Medical Policy

**BlueCross
BlueShield
of Kansas**

An Independent Licensee of the
Blue Cross and Blue Shield Association

Title: Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

Professional
Original Effective Date: July 23, 2004
Revision Date(s): June 7, 2013;
August 18, 2014
Current Effective Date: August 18, 2014

Institutional
Original Effective Date: July 23, 2004
Revision Date(s): June 7, 2013;
August 18, 2014
Current Effective Date: August 18, 2014

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. 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. Subcutaneous injection of allergen-specific

immunotherapy (SCIT) is the standard approach. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, sublingual immunotherapy (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.

FDA Status
In April 2014, the U.S. Food and Drug Administration (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.

POLICY
A   Sublingual immunotherapy using Oralair®, Grastek®, or 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:
   1.   Patient has a history of rhinitis or rhinoconjunctivitis symptoms related to grass or short ragweed pollen exposure.
   2.   Patient has a documented positive pollen-specific skin test or pollen-specific immunoglobulin E (IgE) test (see Policy Guidelines section).
   3.   Patient's symptoms are not adequately controlled by appropriate pharmacotherapy (see Policy Guidelines section).

B.   Sublingual immunotherapy as a technique of allergy immunotherapy is considered **experimental / investigational** for all other uses.

Policy Guidelines
For Oralair®, Grastek®, or Ragwitek®(1-3):

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; and for Grastek® and Ragwitek®, history of eosinophilic esophagitis.

Administration and Dose

1. Prescribing information includes a black box warning for severe allergic reactions including anaphylaxis. Patients must be prescribed an epinephrine auto-injector and be trained on how to use it.
2. 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).
3. 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.
4. All 3 agents are dosed once daily.
5. 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).
6. Grastek® and Ragwitek® both are initiated at the maintenance dose (2800 BAU [bioequivalent allergy unit] and 12 Amb a 1 unit, respectively).

Table 1. Oralair® Dosing in Patients Age 10-17 Years(1)

Day 1	Day 2	Day 3 and Following
100 IR	2 x 100 IR	300 IR

IR, index of reactivity, a potency unit defined by the formation of a 7-mm wheal in 30 sensitized individuals during product development.(1)

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:
1. Treatment should be individualized based on symptom severity and duration, comorbidities, and patient age, preference (eg, route of administration, tolerance for adverse effects), and previous treatment history.
2. Measures to increase treatment adherence (eg, shared decision making, consideration of the patient's school or work schedule, use of a medication calendar or check-off list) are encouraged.
3. Goals of treatment are symptom reduction and improvements in functional capacity and quality of life.
4. A "step-up" (if treatment is inadequate)/"step-down" (if symptom relief is achieved with other interventions, eg, avoidance) approach to treatment is recommended.

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

6. Six medication classes are used to treat allergic rhinitis: H1-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).

7. Treatment should be symptom-specific, eg, 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.

8. For mild or intermittent symptoms, oral or nasal antihistamine may be considered first-line treatment.

9. 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.

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

11. Combination treatment (eg, 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.

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

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

RATIONALE

This policy is based on a 2003 TEC Assessment.(9) The policy was updated with literature reviews using MEDLINE; most recently, the literature was searched through April 28, 2014. Following is a summary of key literature to date.

Allergic Rhinitis

At the time of the 2003 TEC Assessment, there were 21 published randomized controlled trials (RCTs) comparing sublingual immunotherapy (SLIT) to placebo suggesting that SLIT decreased 1 or more symptoms in patients who had pollen or dust mite allergies. Systemic adverse effects occurred in only 1 study, and these were not life-threatening. However, whether SLIT improved health outcomes when compared with subcutaneous allergen-specific immunotherapy (SCIT), the criterion standard comparison, could not be determined from the available evidence. Due to the paucity of studies comparing SLIT with SCIT and the lack of U.S. Food and Drug Administration (FDA)-approved agents for use in SLIT, the use of SLIT for allergen immunotherapy was considered investigational.

Since the TEC Assessment, numerous placebo-controlled RCTs and meta-analyses of RCTs have been published. Some of the representative meta-analyses and reviews of meta-analyses are discussed next, as well as some of the key individual RCTs.

Systematic Reviews. Several reviews of meta-analyses have been published. In 2011, de Bot et al evaluated the quality of systematic reviews and meta-analyses of SLIT for treating allergic rhinitis in children.(10) Investigators used the Assessment of Multiple Systematic Reviews (AMSTAR) quality evaluation tool to rate the reviews. The maximum score on the AMSTAR is 11; scores of 0 to 4 indicate low quality; 5 to 8, moderate quality; and 9 to 11, high quality. The authors identified 10 systematic reviews. None were rated as high quality, 6 were rated as moderate quality, and 4 as low quality. This analysis indicates that although there are numerous systematic reviews on SLIT, methodologic quality is suboptimal. This research suggests that SLIT for children may be promising, but methodologic flaws preclude definitive conclusions.

In 2009, Compalati et al evaluated meta-analyses of RCTs on specific immunotherapy for respiratory allergy.(11) They identified 7 meta-analyses of placebo-controlled RCTs using well-defined inclusion criteria, allergens, doses, and outcome measurements; 5 assessed SLIT, and 2 assessed SCIT. Regarding SLIT, this analysis corroborated existing evidence for efficacy of SLIT compared with placebo and areas of uncertainty, particularly regarding optimal dose. This review highlighted the lack of consistent relationships between treatment dose, duration, and clinical efficacy.

