference in time to onset of asthma (primary endpoint) between the SLIT group (n=398) and the placebo group (n=414). However, there was a 71% relative risk reduction in asthma symptoms and asthma medication use for the entire trial period and for the 2-year follow-up period (odds ratio, 0.28; p<.001). During the 3 years of treatment and 2 follow-up years, the SLIT group had a 22% to 30% reduction in allergic rhinoconjunctivitis symptoms compared with placebo (p<.002). Visual analog scale scores revealed a 22% reduction in symptoms for the SLIT group compared with the placebo group (p=.005). The SLIT group also had a 27% reduction in medication use relative to the placebo group (p<.001).

The most frequently reported adverse events were nasopharyngitis, allergic conjunctivitis, oral pruritus, cough, and gastroenteritis. Compared with placebo, a higher proportion of children in the intervention group dropped out due to adverse events. However, the trial identified no new safety concerns. The authors reported no limitations to the RCT.

Ragwitek

Two pivotal trials on Ragwitek that enrolled adults ages 18 to 50 years are included in the prescribing information. (18) Both trials included individuals with ragweed pollen-induced allergic rhinitis with or without conjunctivitis, positive serum IgE to ragweed pollen, and baseline forced expiratory volume in 1 second of at least 70% of predicted. As shown in Table 5, both trials met the FDA criteria for efficacy.

Table 5. Results of 2 Pivotal Ragwitek Trials in Adults

Trial	N	RD in Combined Score % (95% CI)

Trial 1: Phase 2/3 U.S. and Canada dose-finding trial	375	26 (14 to 38)
Trial 2: Phase 3 U.S., Canada, and Eastern Europe dose-finding trial	394	27 (14 to 39)

CI: confidence interval; RD: relative difference; N=number; U.S.: United States.

A separate trial comparing Ragwitek with placebo was conducted by Nolte et al. (2020) in 1025 children aged 5 to 18 years with ragweed allergic rhinitis, with or without conjunctivitis (Table 6). (19) Additional inclusion criteria were positive serum IgE to ragweed pollen, and baseline forced expiratory volume in 1 second of at least 80% of predicted. The mean age of trial participants was 12 years, and about half (43%) had concomitant asthma. The study found significant differences favoring Ragwitek over placebo in daily symptom score, daily medication score and total combined score over the course of ragweed pollen season (Table 7). Results were consistent across the 3 pollen seasons included in the trial and among patients with comorbid asthma. No study relevance or design and conduct limitations were noted.

Table 6. Study Characteristics of the Pivotal Ragwitek Trial in Children and Adolescents

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Nolte et al. (2020) (19)	United States, Canada, Croatia, Hungary, Serbia, Ukraine	80	July 2015-November 2018	Age 5 years or older with confirmed history of ragweed-induced allergic rhinitis	Ragwitek n=513	Placebo n=512

N: number.

Table 7. Results of the Pivotal Ragwitek Trial in Children and Adolescents

Study	Daily symptom score	Daily medication score	Total combined score
Nolte et al. (2020) (19)			
Ragwitek	n=469 2.27 (2.01 to 2.53)	n=466 1.61 (1.36 to 1.86)	n=466 3.88 (3.44 to 4.33)
Placebo	n=494 3.26 (3.00 to 3.52)	n=491 2.48 (2.22 to 2.73)	n=491 5.75 (5.30 to 6.20)
Mean between group difference (95% CI)	−0.99 (−1.34 to −0.65); p<.01	−0.87 (−1.20 to −0.53); p<.01	−1.86 (−2.46 to −1.27); p<.01
Percent reduction in score (95% CI)	−30.4% (−38.6% to −20.7%)	−35.0% (−38.6% to −22.4%)	−32.4% (−40.7% to −23.3%)

CI: confidence interval; n: number(s).

Safety

The pooled FDA safety database comprised 1057 adults who received at least 1 dose of Ragwitek. The most common TEAEs in this group were throat irritation (17% vs. 3%), oral pruritus (11% vs. 2%), ear pruritus (10% vs. 1%), and oral paresthesia (10% vs. 4%), all versus the placebo group. 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 trials 1 and 2 (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.

