Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the U.S. Food and Drug Administration (FDA) approved sublingual immunotherapy (SLIT) products Ragwitek®‡, Grastek®‡, Oralair®‡, and Odactra™‡ for the treatment of allergen induced allergic rhinitis to be **eligible for coverage.****

Ragwitek

Patient Selection Criteria

The use of Ragwitek will be considered for coverage eligibility when ALL of the following patient selection criteria are met:

- Patient is 18-65 years of age; AND
- Ragwitek therapy is initiated 12 weeks prior to the expected onset of the short ragweed pollen season; AND
- The diagnosis of short ragweed pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions:
    - The patient has a positive skin test response to short ragweed pollen; OR
    - The patient has a positive in vitro test (i.e., a blood test for allergen-specific immunoglobulin E [IgE] antibodies) for short ragweed pollen; AND
- Patient is NOT currently receiving subcutaneous allergen immunotherapy; AND

- Patient must have been unable to achieve adequate symptom control with TWO products (from different classes) from the following drug classes (over the counter products are acceptable within the drug classes when taken at prescription strength doses):
    - Intranasal corticosteroids
    - Oral antihistamines
    - Intranasal antihistamines
    - Leukotriene inhibitors

  *Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Grastek

Patient Selection Criteria

The use of Grastek will be considered for coverage eligibility when ALL of the following patient selection criteria are met:

- Patient is 5-65 years of age; AND
- Grastek therapy is initiated 12 weeks prior to the expected onset of the grass pollen season; AND
- The diagnosis of grass pollen-induced allergic rhinitis is confirmed by meeting ONE of the following:
    - The patient has a positive skin test response to a grass pollen from the Pooideae subfamily of grasses (this includes, but is not limited to sweet vernal, Kentucky blue grass, Timothy grass, orchard, or perennial rye grass); OR
    - The patient has a positive in vitro test (i.e., a blood test for allergen-specific IgE antibodies) for a grass in the Pooideae subfamily of grasses (see examples above); AND
- Patient is NOT currently receiving subcutaneous allergen immunotherapy; AND
- Patient must have been unable to achieve adequate symptom control with TWO products (from different classes) from the following drug classes (over the counter products are acceptable within the drug classes when taken at prescription strength doses):
    - Intranasal corticosteroids
    - Oral antihistamines
    - Intranasal antihistamines
    - Leukotriene inhibitors

*Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Oralair

Patient Selection Criteria

The use of Oralair will be considered for coverage eligibility when ALL of the following patient selection criteria are met:

- Patient is 10-65 years of age; AND
- Oralair therapy is initiated 16 weeks prior to the expected onset of the grass pollen season; AND
- The diagnosis of grass pollen-induced allergic rhinitis is confirmed by meeting ONE of the following:
    - The patient has a positive skin test response to a grass pollen from the Pooideae subfamily of grasses (this includes, but is not limited to sweet vernal, Kentucky blue grass, Timothy grass, orchard, or perennial rye grass); OR
    - The patient has a positive in vitro test (i.e., a blood test for allergen-specific IgE antibodies) for a grass in the Pooideae subfamily of grasses (see examples above); AND
- Patient is NOT currently receiving subcutaneous allergen immunotherapy; AND
- Patient must have been unable to achieve adequate symptom control with TWO products (from different classes) from the following drug classes (over the counter products are acceptable within the drug classes when taken at prescription strength doses):
    - Intranasal corticosteroids
    - Oral antihistamines
    - Intranasal antihistamines
    - Leukotriene inhibitors

*Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Odactra

Patient Selection Criteria

The use of Odactra will be considered for coverage eligibility when ALL of the following patient selection criteria are met:

- Patient is 18-65 years of age; AND
- The diagnosis of house dust mite induced allergic rhinitis is confirmed by ONE of the following:
    - The patient has a positive skin test response to licensed house dust mite allergen extracts; OR
    - The patient has a positive in vitro test (i.e., a blood test for allergen-specific IgE antibodies) to Dermatophagoides farinae or Dermatophagoides pteronyssinus; AND
- Patient is NOT currently receiving subcutaneous allergen immunotherapy; AND
- Patient must have been unable to achieve adequate symptom control with TWO products (from different classes) from the following drug classes (over the counter products are acceptable within the drug classes when taken at prescription strength doses):
    - Intranasal corticosteroids
    - Oral antihistamines
    - Intranasal antihistamines
    - Leukotriene inhibitors