Numerous individual systematic reviews with meta-analyses have been published. In 2013, Lin et al conducted a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) on allergen-specific therapy for treating allergic rhinoconjunctivitis and/or asthma.(12) The authors identified 60 studies comparing SLIT with placebo or another intervention. (Studies that used SCIT as the comparator were evaluated separately; see following section on SLIT compared with SCIT). Over two thirds of the studies (71%) compared SLIT with placebo, 14% compared SLIT with pharmacotherapy or rescue medication, and 15% compared SLIT with another intervention. Most studies (66%) evaluated seasonal allergens, 31% evaluated perennial allergens, and the remainder addressed both types of allergens. About half of studies used only 1 allergen, and the other half used multiple allergens. Only 22% of the studies were rated as having a low risk of bias. Most (68%) were considered to have a moderate risk of bias and 14% to have a high risk of bias. The authors did not pool study findings because of heterogeneity among studies, eg, in types and sources of allergen extracts, treatment duration, and outcome scoring systems used. The review concluded that there was high-grade evidence that SLIT improved asthma symptoms compared with placebo or another intervention (13 RCTs) and moderate-grade evidence that SLIT improved rhinitis / rhinoconjunctivitis symptoms compared with placebo or another intervention (35 RCTs). There was moderate-grade evidence that SLIT improved other outcomes in this population, eg, decreased medication use and increased quality of life. Lin et al also published the findings of the systematic review in a peer-reviewed journal in 2013.(13) The review focused on studies comparing SLIT with placebo, pharmacotherapy, or another SLIT regimen and did not address SCIT. Like the AHRQ review, study findings were not pooled. The authors noted that high-quality studies are needed to determine optimal dosing strategies.

A 2013 systematic review and meta-analyses by the U.K. National Health Service evaluated the effectiveness of SCIT and SLIT for seasonal allergic rhinitis.(14) Literature was searched to April

2011, and 28 placebo-controlled RCTs were included (17 SCIT, 11 SLIT). Statistically significant moderate effect sizes for improvements in symptom scores, medication scores, combined symptom and medication scores, and quality-of-life measures favored active treatment. However, due to substantial heterogeneity in outcome measures, standardized mean differences were used for meta-analyses, rendering conclusions about clinical significance of the results uncertain. Meta-analysis of 9 SLIT studies in children yielded statistically significant results for symptom scores but not for medication scores.

A 2013 systematic review with meta-analyses by researchers in China evaluated SLIT for allergic asthma.(15) Literature was searched to May 2012, and 16 double-blind, placebo-controlled RCTs were included. Statistically significant reductions in symptom scores (standardized mean difference [SMD], 0.74, p=0.006) and medication scores (SMD=0.78, p=0.02) favored SLIT. The relative risk of adverse events was 2.23 (p=0.01). Also in 2013, researchers from Johns Hopkins University reported a systematic review of SCIT and SLIT in pediatric asthma and rhinoconjunctivitis.(16) Literature was searched through May 2012, and 34 RCTs were included. For SLIT, strength of evidence was high that SLIT improves asthma symptoms and moderate that SLIT improves rhinitis and conjunctivitis symptoms and decreases medication usage compared with placebo. Local adverse reactions were frequent.

A 2012 meta-analysis by Di Bona et al focused on studies of immunotherapy in adults and children with seasonal allergic rhinitis.(17) Inclusion criteria were double-blind, placebo-controlled trials that evaluated natural grass pollen extracts for treating people with a history of grass pollen allergy. The authors identified 22 trials on SLIT versus placebo; 10 used sublingual drops, and 12 used tablets. The authors also identified 14 studies on SCIT versus placebo. The investigators conducted an indirect meta-analysis, evaluating the impact of SLIT and SCIT on outcomes, compared with placebo. Results of the meta-analysis indicated reduced symptoms and reduced medication use. Because studies used different scoring symptoms, effect size was calculated as SMD. Compared with placebo, both SCIT and SLIT (drops and tablets) resulted in significantly greater reductions in symptom and medication scores. For symptom scores versus placebo, effect sizes were SMD of -0.92 (95% confidence interval [CI], -1.26 to -0.58) for SCIT; SMD of -0.40 (95% CI, -0.54 to -0.27) for SLIT administered as tablets; and SMD of -0.25 (95% CI, -0.45 to -0.05) for SLIT administered as drops. Results were similar for medication use. Investigators noted that in pooled analysis, effect sizes were larger for SCIT versus placebo than for SLIT versus placebo.

A 2011 Cochrane review addressed SLIT for treating allergic conjunctivitis in adults and/or children.(18) Fifty-seven trials met inclusion criteria, and 42 of these had data available for meta-analysis. All trials were conducted in countries other than the U.S. The primary outcome of the meta-analysis was the total ocular symptom score. In a pooled analysis of 36 trials (total N=3399), there was a significantly greater reduction in total ocular symptom scores in the SLIT group compared with placebo (SMD=-0.41; 95% CI, -0.53 to -0.28; p<0.001). This review supported the conclusion that SLIT is moderately effective in reducing ocular symptom scores compared with placebo. Concerns about the overall quality of the evidence base remain.
In 2011, Radulovic et al published a meta-analysis of double-blind, placebo-controlled RCTs on SLIT for allergic rhinitis in adults and/or children.(19) Sixty studies met inclusion criteria, and 49 of these (total N=4589) had available efficacy data suitable for meta-analysis. Most studies (n=23) used grass pollen allergen extract; other allergens included ragweed, house dust mites, and trees. In a pooled analysis of study findings, there was a significantly greater reduction in

symptom scores with active SLIT treatment compared with placebo (SMD=-0.49; 95% CI, -0.64 to -0.34; p<0.001). Additionally, pooled analysis found a significantly greater reduction in medication use scores with SLIT versus placebo (SMD=-0.32; 95% CI, -0.43 to -0.21; p<0.001).