In the trial conducted in patients aged 5 to 18 years, serious adverse events were rare in both the Ragwitek and placebo groups (0.6% vs. 0.2%), though patients in the Ragwitek group had higher adverse event rates, including throat irritation (48.5%), oral pruritus (47.6%), and ear pruritus (33.9%) compared with patients in the placebo group (18.1%, 11.6% and 6.3%, respectively). (20, 19)

Section Summary: Allergic Rhinitis or Rhinoconjunctivitis

Three sublingual pollen extracts (1 multiple-allergen product [Oralair], 2 single-allergen products [Grastek, Ragwitek]) are FDA approved for the 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 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. Notably, the largest pediatric trial to date found SLIT to have a positive, long-term impact on allergic rhinoconjunctivitis symptoms and medication use relative to placebo but did not reduce time to asthma onset. A recent placebo-controlled, double-blinded randomized trial of adults, however, found no significant difference between SLIT and placebo in the improvement of allergic rhinoconjunctivitis symptoms at 3-year follow-up, 1 year following discontinuation of treatment. Additionally, subgroup analysis from a 2017 meta-analysis of placebo-controlled randomized trials evaluating SLIT in children found the intervention to be effective for allergic rhinitis but not medication use.

House Dust Mite-Specific Allergy

Clinical Context and Therapy Purpose

The purpose of SLIT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with house dust mite-specific allergy.

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with house dust mite-specific allergy.

Interventions
The therapy being considered is SLIT.

Comparators
Comparators of interest include SCIT and standard care without allergen-specific immunotherapy.

Outcomes
The general outcomes of interest are symptoms, quality of life, hospitalizations, medication use, and treatment-related morbidity. Though not completely standardized, follow-up for allergic symptoms would typically occur periodically for months to years after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
See the systematic review by Yang et al. (2018) summarized in Indication 1 for their assessment of SLIT for relief of allergic conjunctivitis or allergic rhinoconjunctivitis in patients aged 3 to 18 years. (3) They found that SLIT significantly reduced pollen-induced allergic conjunctivitis ($p<.001$) but not house dust mite-induced allergic conjunctivitis ($p=.34$).

Feng et al. (2017) conducted a meta-analysis of 25 placebo-controlled randomized trials (published from 1990 to 2016) on the efficacy of SLIT for house dust mite-induced allergic rhinitis in adults and children. (21) Most trials were double-blinded, deemed to be of high quality, and included 2 phase 3 trials. All studies compared the intervention with a placebo for a period of 6 to 36 months. In total, there were 3674 randomized patients, and the largest trial included 992 participants. There were 12 pediatric trials, with ages ranging from 3 to 18 years. Of 23 studies that reported discontinuation rates, 539 (14.6%) participants dropped out due to the following: adverse events (3.0%; most commonly oral pruritis), loss to follow-up (2.0%), noncompliance (1.9%), and poor efficacy (0.9%). Primary endpoints were symptom scores and

medication use. Symptom scores varied by type, including rhinitis symptoms only, rhinoconjunctivitis symptoms, or rhinoconjunctivitis and asthma symptoms. Overall, there was a significant reduction in symptoms in the SLIT group relative to placebo (SMD, 1.23; 95% CI, 1.74 to 0.73; p<.001). A subgroup analysis of trials using different modalities (drops, n=19; tablets, n=6) found a significant reduction in symptom scores with the use of tablets (SMD, -1.81; 95% CI, -2.94 to -0.68; p=.002) relative to drops (SMD, -1.06; 95% CI, -1.67 to -0.44; p<.001). Medication type also varied, including systemic and topical antihistamines, decongestants, and both systemic and topical nasal corticosteroids. Data on medication use were available in 18 RCTs, but the final analysis included only 15 RCTs due to substantial differences in how data were evaluated. Overall, there was a significant reduction in medication use in the SLIT group relative to the placebo group (SMD, -1.39; 95% CI, -1.90 to -0.88; p<.001). Additionally, the significant reductions in medication use found among adults were not found in children (p=.060), possibly due to dosage, lack of compliance, or small sample size. Reviewers pointed out several important limitations to the meta-analysis, including significant heterogeneity among studies, inadequate reporting of blinding procedures, potential publication bias, small sample sizes, and variations in assessment scores, study protocols, pharmaceutical preparations, baseline symptom severity, and the prevalence of respiratory allergic complications among patients. An SMD measure, a random-effects model, and sensitivity analysis were used to mitigate these limitations.