  *Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Ragwitek, Grastek, Oralair, or Odactra without first attempting symptom control of allergic rhinitis with at least TWO products from the intranasal corticosteroids, oral or intranasal antihistamines, or leukotriene inhibitors (each product coming from a different class) is considered to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers FDA approved SLIT as a technique of allergy immunotherapy for all other uses not mentioned in the specific drug's patient selection criteria to be **investigational.***

Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

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Based on review of available data, the Company considers non-FDA approved SLIT to be **investigational.***

Background/Overview

SLIT is a potential alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy. It is proposed as a more convenient alternative delivery route for treating a variety of allergic disorders. There are now four FDA approved SLITs available. These include Ragwitek, Grastek, Oralair, and Odactra. Ragwitek is approved for the treatment of short ragweed pollen-induced allergic rhinitis in adults 18-65 years of age. It is dosed as one 12 Amb a 1-Unit sublingual tablet daily. Ragwitek should be initiated at least 12 weeks before the expected onset of the ragweed pollen season. Grastek is approved for the treatment of grass pollen induced allergic rhinitis in persons 5-65 years of age. Grastek is dosed as one 2800 bioequivalent allergy unit (BAU) sublingual tablet daily and should be initiated at least 12 weeks prior to the start of each grass pollen season. Oralair is approved for the treatment of grass pollen induced allergic rhinitis. It has aged based dosing. For those individuals aged 10-17, the dosing is 100 IR (index of reactivity) the first day, 200 IR the second day, and 300 IR daily thereafter. Oralair is available in 100 IR and 300 IR sublingual tablets. For those individuals 18-65, Oralair is dosed at 300 IR daily. Odactra is approved in persons 18-65 years of age for the treatment of house dust mite induced allergic rhinitis. The dosage of Odactra is one tablet (12 SQ-HDM) daily.

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 is the standard approach. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, SLIT is the most prominent. SLIT targets absorption to the sublingual and buccal mucosa. Allergen preparations used for SLIT are held under the tongue for one to several minutes and then swallowed or spit out.

Pharmacotherapy of Pollen-Induced Allergic Rhinitis

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

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

Various medication classes are used to treat allergic rhinitis including antihistamines (oral and intranasal), intranasal corticosteroids, and leukotriene receptor antagonists. For patients with persistent or moderate to severe symptoms, intranasal glucocorticoids (e.g., fluticasone, mometasone) show good efficacy. If the nasal glucocorticoids aren't desirable, then other products demonstrating efficacy in this group of patients are antihistamine sprays (e.g., azelastine) and leukotriene inhibitors (e.g., montelukast). It is recommended that if single therapy isn't adequate, combination therapy should be utilized.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Various products were approved for allergic rhinitis:

- On April 1, 2014, 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, 2014, FDA approved Grastek (Merck, Darmstadt, Germany) 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, 2014, FDA approved Ragwitek (Merck, Darmstadt, Germany) short ragweed pollen allergen extract for patients 18 to 65 years of age.
- On March 1, 2017, FDA approved Odactra (Merck, Catalent Pharma Solutions, United Kingdom) house dust mite allergen extract for patients 18 to 65 years of age.

Rationale/Source

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

Allergic Rhinitis

Systematic Reviews

A 2003 TEC Assessment concluded that, due to the paucity of studies comparing SLIT with SCIT and the lack of FDA–approved agents for use in SLIT, the evidence was insufficient on the use of SLIT for allergen immunotherapy.