Individual RCTs. There are dozens of RCTs in the published literature, and a comprehensive review of all RCTs is beyond the scope of this review. 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 (ie, 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 (approximately 16% across all trials); all other patients with asthma were excluded. Polysensitized people were included in some trials. Precoseasonal dosing, ie, 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% CI, was required to demonstrate clinical efficacy. Analyses were intent-to-treat.(20,21)

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 U.S.), 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 (eg, 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 2, all studies satisfied the FDA requirement for efficacy.(1,20) A sixth pivotal trial used a 2-month preseason treatment period and did not meet FDA criteria for efficacy.(22)

Table 2. 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
[a] Rhinoconjunctivitis Total Symptom Score

Trial 1: Phase 3, Multicenter U.S. Trial(23)

Adults (N=473) age 18 to 65 years who had baseline RTSS of 12 or greater were randomized 1:1 to Oralair® 300 IR (index of reactivity) or placebo. Median duration of the grass pollen season was 43 days (range, 11-70). Median average pollen count was 32 grains/m^3 (range, 4-215). Mean (SD) treatment duration was 180 (14) days, 127 (11) days before and 43 (15) days during the pollen period. Treatment adherence was 99% in both groups. Relative difference in the CS was 28% (95% CI, 13 to 43) favoring Oralair®.

Trial 2: European Dose-Finding Trial (24)

Adults (N=628) age 18 to 45 years were randomized 1:1:1:1 to 1 of 3 doses of Oralair® (100 IR, 300 IR, or 500 IR) or placebo. Mean (SD) duration of the pollen season was 30 (10) days. (Pollen season was defined by the first of 3 consecutive days with a grass pollen count above 30 grains/m^3 to the last of 3 consecutive days with a pollen count below 30 grains/m^3.) Mean treatment duration before the pollen period was 125 days. Adherence was 88% in the Oralair® 300 IR group and 96% in the placebo group. CS was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS for 136 patients randomized to Oralair® 300 IR and 148 patients randomized to placebo was 30% (95% CI, 16 to 43) favoring Oralair®.

Trial 3: Phase 3, 3-Year European Trial (25, 26)

Adults (N=633) age 18 to 50 years who had baseline RTSS of 12 or greater were randomized 1:1:1 to 1 of 3 groups: Oralair® 300 IR initiated 4 months or 2 months before the grass pollen season or placebo. All patients were treated for 3 consecutive seasons, and efficacy outcomes were assessed during the third pollen season. Mean treatment duration for all 3 groups was 5.5 months per year. Treatment adherence exceeded 97%. CS was not the original primary end point, and FDA analyzed results post hoc. For 207 patients randomized to the 4-month Oralair® pretreatment group and 219 patients randomized to placebo, relative difference in the CS during the third pollen season was 38% (95% CI, 22 to 55) favoring Oralair®. In years 4 and 5, patients received no treatment. Relative differences in the CS did not meet FDA's requirement for efficacy at these time points.

Trial 4: Phase 3, European Pediatric Trial (27)

Children and adolescents (N=278) age 5 to 17 years (mean [SD], 11 [3] years) who had baseline RTSS of 12 or greater were randomized 1:1 to Oralair® or placebo. The Oralair® group was dosed 100 IR on Day 1, 200 IR on Day 2, and 300 IR on each subsequent day. Mean (SD) duration of the pollen season was 39 (16) days. Mean (SD) treatment duration before

pollen season was 113 (10) days. Treatment adherence was approximately 95% in both groups. CS was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS was 30% (95% CI, 13 to 47) favoring Oralair®.

Trial 5: European Environmental Exposure Chamber (EEC) Trial

Adults (N=89) age 18 to 50 years were randomized 1:1 to Oralair® or placebo for 4 months. Patients had pretreatment RTSS greater than 7 after challenge in an EEC with 4 of the 5 grass pollens contained in Oralair®. Patients were again allergen challenged in the EEC at month 4. Because rescue medications are not permitted in the EEC, the primary efficacy end point was the mean RTSS during the 4-hour allergen challenge. Relative difference in mean RTSS was 29% (95% CI, 14 to 44) favoring Oralair®.

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 Oralair® recipients (1.3%) and 5 placebo recipients (0.6%). 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®. (One laryngeal edema episode responded to intravenous prednisolone, and 1 severe hypersensitivity episode, characterized by violent coughing and extreme dyspnea, responded to antihistamine, beta-2 agonist, and prednisolone.) 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 comprises 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.

Based on these findings, FDA considered Oralair® 300 IR safe in patients age 10 to 65 years.

"Because the small diameter of the upper airway of younger children may be more easily occluded during a laryngopharyngeal allergic reaction, and because of the low number of young children who have been studied in the pediatric clinical trial with Oralair®, CBER [Center for Biologics Evaluation and Research] has limited the indication of Oralair® to children 10-17 years

of age. The indication for children 5-9 years of age will be re-evaluated upon completion of safety studies in these children, as mandated by PREA [Pediatric Research Equity Act]."(20)

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 (FEV_1) 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 FDA criteria for efficacy (see Table 3).

Table 3. 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(21)	3094[c]	20% (16 to 24)

[a] Year 1
[b] Did not meet FDA criteria for efficacy
[c] Does not account for 407 patients (12%)

Trial 1: U.S. and Canada Adult and Pediatric Trial(28)
Patients (N=1501) age 5 to 65 years were randomized. Eighty-five percent of patients were polysensitized, and 25% had mild intermittent asthma. Median preseason treatment duration was 19 weeks (range, 11-27). Mean pollen season duration was 54 days. Mean pollen count was 23 grains/m^3, consistent with a relatively weak pollen season. Relative difference in the CS was 23% (95% CI, 13 to 36) favoring Grastek® and meeting FDA criteria for efficacy.