A second systematic review assessing the effect of SLIT on house dust mite-induced allergic rhinitis only included studies conducted in children aged 4 to 18 years. (22) The review included 16 placebo-controlled trials (N=1929) of SLIT drops or tablets for 6 to 24 months. Pooled outcomes included nasal symptom, medication, and ocular symptom scores. The review did not report discontinuation rates. Nasal symptom scores, reported in 16 studies, were significantly lower with SLIT versus placebo (SMD, -1.73; 95% CI, -2.62 to -0.84), but heterogeneity was very high (I^2=98%). Total medication scores were also significantly lower with SLIT versus placebo based on evidence from 11 studies (SMD, -1.21; 95% CI, -1.75 to -0.67), but again heterogeneity was high (I^2=94%). For both outcomes, the review found evidence of publication bias, but even after adjustment for bias, SLIT was more effective than placebo for both outcomes (p=.02 and p<.0001, respectively). Ocular symptom scores were only reported in 6 of the studies. When pooled, there was no clear difference between SLIT and placebo (p=.31), however subgroup analysis found SLIT tablets (SMD, -0.28; 95% CI, -0.42 to -0.14) more effective than SLIT drops (SMD, 0.13; 95% CI, -0.20 to 0.60), relative to placebo.

Liao et al. (2015) published a meta-analysis of studies on dust mite SLIT for treating children with asthma. (23) Reviewers 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 with placebo and/or pharmacotherapy. Findings of the meta-analysis were mixed. A pooled analysis of 8 studies found that an asthma symptom score decreased significantly more in the SLIT groups than in the control groups (SSD, -1.20; 95% CI, -2.07 to -0.33; p=.007). A pooled analysis of 3 studies did not find significant differences between groups in change in medication usage (SSD, -0.52; 95% CI, -1.753 to 0.713; p=.408). Groups 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=.076). In all analyses, there were high levels of heterogeneity among studies.

Gendelman and Lang (2015) published a systematic review of house dust mite SLIT in atopic dermatitis. (24) Five studies (N=344 patients) were identified but low methodologic quality limited conclusions that could be drawn. Bae et al. (2013) also published a systematic review and meta-analysis of immunotherapy for children and adults with house dust mite-induced atopic dermatitis. (25) Literature was searched through November 2012, and 8 placebo-controlled randomized trials 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 the use of a nonstandard outcome measure.

Kim et al. (2021) published a network meta-analysis comparing SCIT with SLIT in patients with a house dust mite allergy. (26) A total of 26 RCTs (N=6743) were included. Ten studies (n=5744) with SLIT tablets found significant improvement in symptom scores with SLIT compared with placebo (SMD, -0.329; 95% CI, -0.426 to -0.231; p<.01) while 9 studies (n=5725) found improvement in medication score (SMD, -0.227; 95% CI, -0.371 to -0.083; p<.01). The SCIT group had greater efficacy in the symptom score compared with SLIT tablets in network meta-analysis (SMD, -0.819; 95% CI, -1.242 to -0.397). Medication scores were also improved with SCIT (SMD, -0.517; 95% CI, -0.914 to -0.121). The analysis is limited by high levels of heterogeneity in the SLIT studies.

Randomized Controlled Trials

Included in the recent meta-analyses, was a phase 3 double-blind RCT by Demoly et al. (2016) of Odactra as a treatment for moderate-to-severe house dust mite-induced allergic rhinitis despite pharmacotherapy. (27) Adults were randomized to daily Odactra 6 SQ-house dust mite (HDM) (n=336), Odactra 12 SQ-HDM (n=318), or placebo (n=338) for 52 weeks. Total Combined Rhinitis Score (TCRS), which integrated patient-reported symptoms of rhinitis or conjunctivitis and use of pharmacotherapy, met the prespecified threshold of clinical relevance (TCRS >1) after 14 weeks of treatment and at all subsequent time points, for both dosages of Odactra. The primary endpoint of TCRS in the efficacy period (8 weeks after completing 52 weeks of treatment) showed an absolute reduction from placebo for both 6 SQ-HDM (1.18; p=.002) and 12 SQ-HDM (1.22; p=.001). The most common adverse events were oral pruritus, throat irritation, and mouth edema. Serious adverse events were noted in the placebo (n=8) and 6 SQ-HDM (n=4) treatment groups; none were deemed to be related to treatment. One patient required adrenaline on the first dose of 12 SQ-HDM Odactra to treat laryngeal edema.