In 2014, FDA approved 3 sublingual allergen products for the treatment of allergic rhinitis or rhinoconjunctivitis. As part of a 2015 systematic review, Di Bona et al conducted a meta-analysis of studies on FDA-approved grass pollen SLIT tablets. 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 standardized mean difference (SMD) for the treatment effect was -0.28 (95% confidence interval [CI], -0.37 to -0.19; $p<0.001$). Findings were similar in an analysis that excluded the 5 studies at high or moderate risk of bias.

SLIT vs. SCIT

A few head-to-head trials have compared SLIT with SCIT indirectly. Two indirect comparative effectiveness analyses published in 2014 and 2015 reached similar conclusions on the relative efficacy of SLIT and SCIT for grass pollen allergies. Both studies showed comparable reductions in allergic rhinitis symptoms with SLIT and SCIT, and 1 study showed comparable reductions in medication use. Both studies found evidence of publication bias.

In 2013, Dretzke et al published a systematic review that included an indirect comparison of SCIT and SLIT for seasonal allergic rhinitis, using data from placebo-controlled trials. Several outcomes were examined. For symptom score, the overall standardized score difference (SSD) was 0.35 (95% CI, 0.13 to 0.59), a statistically significant result that favored SCIT. The overall SSD for medication score was 0.27 (95% CI, 0.03 to 0.53), which was statistically significant in favor of SCIT. 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.

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 FDA for the treatment of pollen-induced (i.e., seasonal) allergic rhinitis with or without conjunctivitis was obtained from FDA documentation and prescribing information. Published RCTs are cited when identified. All RCTs were placebo-controlled and double-blinded. Patients had had a minimum 2-year history of allergic rhinitis or rhinoconjunctivitis and received treatment for their symptoms during the previous pollen season. Patients with mild intermittent asthma were included (≈16% across all trials); all other patients with asthma were excluded. Polysensitized people were included in some trials. 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 end point 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, 0-18).
- RMS measures the potency of rescue medications used. For Oralair (and for 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. 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, 0-3). For Grastek and Ragwitek, RTSS and RMS were summed (range, 0-54).

Although the combined score 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 (as well as 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 (ITT).

Oralair

Five pivotal trials were submitted to FDA in support of the biologics license application for Oralair; four were natural field trials (three European, one United States) and one 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 IgE to Timothy grass; patients in U.S. trials had a positive skin prick test to Timothy grass pollen extract. Polysensitive people exposed to additional allergens during grass pollen season (e.g., who lived in areas where grass pollen season overlapped with tree or ragweed pollen season) were excluded. The pregrass pollen season treatment duration was 4 months in most trials. All studies satisfied the FDA requirement for efficacy. A sixth pivotal trial used a 2-month preseason treatment period and did not meet FDA criteria for efficacy.

In the pooled FDA safety database, 1192 patients (13% children and adolescents) received Oralair 300 IR. Adverse events that occurred only at higher doses were noted as potential safety signals. In the pooled adult sample, the most common treatment-emergent adverse events (TEAEs) reported at higher frequencies with Oralair than with placebo were oral pruritus (33% vs 7%) and throat irritation (21% vs 4%). Other TEAEs reported in more than 2.5% of Oralair recipients and more commonly than in placebo recipients included tongue and ear pruritus; edema of the mouth, lip, tongue, or pharynx; oral paresthesia; and dyspepsia. Five percent of Oralair recipients and 1% of placebo recipients withdrew from trials due to TEAEs. Serious adverse events occurred in 13 (1.3%) Oralair recipients and 5 (0.6%) placebo recipients. Of those occurring in Oralair recipients, 1 episode of gastroenteritis requiring hospitalization was considered "possibly related" to Oralair, and 2 episodes of laryngopharyngeal disorders occurring within 5 minutes of receiving the first dose of Oralair were considered 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. 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 2015 meta-analysis by Didier and Bons reviewed safety data on Oralair. The 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%) of 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 2008 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

Six phase 3 pivotal trials were submitted to FDA in support of the biologics license application for Grastek. All were natural field trials; four were conducted in North America and two in Europe. Trial participants had a history of grass pollen-induced rhinitis with or without conjunctivitis, positive serum IgE to Timothy grass pollen, and baseline forced expiratory volume in 1 second (FEV1) greater than 70% of predicted value. Polysensitized patients who required treatment for nongrass pollen allergies during grass pollen season were excluded. Patients were randomized 1:1 to daily Grastek 2800 BAU or placebo. In 1 trial (trial 3), patients continued dosing for 3 years continuously. Three (trials 1-3) of 6 studies (2480/3501 [71%] of total patients) met the FDA criteria for efficacy. 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.