Trial 2: U.S. and Canada Pediatric Trial (29)
Children and adolescents (N=345) age 5 to 18 years (mean, 12 years) were randomized. Eighty-nine percent of patients were polysensitized, and 26% had mild intermittent asthma. Median duration of grass pollen season was 56 days. Mean grass pollen count was 28 grains/m^3. Median preseason treatment duration was 16 weeks (range, 2 days-22 weeks). Relative difference in the CS was 26% (95% CI, 10 to 38) favoring Grastek® and meeting FDA criteria for efficacy.

Trial 3: European Sustained Effect Trial(30,31)
Adults (N=634) age 18 to 65 years were randomized. Median preseasonal treatment duration was 27 weeks (range, 16-35). Patients continued treatment during 3 consecutive grass pollen seasons. Mean (SD) duration of the first pollen season was 58 (14) days (range, 16-86). CS was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS at the end of treatment years 1, 2, and 3 were 34% (95% CI, 26 to 42), 41% (95% CI, 30 to 52), and 34% (95% CI, 21 to 46), respectively, all favoring Grastek® and meeting FDA

criteria for efficacy. For 257 patients who remained on-study for 1 year after discontinuing Grastek®, relative difference in the CS was 27% (95% CI, 12 to 40) favoring Grastek® and meeting FDA criteria for efficacy. For 241 patients who remained on-study for 2 years after discontinuing Grastek®, relative difference in the CS was 23% (95% CI, 6 to 37) favoring Grastek® but no longer meeting FDA criteria for efficacy.

Trial 4: German Pediatric Trial
Children and adolescents (N=253) age 5 and 16 years were randomized. Patients initiated treatment with approximately 17 weeks (range, 8 to 23) before grass pollen season. CS was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS was 24% (95% CI, 5 to 41) favoring Grastek® but failing to meet FDA criteria for efficacy.

Trial 5: U.S. Adult Trial
Adults (N=329) age 18 to 65 years were randomized. Median preseason treatment duration was 16 weeks (range, 6-24). CS was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS was 10% (95% CI, 4 to 24) favoring Grastek® but failing to meet FDA criteria for efficacy. Post-hoc analyses suggested that baseline symptom scores and overlapping pollen seasons may have affected results.(32)

Trial 6: U.S. and Canada Adult Trial
Adults (N=439) age 18 to 63 years were randomized. Median preseason treatment duration was 17 weeks (range, 7-24). Relative difference in the CS was 21% (95% CI, 6 to 33) favoring Grastek® but failing to meet FDA criteria for efficacy.

Safety
The pooled FDA safety database comprises 2389 patients who received Grastek® (20% children and adolescents), 2116 (86%) of whom received Grastek® 2800 BAU.(21) An overview of TEAEs in the adult and child-adolescent pooled safety databases is shown in Table 4. The pattern of adverse events observed in the FDA safety database was similar to that in post-European registration market support trials of Grazax® (total N=1666).(32)

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 (eg, 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.(32)

Based on these data, FDA estimated a 0.1% to 0.5% risk of severe or serious laryngopharyngeal or systemic reactions with Grastek®.(33)

Table 4. Overview of Treatment-Emergent Adverse Events in Grastek® Pooled Safety Databases

	Adults		Children and Adolescents	
	Grastek®	Placebo	Grastek®	Placebo
TEAEs	66	23	58	24
Oral pruritus	27	4	24	2
Throat irritation	23	3	21	3
Ear pruritus	13	1	NR	NR
Oral edema	11	<1	10	<1
Tongue pruritus	NR	NR	9	<1
Treatment discontinuation due to TEAE	5	1	6	<1

NR, not reported

Ragwitek®

FDA documents for Ragwitek® currently are unavailable; 2 pivotal trials are included in the prescribing information. (3) Both natural field trials that enrolled adults age 18 to 50 years who had ragweed pollen-induced allergic rhinitis with or without conjunctivitis, positive serum IgE to ragweed pollen, and baseline FEV_1 at least 70% of predicted. As shown in Table 5, both trials met FDA criteria for efficacy.

Table 5. Results of 2 Pivotal Ragwitek® Trials in Adults

Trial	N	Relative Difference 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)

Trial 1: Phase 2/3 U.S. and Canada Dose-Finding Trial (34)

Adults (N=565) were randomized 1:1:1 to daily Ragwitek® 6 or 12 Amb a 1 units or placebo. (Amb a 1 units are FDA reference units; 1 Amb a 1 unit equals 1 mcg of the major short ragweed allergen, *Ambrosia artemisiifolia*). Patients began treatment approximately 12 weeks before short ragweed pollen season and continued treatment during and after the season, for a total treatment duration of 52 weeks. Approximately 85% of patients were polysensitized, and 22% had mild intermittent asthma. Mean ragweed season duration was 44 days. Mean pollen count was 122 grains/m^3. For 187 patients in the Ragwitek® 12 Amb a 1 unit group and 188 patients in the placebo group, relative difference in CS was 26% (95% CI, 14 to 38) favoring Ragwitek® and meeting FDA criteria for efficacy.

Trial 2: Trial 2: Phase 3 U.S., Canada, and Eastern Europe trial(35)

Adults (N=784) were randomized 1:1:1:1 to Ragwitek® 1.5, 6, or 12 Amb a 1 unit or placebo. Patients began treatment approximately 16 weeks before short ragweed pollen season and continued treatment during and after the season, for a total treatment duration of 52 weeks. Approximately 78% of patients were polysensitized, and 17% had mild intermittent asthma. The short ragweed pollen season lasted approximately 46 days. Mean pollen count was approximately 127 grains/m^3. For 194 patients in the Ragwitek® 12 Amb a 1 unit group and 198 patients in the placebo group, relative difference in CS was 27% (95% CI, 14 to 39) favoring Ragwitek® and meeting FDA criteria for efficacy.