Another large RCT by Nolte et al. (2016) (included in the 2021 meta-analysis) was a phase 3, double-blind, RCT evaluating Odactra (12 SQ-HDM) and placebo for treatment of house dust mite-induced allergic rhinitis, with or without conjunctivitis, and with or without asthma. (28) Patients ages 12 years and older (N=1482) were randomized to Odactra or placebo once daily for 52 weeks. Improvement in the average TCRS after treatment, compared with placebo, was

17% (95% CI, 10% to 25%). This primary efficacy endpoint, which integrated symptoms and medication use, met prespecified targets for clinical significance. Patients also demonstrated improvement in average conjunctivitis scores, with improvement over placebo of 33% (95% CI, 19% to 47%). Seven patients were treated with epinephrine for adverse events; 1 patient experienced severe "throat tightness" after the first dose. Adverse events were typically mild to moderate in severity, with most events consisting of throat irritation, oral pruritus, and ear pruritus. No treatment-related serious adverse events were reported.

Section Summary: House Dust Mite-Specific Allergy

A number of RCTs have evaluated SLIT for patients with dust mite allergies, mainly placebo-controlled trials. Meta-analyses found high levels of heterogeneity among studies. A meta-analysis published in 2015 had mixed findings; some outcomes, but not others, favored SLIT over placebo or pharmacologic treatment. A 2017 meta-analysis found SLIT to be associated with a significant reduction in house dust mite-induced allergic rhinitis symptoms and medication use relative to placebo in adults but found no statistically significant reduction for children. However, a 2020 systematic review of studies conducted in children found SLIT associated with significantly lower nasal symptom and medication use scores. Finally, a 2021 meta-analysis found improved outcomes with SLIT compared with placebo, but SCIT was superior to SLIT. More recent large, well-designed RCTs supporting the marketing applications for these products have provided consistent evidence of efficacy and safety. Although these trials were also placebo-controlled, rather than SCIT-controlled, minimum clinically important criteria for demonstrating efficacy were prespecified and met in the largest studies.

Food Allergy

Clinical Context and Therapy Purpose

The purpose of SLIT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with food allergy.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with food allergy.

Interventions

The therapy being considered is SLIT.

Comparators

The following therapies and practices are currently being used to treat food allergies: SCIT and standard care without allergen-specific immunotherapy.

Outcomes

The general outcomes of interest are symptoms, quality of life, hospitalizations, medication use, treatment-related morbidity, and treatment-related mortality. Specific symptoms of interest are a reduction in the frequency of anaphylaxis, angioedema, bronchospasm/wheezing,

and urticaria. Quality of life scales measuring the reduction in parental time off from work and expanded activities for a child would be of interest. The treatment-related morbidity outcomes are systemic reactions, skin reactions, gastrointestinal reactions, serious adverse events, and adverse events leading to treatment discontinuation. Desensitization is an intermediate outcome measure. Though not completely standardized, follow-up for allergic symptoms would typically occur periodically for months to years after starting treatment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

de Silva et al. (2014) review identified 5 randomized trials of SLIT in patients with food allergies (fruit, peanut), 4 of which showed symptom improvement compared with placebo. (29) The trial that did not demonstrate benefit of SLIT compared with placebo was conducted in patients with apple allergy. All trials were considered low quality (e.g., most did not include symptom assessments off treatment).

Additionally, Romantsik et al. (2014) reported on a Cochrane review of oral immunotherapy and SLIT for egg allergy. (30) No RCTs of SLIT were identified in their literature search (through November 2013).

Randomized Controlled Trials

Several RCTs have been published since the systematic reviews. Narisety et al. (2015) published a double-blind RCT comparing oral immunotherapy with SLIT in 21 children who had peanut allergies. (31) Five (24%) children dropped out. Adverse events, generally mild, were significantly more common in the oral immunotherapy group. Among the remaining 16 patients, those in the oral immunotherapy group had a significantly greater challenge threshold at 12 months than those in the SLIT group (p=.01). However, only 4 patients (19%) had sustained unresponsiveness. Long-term, open-label follow-up of an RCT included in the da Silva systematic review assessing the effect of SLIT on peanut allergy reported a similar proportion of patients with sustained unresponsiveness (10/48; 21%). (32)

An RCT by Burks et al. (2015) reported on a placebo-controlled SLIT study in 40 patients (20 per group) with peanut allergy. (33) 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 high dose SLIT, and 7 (44%) were considered responders after 44 weeks.