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 and 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.

House Dust Mite -Specific Allergy
Several placebo-controlled RCTs published in 2013 and 2014 assessed house dust mite (HDM)-SLIT in children and adults sensitized to HDM (primarily *Dermatophagoides* species) who have rhinitis(36-38) or asthma.(39) HDM-SLIT generally showed statistically significant reductions in rhinitis symptom scores in these trials, with reductions of approximately 20% in 1 study.(37) In 2013, Bae et al published a systematic review and meta-analysis of HDM immunotherapy for children and adults with HDM-induced atopic dermatitis.(40) Literature was searched through November 2012, and 8 placebo-controlled RCTs were included (6 SCIT [total N=307] , 2 SLIT [total 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.

Food Allergy
Several authors have examined the role of SLIT in desensitizing people with food allergies. Two studies suggested that SLIT may be safely used to desensitize children and adolescents with peanut allergy in comparison with oral immunotherapy(41) or placebo,(41,42) but these studies were small (total N=90) and results are preliminary.

SLIT Compared With SCIT
Few published RCTs have compared SLIT and SCIT head-to-head. A 2012 review by Bahceciler and Galip listed 8 RCTs comparing SLIT and SCIT.(43) Sample sizes ranged from 20 to 58 participants. Three studies were published in the 1990s, and the other 5 were published between 2004 and 2012. Pipet et al reported that none of the studies from the 1990s found a statistically significant difference in efficacy between the 2 routes of administration.(44)

Allergic Rhinoconjunctivitis and Asthma. The 2013 AHRQ comparative effectiveness review, discussed earlier, identified 8 RCTs comparing sublingual and subcutaneous immunotherapy.(12) The report stated that only 1 study was considered to be at low risk of bias, and most studies had biases related to improper allocation concealment, unblinded

interventions, and incomplete reporting of missing data. The authors were unable to pool studies due to heterogeneity. Regarding the question of comparative effectiveness of SLIT and SCIT, the report concluded that there was low-grade evidence that SCIT was more effective than SLIT at controlling allergy symptoms and dust mite allergy symptoms. Moreover, the report concluded that there was moderate-grade evidence that SCIT provided better symptom control for allergic nasal and/or eye symptoms than SLIT.

Also 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.(45) 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.

A 2013 systematic review by researchers at Johns Hopkins University reviewed SCIT and SLIT for pediatric asthma and rhinoconjunctivitis.(16) Three head-to-head studies published before June 2012 were identified. Low strength of evidence supported SCIT over SLIT for improving asthma and rhinitis symptoms and for decreasing medication usage. This same group subsequently reviewed head-to-head RCTs comparing SCIT and SLIT in adults and children.(46) Literature was searched through November 2012, and 8 RCTs were included. Moderate-grade evidence supported the greater effectiveness of SCIT compared with SLIT for improving nasal and eye symptoms. Low-grade evidence supported greater effectiveness of SCIT compared with SLIT for improving asthma symptoms and combined rhinitis symptom and medication scores.

In 2011, Sieber et al published a meta-analysis of individual patient data from 4 observational studies on treatment of allergic rhinitis.(47) A total of 665 patients were treated with SLIT and 182 with SCIT. Median rhinitis symptom score decreased from 3.00 to 2.00 (range, 1.00-4.00) in both treatment groups (p<0.001 for within-group changes). Median conjunctivitis symptom score decreased from 2.00 to 1.00 (range, 0.00-3.00) in each group (p<0.001 for within-group changes). Additionally, median asthma symptom score decreased from 3.00 to 2.00 (range, 1.00-4.00) in each group (p<0.001 for within-group changes). There were no significant differences in symptom scores when the SLIT group was compared with the SCIT group.

In terms of the relative safety of SCIT and SLIT, the 2009 Pipet review(44) cites reports of fatalities after SCIT, although subsequent examination of 13 deaths occurring between 1992 and 1996 suggested that unstable asthma was a major risk factor. It is generally believed that SCIT is safe when performed with proper patient selection and established security principles. A 2012 review of SLIT for allergic rhinitis stated that no SLIT-related fatalities had been reported.(48) There may be a larger number of mild-to-moderate adverse effects with SLIT than with SCIT. The 2012 meta-analysis by Di Bona et al(17) included 22 placebo-controlled studies on SLIT and 14 on SCIT. Investigators identified 960 adverse events (AEs) in patients who received SCIT (0.86 AE per patient) and 4046 AEs in patients who received SLIT (2.13 AEs per patient). Most AEs were moderate severity. Although the authors did not report the total number of serious AEs, they stated that there were 12 episodes of anaphylaxis requiring epinephrine treatment in patients treated with SCIT and only 1 in patients treated with SLIT.

There also were 2 reported episodes of anaphylaxis in patients treated with placebo in the SCIT studies.

A 2013 systematic review and meta-analyses by the U.K. National Health Service reviewed studies of seasonal allergic rhinitis published before April 2011.(14) AEs were common with both SCIT and SLIT, but most were local reactions at the point of administration and resolved spontaneously without treatment. Systemic reactions were less common, occurring with approximately 4% of injections for SCIT, and most were mild or moderate in severity. Of all systemic reactions, 19% were considered severe in patients taking SCIT compared with 2% in patients taking SLIT. Three percent of patients in both group discontinued treatment due to adverse events. No deaths occurred in any of the trials.

HDM-Specific Allergy
Three RCTs published in 2010 and 2011 compared the efficacy of dust-mite specific SLIT and SCIT and were published by investigators in Turkey.(49-51) Similar to older studies, none 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.(49) 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 HDM-SCIT and HDM-SLIT in children with rhinitis and asthma who were monosensitized to HDM.(52) 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.

Ongoing Clinical Trials
A search of the online database, ClinicalTrials.gov, found 9 active trials of SLIT for allergies. These are summarized in Table 6. The first trial listed (NCT01335139) compares SLIT with SCIT using a double-placebo design in patients with seasonal allergic rhinitis. Several studies investigate HDM SLIT, and 1 (NCT02052934) investigates SLIT for enterotoxigenic *Escherichia Coli* (ETEC).

Table 6. Active Trials of Sublingual Immunotherapy for Allergies

NCT Number	Title	Age Group	Phase	N[a]	Primary Completion Date[a]
NCT01335139	Long-Term Effects of Sublingual Grass Therapy	Adult	2	90	Sep 2014
NCT02014623	Immunological Mechanisms of Oralair® in Patients With Seasonal Allergic Rhinitis	Child, adult	4	40	May 2015
NCT02005627	Grass Pollen Allergen Immunotherapy Tablet (AIT) Time Course Study (POLLEN+)	Adult	2	44	Feb 2015
NCT01930461	Dose-Ranging Study of SLIT Tablets of House Dust Mite Allergen Extracts (HDM) in Adults With HDM-associated Allergic Asthma	Adult	2	480	Mar 2015

NCT Number	Title	Age Group	Phase	N[a]	Primary Completion Date[a]
NCT01608243	Safety Study of Sublingual Immunotherapy Tablets of House Dust Mite Allergen Extracts	Adult	1	96	Oct 2013[b]
NCT01052610	Assessment of Sublingual Immunotherapy in Children Allergic to House Dust Mites	Child, adult	4	100	Sep 2013[b]
NCT01700192	Long-Term Efficacy and Safety Study of SCH 900237/MK-8237 in Children and Adults With House Dust Mite-Induced Allergic Rhinitis/Rhinoconjunctivitis (P05607)	Child, adult, senior	3	1500	Feb 2015
NCT01852825	MK-8237 (SCH900237) Biomarker Study in Participants With Allergic Rhinitis or Rhinoconjunctivitis (8237-009)	Adult	1	34	Jan 2015
NCT02052934	Safety of Sublingual dmLT [Double Mutant Heat-Labile Toxin] for ETEC [Enterotoxigenic Escherichia Coli]	Adult	1	52	Sep 2015

[a] Estimated
[b] Although ClinicalTrials.gov record is current, estimated completion date has passed

Summary

Sublingual immunotherapy (SLIT) is a potential alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy. Three new 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. Patients in these trials had received previous treatment for their pollen-induced rhinitis or rhinoconjunctivitis symptoms. Therefore, SLIT using Oralair®, Grastek®, or Ragwitek® may be considered medically necessary in patients with pollen-induced allergic rhinitis or rhinoconjunctivitis who have symptoms uncontrolled by pharmacologic treatment.

SLIT is being investigated for other allergies, eg, other seasonal allergies, food allergies, and in patients sensitized to house dust mites. Current evidence is insufficient to form any conclusion about the use of SLIT for these indications, and FDA-approved allergy extracts for these uses are lacking. Therefore, SLIT is investigational for all other uses.

Some evidence from clinical trials has been published on the comparative effectiveness of SLIT versus SCIT, but the quantity and quality of evidence is less than that for efficacy versus placebo. Several 2013 systematic reviews tended to find better outcomes with SCIT than with SLIT, but findings were inconclusive due to small numbers of trials and variability in study design. There also are insufficient data to draw firm conclusions about the relative safety of SLIT versus SCIT. A 2012 meta-analysis of placebo-controlled trials suggested that there may be more mild-to-moderate adverse events with SLIT than with SCIT, but there are data only on a few serious adverse events.

Practice Guidelines and Position Statements

AAAAI/EAACI

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.(53) The report summarized the literature and current practices in the U.S. 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..."

AAAAI Joint Task Force on Practice Parameters

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.(54) 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.

World Allergy Organization

In 2013, WAO updated its position paper on SLIT.(55) 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 (ie, 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.

CODING

> **The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

CPT/HCPCS
95199   Unlisted allergy / clinical immunologic service or procedure
J3490   Unclassified drugs
There are no specific HCPCS codes for the drugs listed in this policy.

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

ICD-9 Diagnoses
477.0   Allergic rhinitis; due to pollen

ICD-10 Diagnoses (Effective October 1, 2015)
J30.1   Allergic rhinitis due to pollen

REVISIONS

06-07-2013	Policy added to the bcbsks.com web site.
08-18-2014	Description section updated
	In Policy section:
	▪ Revised policy from experimental / investigational to medically necessary adding,
	"Sublingual immunotherapy using Oralair®, Grastek®, or 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:
	1. Patient has a history of rhinitis or rhinoconjunctivitis symptoms related to grass or short ragweed pollen exposure.
	2. Patient has a documented positive pollen-specific skin test or pollen-specific immunoglobulin E (IgE) test (see Policy Guidelines section).
	3. Patient's symptoms are not adequately controlled by appropriate pharmacotherapy (see Policy Guidelines section)."
	▪ Revised E/I statement adding "for all other uses" to read,
	"Sublingual immunotherapy as a technique of allergy immunotherapy is considered experimental / investigational for all other uses."
	▪ Added Policy Guidelines:
	"For Oralair®, Grastek®, or Ragwitek®(1-3):
	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

Current Procedural Terminology © American Medical Association. All Rights Reserved.