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

Interventional Study

Kim et al. (2023) performed an open-label study of the safety, efficacy, and persistence of desensitization associated with SLIT in pediatric patients aged 1 to 11 years with peanut allergy. (34) Patients received sublingual peanut protein in a build-up phase over approximately 5 months to a target maintenance dose of 4 mg once daily; treatment continued for a total of 48 months. Reaction thresholds to peanut were assessed by double-blind, placebo-controlled food challenges performed at baseline (as part of study screening), after 48 months of SLIT, and after a subsequent randomly assigned avoidance phase of 1 to 17 weeks of peanut and SLIT avoidance. Clinically significant desensitization was defined as a successfully consumed peanut dose of at least 800 mg. Among 54 participants who received SLIT, mean age was 7.1 years; 47 participants completed SLIT and were included in the per-protocol analysis of desensitization at 48 months. Mean successfully consumed peanut dose increased significantly between baseline (48.4 ± 93.2 mg) and 48 months (2723 ± 1904 mg; p<.0001), with clinically significant desensitization achieved in 70.2% and no reaction throughout SLIT in 36% of participants. Among 37 patients who completed the post-SLIT avoidance phase, median estimated time to loss of clinically significant desensitization was 22 weeks. Dosing symptoms (e.g., oropharyngeal itching, lip swelling) were reported with 4.0% of home-administered doses; antihistamines were administered for symptoms associated with 0.14% of total doses administered and no epinephrine was administered. Three patients withdrew from the study after initiating SLIT due to abdominal side effects.

Kim et al. (2024) performed a double-blind study of the safety and efficacy of SLIT in pediatric patients aged 1 to 4 years with documented peanut allergy. (35) The study was conducted at 2 U.S. academic centers and randomized 50 children to 4 mg peanut SLIT or placebo. Peanut protein was initiated at 2.5 mcg and escalated to 4 mg. At month 36, the double-blind food challenge was conducted to a cumulative dose of 4443 mg and administered in 7 doses as follows: 3, 10, 30, 100, 300, 1000, and 3000 mg. Those who tolerated at least 443 mg at month 36 then discontinued the study drug, avoided peanuts for 3 additional months, and returned for a final food challenge at month 39. The median cumulative dose tolerated in peanut SLIT participants was 4443 mg vs 143 mg for placebo at 36 months. At month 36, 60% of individuals in the peanut SLIT group ingested the full dose vs 0 placebo-treated patients when analyzed by ITT (p<.0001). At 39 months, 48% of peanut SLIT-treated patients were considered in remission compared with 0 placebo-treated patients when analyzed by ITT. Oropharyngeal itching after dosing was significantly more common in peanut-treated patients (80% vs. 28%; p=.0005). No patients in either group required epinephrine, but 56% of patients in the peanut group and 36% of patients in the placebo group required an antihistamine within 2 hours of dosing.

Section Summary: Food Allergy

A few RCTs have evaluated SLIT for treatment of food allergies. These trials 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 in patients with non-peanut allergies; in patients with peanut allergy, while available evidence consistently

indicates efficacy of SLIT relative to placebo or pre-treatment baseline, SLIT has not been found to be as effective as 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 (SLIT), 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 approved by the Food and Drug Administration (FDA) 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 subcutaneous immunotherapy (SCIT)-controlled, minimum clinically important criteria for demonstrating efficacy were prespecified and met in most studies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have house dust mite-specific allergy who receive SLIT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, quality of life, hospitalizations, medication use, and treatment-related morbidity. One sublingual extract is approved by the FDA for treatment of house dust mite-induced allergic rhinitis with or without conjunctivitis. Most RCTs evaluating SLIT for individuals with dust mite allergies have been placebo-controlled. Meta-analyses have found high levels of heterogeneity among studies. A more recent meta-analysis, published in 2015, had mixed findings; some outcomes, but not others, favored SLIT over placebo or pharmacologic treatment. However, more recent large, well-designed RCTs supporting the marketing applications for these products have provided consistent evidence of efficacy and safety. Although trials were also placebo-controlled, rather than SCIT-controlled, minimum clinically important criteria for demonstrating efficacy were prespecified and met in the largest studies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have food allergy who receive SLIT, the evidence includes RCTs, systematic reviews, and 2 interventional studies. 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 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 in individuals with non-peanut allergies; in individuals with peanut allergy, while available studies indicate efficacy of SLIT relative to placebo or pre-treatment baseline, SLIT has not been found to be as effective as oral immunotherapy. No RCTs were identified that compared SLIT with SCIT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Otolaryngology -Head and Neck Surgery Foundation