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; and for Grastek® and Ragwitek®, history of eosinophilic esophagitis.

Administration and Dose

1. Prescribing information includes a black box warning for severe allergic reactions including anaphylaxis. Patients must be prescribed an epinephrine auto-injector and be trained on how to use it.
2. 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).
3. 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.
4. All 3 agents are dosed once daily.
5. 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).
6. Grastek® and Ragwitek® both are initiated at the maintenance dose (2800 BAU [bioequivalent allergy unit] and 12 Amb a 1 unit, respectively).

Table 1. Oralair® Dosing in Patients Age 10-17 Years(1)

Day 1	Day 2	Day 3 and Following
100 IR	2´ 100 IR	300 IR

IR, index of reactivity, a potency unit defined by the formation of a 7-mm wheal in 30 sensitized individuals during product development.(1)

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:

1. Treatment should be individualized based on symptom severity and duration, comorbidities, and patient age, preference (eg, route of administration, tolerance for adverse effects), and previous treatment history.
2. Measures to increase treatment adherence (eg, shared decision making, consideration of the patient's school or work schedule, use of a medication calendar or check-off list) are encouraged.
3. Goals of treatment are symptom reduction and improvements in functional capacity and quality of life.
4. A "step-up" (if treatment is inadequate)/"step-down" (if symptom relief is achieved with other interventions, eg, avoidance) approach to treatment is recommended.
5. Allergen avoidance is the first step of treatment but may be unrealistic for some patients.
6. Six medication classes are used to treat allergic rhinitis: H1-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).
7. Treatment should be symptom-specific, eg, 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.
8. For mild or intermittent symptoms, oral or nasal antihistamine may be considered first-line treatment.

	9. 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. 10. Intranasal corticosteroids may be effective for more severe or persistent symptoms. 11. Combination treatment (eg, 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. 12. Oral sympathomimetics may cause insomnia; their use is limited in patients with certain comorbidities (eg, diabetes mellitus, unstable hypertension). 13. Oral leukotriene receptor antagonists may reduce asthma exacerbations in patients with comorbid asthma.
	Rationale section updated
	In Coding section: ▪ Added ICD-9 Code: 477.0 ▪ Added ICD-10 Code: J30.1 ▪ Removed "Experimental / Investigational on all diagnoses related to this medical policy."
	References updated

REFERENCES

1. Stallergenes S.A. Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract) tablet for sublingual use package insert, April 2014. Available online at: http://www.fda.gov/biologicsbloodvaccines/allergenics/ucm391287.htm. Last accessed April 2014.

2. Merck & Co., Inc. Grastek® (Timothy grass pollen allergen extract) tablet for sublingual use prescribing information, April 2014. Available online at: http://www.grastek.com/. Last accessed April 2014.

3. Merck & Co., Inc. Ragwitek® (short ragweed pollen allergen extract) tablet for sublingual use prescribing information, April 2014. Available online at: http://www.ragwitek.com/. Last accessed April 2014.

4. Benninger M, Farrar JR, Blaiss M et al. Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class. Ann Allergy Asthma Immunol 2010; 104(1):13-29.

5. Brozek JL, Bousquet J, Baena-Cagnani CE et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010; 126(3):466-76.

6. van Cauwenberge P, Bachert C, Passalacqua G et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy 2000; 55(2):116-34.

7. Wallace DV, Dykewicz MS, Bernstein DI et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008; 122(2 Suppl):S1-84.

8. Glacy J, Putnam K, Godfrey S et al. *Treatments for Seasonal Allergic Rhinitis* . Rockville MD2013.

9. Blue Cross Blue Shield Association Technology Evaluation Center (TEC). Sublingual immunotherapy for allergies. TEC Assessment 2003; Volume 18, Tab 4.

10. De Bot C. M., Moed H, Berger MY et al. Sublingual immunotherapy in children with allergic rhinitis: quality of systematic reviews. Pediatr Allergy Immunol 2011; 22(6):548-58.

11. Compalati E, Penagos M, Tarantini F et al. Specific immunotherapy for respiratory allergy: state of the art according to current meta-analyses. Ann Allergy Asthma Immunol 2009; 102(1-Jan):22-8.

12. Lin SY, Erekosima N, Suarez-Cuervo C et al. Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review No. 111. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 13-EHC061-EF. 2013. Available online at: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1427. Last accessed April 2014.

13. Lin SY, Erekosima N, Kim JM et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA : the journal of the American Medical Association 2013; 309(12):1278-88.

14. Meadows A, Kaambwa B, Novielli N et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. Health technology assessment (Winchester, England) 2013; 17(27):vi, xi-xiv, 1-322.

15. Tao L, Shi B, Shi G et al. Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials. The clinical respiratory journal 2014; 8(2):192-205.

16. Kim JM, Lin SY, Suarez-Cuervo C et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. Pediatrics 2013; 131(6):1155-67.

17. Di Bona D, Plaia A, Leto-Barone MS et al. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. J Allergy Clin Immunol 2012; 130(5):1097-107 e2.

18. Calderon MA, Penagos M, Sheikh A et al. Sublingual immunotherapy for treating allergic conjunctivitis. Cochrane Database Syst Rev 2011; (7):CD007685.

19. Radulovic S, Wilson D, Calderon M et al. Systematic reviews of sublingual immunotherapy (SLIT). Allergy 2011; 66(6):740-52.

20. FDA. Summary basis for regulatory action template - March 31, 2014. Available online at: http://www.fda.gov/biologicsbloodvaccines/allergenics/ucm391287.htm. Last accessed April 2014.

21. FDA. Statistical review: Grastek. Available online at: http://www.fda.gov/biologicsbloodvaccines/allergenics/ucm393162.htm. Last accessed April 2014.

22. FDA. Briefing document: Oralair, Allergenic Products Advisory Committee (APAC) meeting December 11, 2013. Available online at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/ucm367268.htm. Last accessed April 2014.

23. Cox LS, Casale TB, Nayak AS et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. J Allergy Clin Immunol 2012; 130(6):1327-34 e1.

24. Didier A, Malling HJ, Worm M et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol 2007; 120(6):1338-45.

25.   Didier A, Worm M, Horak F et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 2011; 128(3):559-66.
26.   Didier A, Malling HJ, Worm M et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. Clin Exp Allergy 2013; 43(5):568-77.
27.   Wahn U, Tabar A, Kuna P et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol 2009; 123(1):160-66 e3.
28.   Maloney J, Bernstein DI, Nelson H et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Ann Allergy Asthma Immunol 2014; 112(2):146-53 e2.
29.   Blaiss M, Maloney J, Nolte H et al. Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. J Allergy Clin Immunol 2011; 127(1):64-71, 71 e1-4.
30.   Dahl R, Kapp A, Colombo G et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. J Allergy Clin Immunol 2008; 121(2):512-18 e2.
31.   Dahl R, Kapp A, Colombo G et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006; 118(2):434-40.
32.   FDA. Briefing document: Grastek, Allergenic Products Advisory Committee (APAC) meeting December 12, 2013. Available online at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/AllergenicProductsAdvisoryCommittee/ucm367268.htm. Last accessed April 2013.
33.   FDA. Clinical review: Grastek. Available online at: http://www.fda.gov/biologicsbloodvaccines/allergenics/ucm393162.htm. Last accessed April 2014.
34.   Nolte H, Hebert J, Berman G et al. Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults. Ann Allergy Asthma Immunol 2013; 110(6):450-56 e4.
35.   Creticos PS, Esch RE, Couroux P et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. J Allergy Clin Immunol 2014; 133(3):751-8.
36.   Aydogan M, Eifan AO, Keles S et al. Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: a double-blind-placebo-controlled randomised trial. Respir Med 2013; 107(9):1322-9.
37.   Bergmann KC, Demoly P, Worm M et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. J Allergy Clin Immunol 2013.
38.   Wang DH, Chen L, Cheng L et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. The Laryngoscope 2013; 123(6):1334-40.
39.   Tian M, Wang Y, Lu Y et al. Effects of sublingual immunotherapy for Dermatophagoides farinae on Th17 cells and CD4(+) CD25(+) regulatory T cells in peripheral blood of children with allergic asthma. International forum of allergy & rhinology 2014; 4(5):371-5.

40.   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 2013; 132(1):110-7.
41.   Chin SJ, Vickery BP, Kulis MD et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol 2013; 132(2):476-8 e2.
42.   Fleischer DM, Burks AW, Vickery BP et al. Sublingual immunotherapy for peanut allergy: A randomized, double-blind, placebo-controlled multicenter trial. Journal of Allergy and Clinical Immunology 2013; 131(1):119-27.e7.
43.   Bahceciler NN, Galip N. Comparing subcutaneous and sublingual immunotherapy: what do we know? Current opinion in allergy and clinical immunology 2012; 12(6):640-7.
44.   Pipet A, Botturi K, Pinot D et al. Allergen-specific immunotherapy in allergic rhinitis and asthma: Mechanisms and proof of efficacy. Respir Med 2009; 103(6):800-12.
45.   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 2013.
46.   Chelladurai Y, Suarez-Cuervo C, Erekosima N et al. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. The journal of allergy and clinical immunology. In practice 2013; 1(4):361-9.
47.   Sieber J, Shah-Hosseini K, Mosges R. Specific immunotherapy for allergic rhinitis to grass and tree pollens in daily medical practice- symptom load with sublingual immunotherapy compared to subcutaneous immunotherapy. Ann Med 2011; 43(6):418-24.
48.   Wise SK, Schlosser RJ. Evidence-based practice: sublingual immunotherapy for allergic rhinitis. Otolaryngologic clinics of North America 2012; 45(5):1045-54.
49.   Eifan AO, Akkoc T, Yildiz A et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010; 40(6):922-32.
50.   Yukselen A, Kendirli SG, Yilmaz MEoo-ys et al. Int Arch Allergy Immunol. 2011; 157(3-Jan):288-98.
51.   Keles S, Karokov-Aydiner E, Ozen A et al. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. J Allergy Clin Immunol 2011; 128(4):808-15.
52.   Yukselen A, Kendirli SG, Yilmaz M et al. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. Asian Pacific journal of allergy and immunology / launched by the Allergy and Immunology Society of Thailand 2013; 31(3):233-41.
53.   Burks AW, Calderon MA, Casale T et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. J Allergy Clin Immunol 2013.
54.   Cox L, Nelson H, Lockey R et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011; 127(1 Suppl):S1-55.
55.   Canonica GW, Cox L, Pawankar R et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. The World Allergy Organization journal 2014; 7(1):6.

Other References
1.   Blue Cross and Blue Shield of Kansas, Family Practice Liaison Committee, July 2003; July 2004.
2.   Blue Cross and Blue Shield of Kansas, Pediatric Liaison Committee, July 2003; July 2004, July 2014.
3.   Blue Cross and Blue Shield of Kansas, Otolaryngology Liaison Committee, August 2003; December 2003, August 2004, July 2014.
4.   Blue Cross and Blue Shield of Kansas, Otolaryngology Liaison Committee Consent Ballot, October 2012.