In 2024, the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) published clinical practice guidelines on allergen immunotherapy in patients with inhalant allergy. (36) They issued a strong recommendation for offering immunotherapy to patients with allergic rhinitis with or without allergic asthma if symptoms are inadequately controlled with medical therapy, allergen avoidance, or both, or have a preference for immunomodulation. A minimum treatment duration of 3 years is recommended for patients who respond. The guidelines recommended patient education on the differences between subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) but did not state a preference for a particular administration route.

In 2015, the AAO-HNSF published clinical practice guidelines on allergic rhinitis that contained the following statement (37):
"Clinicians should offer, or refer to a clinician who can offer, immunotherapy (sublingual or subcutaneous) for patients with AR [allergic rhinitis] who have inadequate response to symptoms with pharmacologic therapy with or without environmental controls. Recommendation based on RCTs [randomized controlled trials] and systematic reviews, with a preponderance of benefit over harm."

American Academy of Allergy, Asthma and Immunology et al.
In 2020, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) recommended allergen immunotherapy (either SCIT or SLIT) be offered to patients with moderate or severe allergic rhinitis who are not controlled with allergen avoidance or pharmacotherapy; prefer immunotherapy; or those who may benefit due to comorbid conditions such as asthma. (38)

In 2017, the AAAAI and the ACAAI jointly published updated practice parameters on SLIT. (39) These recommendations apply to the use of SLIT agents approved by the U.S. Food and Drug Administration at time of publication: 5-grass (Oralair), Timothy grass (Grastek), and ragweed (Ragwitek). Table 8 summarizes statements made.

Table 8. Recommendations on Use of SLIT

Recommendation	SOR	LOE
FDA-approved SLIT should be used to treat allergic rhinitis/rhinoconjunctivitis, and not for any other condition	Strong	A/B
SLIT may not be suitable for patients who have conditions that reduce their ability to survive a systemic reaction or the associated treatment	Strong	D
Given insufficient information on the safety of initiating or continuing SLIT during pregnancy or breastfeeding, it should be used very cautiously in pregnant or breastfeeding patients	Weak	C
Dosing equivalence should not be assumed between SLIT tablets and extracts of the same allergen; each formulation should have its own safety profile established	Weak	C

First doses of SLIT should be administered in a medical facility under the supervision of a physician or other health care professional with experience in the diagnosis and treatment of anaphylaxis. The patient should be observed in the medical facility for 30 minutes after the administration of SLIT	Strong	D
Epinephrine should be prescribed to patients receiving SLIT tablets, and patients should be trained in its use	Strong	D
The SLIT dose should be reduced if a patient misses treatment for >1 week	Weak	D
Patients receiving SLIT should be scheduled for regular follow-up care with a specialist	Moderate	D

FDA: Food and Drug Administration; LOE: level of evidence: SLIT: sublingual immunotherapy; SOR: strength of recommendation.

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this policy are listed in Table 9.

Table 9. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05113394	Preventing Childhood Asthma Using Prophylactic House Dust Mite Allergen Immunotherapy	270	Aug 2029
NCT05476484	Comparative Real-World Effectiveness of SQ Sublingual Immunotherapy (SLIT)-Tablets vs. Controls in Allergic Rhinitis and Asthma – Outcomes From a Multinational Register Study	49,844	Jun 2024
NCT05521711	TRADE Trial – Tree Nut Immunotherapy Route Development and Evaluation	60	Jan 2027
Unpublished			
NCT04881461	A Randomised, Parallel-group, Double-blind, Placebo-controlled Phase III Trial Assessing the Efficacy and Safety of 5-grass Mix SLIT-drops in Adults With Grass Pollen-induced Rhinoconjunctivitis	445	Sept 2023

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	95199
HCPCS Codes	J3490, J8499

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. Moote W, Kim H, Ellis AK. Allergen-specific immunotherapy. Allergy Asthma Clin Immunol. 2018; 14(Suppl 2):53. PMID 30275845
2. Meltzer EO, Wallace D, Friedman HS, et al. Meta-analyses of the efficacy of pharmacotherapies and sublingual allergy immunotherapy tablets for allergic rhinitis in adults and children. Rhinology. Oct 01 2021; 59(5):422-432. PMID 34463311
3. Yang J, Zhang L, Zhao Z, et al. Sublingual immunotherapy for pediatric allergic conjunctivitis: a meta-analysis of randomized controlled trials. Int Forum Allergy Rhinol. Nov 2018; 8(11):1253-1259. PMID 29782067
4. Di Bona D, Plaia A, Leto-Barone MS, et al. Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinoconjunctivitis: a systematic review and meta-analysis. JAMA Intern Med. Aug 2015; 175(8):1301-1309. PMID 26120825
5. Dretzke J, Meadows A, Novielli N, et al. Subcutaneous and sublingual immunotherapy for seasonal allergic rhinitis: a systematic review and indirect comparison. J Allergy Clin Immunol. May 2013; 131(5):1361-1366. PMID 23557834
6. Tie K, Miller C, Zanation AM, et al. Subcutaneous Versus Sublingual Immunotherapy for Adults with Allergic Rhinitis: A Systematic Review with Meta-Analyses. Laryngoscope. Mar 2022; 132(3):499-508. PMID 33929726
7. Nelson H, Cartier S, Allen-Ramey F, et al. Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy. J Allergy Clin Immunol Pract. Mar-Apr 2015; 3(2):256-266. PMID 25609326
8. Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost. J Eval Clin Pract. Jun 2014; 20(3):225-238. PMID 24444390
9. Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Statistical Review: Oralair. Apr 07 2014. Available at <https://www.fda.gov> (accessed August 12, 2024).
10. Didier A, Bons B. Safety and tolerability of 5-grass pollen tablet sublingual immunotherapy: pooled analysis and clinical review. Expert Opin Drug Saf. May 2015: 14(5):777-788. PMID 25732009
11. Food and Drug Administration (FDA). Statistical review: Grastek. 2014. Available at <https://www.fda.gov> (accessed August 9, 2024).

12. Food and Drug Administration (FDA), Center for Biologics Evaluation and Research. 26th Meeting of the Allergenic Products Advisory Committee, December 12, 2013. Available at <https://www.fda.gov> (accessed August 11, 2024).
13. Food and Drug Administration (FDA). Clinical review: Grastek. Available at <https://www.fda.gov> (accessed August 10, 2024).
14. Maloney J, Durham S, Skoner D, et al. Safety of sublingual immunotherapy Timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma. Allergy. Mar 2015; 70(3):302-309. PMID 25495666
15. Feng B, Wu J, Chen B, et al. Efficacy and safety of sublingual immunotherapy for allergic rhinitis in pediatric patients: A meta-analysis of randomized controlled trials. Am J Rhinol Allergy. Jan 01 2017; 31(1):27-35. PMID 28234149
16. Scadding GW, Calderon MA, Shamji MH, et al. Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate to severe seasonal allergic rhinitis: The GRASS Randomized Clinical Trial. JAMA. Feb 14 2017; 317(6):615-625. PMID 28196255
17. Valovirta E, Petersen TH, Piotrowska T, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol. Feb 2018; 141(2):529-538.e513. PMID 28689794
18. ALK-Abell. Highlights of Prescribing Information: Ragwitek® (short ragweed pollen allergen extract). 2022. Available at <https://www.dailymed.nlm.nih.gov> (accessed August 12, 2024).
19. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy and Safety of Ragweed SLIT-Tablet in Children with Allergic Rhinoconjunctivitis in a Randomized, Placebo-Controlled Trial. J Allergy Clin Immunol Pract. Jul 2020; 8(7):2322-2331.e5. PMID 32304832
20. FDA Statistical Review - Ragwitek. Available at <https://www.fda.gov> (accessed August 12, 2024).
21. Feng B, Xiang H, Jin H, et al. Efficacy of sublingual immunotherapy for house dust mite-induced allergic rhinitis: a meta-analysis of randomized controlled trials. Allergy Asthma Immunol Res. May 2017; 9(3):220-228. PMID 28293928
22. Chen L, Lei L, Cai Y, et al. Specific sublingual immunotherapy in children with perennial rhinitis: a systemic review and meta-analysis. Int Forum Allergy Rhinol. Nov 2020; 10(11):1226-1235. PMID 32329187
23. Liao W, Hu Q, Shen LL, et al. Sublingual immunotherapy for asthmatic children sensitized to house dust mite: a meta-analysis. Medicine (Baltimore). Jun 2015; 94(24):e701. PMID 26091451
24. Gendelman SR, Lang DM. Sublingual immunotherapy in the treatment of atopic dermatitis: a systematic review using the GRADE system. Curr Allergy Asthma Rep. Feb 2015; 15(2):498. PMID 25504262
25. Bae JM, Choi YY, Park CO, et al. Efficacy of allergen-specific immunotherapy for atopic dermatitis: a systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol. Jul 2013; 132(1):110-117. PMID 23647790
26. Kim JY, Jang MJ, Kim DY, et al. Efficacy of Subcutaneous and Sublingual Immunotherapy for House Dust Mite Allergy: A Network Meta-Analysis-Based Comparison. J Allergy Clin Immunol Pract. Dec 2021; 9(12):4450-4458.e6. PMID 34464748

27. Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol. Feb 2016; 137(2):444-451 e448. PMID 26292778
28. Nolte H, Bernstein DI, Nelson HS, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol. Dec 2016; 138(6):1631-1638. PMID 27521719
29. de Silva D, Geromi M, Panesar SS, et al. Acute and long-term management of food allergy: systematic review. Allergy. Feb 2014; 69(2):159-167. PMID 24215577
30. Romantsik O, Bruschettini M, Tosca MA, et al. Oral and sublingual immunotherapy for egg allergy. Cochrane Database Syst Rev. Nov 18 2014; 11(11):CD010638. PMID 25405335
31. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol. May 2015; 135(5):1275-1282.e1217-1276. PMID 25528358
32. Kim EH, Yang L, Ye P, et al. Long-term sublingual immunotherapy for peanut allergy in children: Clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. Nov 2019; 144(5):1320-1326.e1. PMID 31493887
33. Burks AW, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol. May 2015; 135(5):1240-1248. PMID 25656999
34. Kim EH, Keet CA, Virkud YV, et al. Open-label study of the efficacy, safety, and durability of peanut sublingual immunotherapy in peanut-allergic children. J Allergy Clin Immunol. Jun 2023; 151(6):1558-1565.e6. PMID 36828080
35. Kim EH, Bird JA, Keet CA, et al. Desensitization and remission after peanut sublingual immunotherapy in 1- to 4-year-old peanut-allergic children: A randomized, placebo-controlled trial. J Allergy Clin Immunol. Jan 2024; 153(1):173-181.e10. PMID 37815782
36. Gurgel RK, Baroody FM, Damask CC, et al. Clinical Practice Guideline: Immunotherapy for Inhalant Allergy. Otolaryngol Head Neck Surg. Mar 2024; 170 Suppl 1:S1-S42. PMID 38408152
37. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. Otolaryngol Head Neck Surg. Feb 2015; 152(1 Suppl):S1-43. PMID 25644617
38. Dykewicz MS, Wallace DV, Amrol, DJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol. Oct 2020; 146(4):721-767. PMID 32707227
39. Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual immunotherapy: A focused allergen immunotherapy practice parameter update. Ann Allergy Asthma Immunol. Mar 2017; 118(3):276-282.e2. PMID 28284533

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/15/2024	Document updated with literature review. Coverage unchanged. Added/updated references 35, 36, and 39.
12/01/2023	Document updated with literature review. Coverage unchanged. Added/updated references 1, 2, 6, 26, 34 and 36.
01/01/2023	Reviewed. No changes.
01/01/2022	Document updated with literature review. Coverage unchanged. The following references were added/updated: 2, 17, 18, 20, 34 and 36.
09/15/2020	Reviewed. No changes.
08/01/2019	New medical document. Information on sublingual immunotherapy (SLIT) as a technique of allergen-specific therapy was previously housed on medial policy MED206.001 Allergy Management. Coverage for SLIT previously noted on MED206.001 has not changed and may be considered medically necessary when criteria are met. Coverage for Odactra has been added to the new medical document and is considered medically necessary when criteria is met.