The pooled FDA safety database comprised 2389 patients who received Grastek (20% children and adolescents), 2116 (86%) of whom received Grastek 2800 BAU. The most common TEAEs that led to trial discontinuation were oral pruritus (n=12), oral edema (n=7), and swollen tongue (n=6) among

Grastek-treated adults, and throat irritation (n=6) and oral edema (n=5) among Grastek-treated children or adolescents. One adult patient who had severe swollen tongue required treatment with epinephrine. Systemic treatment-related allergic reactions (e.g., angioedema, dysphagia, cough) developed in 6 Grastek-treated adults and 1 Grastek-treated adolescent. All were considered nonserious, 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. Based on these data, FDA estimated a 0.1% to 0.5% risk of severe or serious laryngopharyngeal or systemic reactions with Grastek.

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

Ragwitek

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

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 vs 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.

Grazax

A 2017 double-blinded, placebo-controlled randomized trial by Scadding et al 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. Patients were randomized to SLIT with placebo, SCIT with placebo, or double-placebo, and 92 patients completed the study overall. The primary end point was measurement of the Total Nasal Symptom Score (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 ITT population included all randomized patients, only those with an evaluable endpoint were included in the analysis (modified ITT).

The reported between-group difference was -0.18 (95% CI, -1.25 to 0.90; p=0.75), adjusted for baseline, demonstrating no statistically significant improvement in the primary outcome compared with placebo.

Secondary end points 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 effects from treatment, the SCIT group had a greater number of adverse events overall.
Statistically significant differences between SLIT and placebo included hypersensitivity (p=0.19) and dyspepsia (p=0.03).

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 effects, 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 (2017) assessed the impact of SLIT on grass pollen allergic rhinoconjunctivitis symptoms, medication use, immunologic markers, and notably, the onset of asthma. 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 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 end point) 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; $p<0.001$). Assessment of secondary end points is as follows. During the 3 years of treatment and 2 follow-up years, the SLIT group had a 22% to 30% reduction in allergic rhinoconjunctivitis symptoms when compared with placebo ($p<0.002$). Visual analog scale scores revealed a 22% reduction in symptoms for the SLIT group compared with the placebo group ($p=0.005$). The SLIT group also had a 27% reduction in medication use relative to the placebo group ($p<0.001$).

The most frequently reported adverse effects 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 effects. However, the study identified no new safety concerns. The authors reported no limitations to the RCT.

A 2017 meta-analysis of placebo-controlled randomized trial by Feng et al evaluated the efficacy and safety of SLIT use in pollen-induced allergic rhinitis in children ages 3 to 18 years. 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 evidence review.

Nasal symptom and medication scores were assessed using mean differences and SMD.

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 effect in children who were receiving SLIT. Although the study addressed heterogeneity and potential of bias overall, neither was specifically reported for the studies included in the subgroup analysis.

Summary

Three sublingual pollen extracts (one multiple-allergen product [Oralair], two single-allergen products [Grastek and Ragwitek]) have been FDA-approved for treatment of pollen-induced allergic rhinitis with or without conjunctivitis. Large, well-designed, RCTs supporting the marketing applications for these products have provided consistent evidence of efficacy and safety. Although trials were placebo-controlled, rather than SCIT-controlled, minimum clinically important criteria for demonstrating efficacy were prespecified and 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 vs 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

Systematic Reviews

In 2015, Liao et al published a meta-analysis of studies on dust mite SLIT for treating children with asthma. 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=0.007). 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=0.408). 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=0.076). In all analyses, there were high levels of heterogeneity among studies.

In 2015, Gendelman and Lang published a systematic review of house dust mite SLIT in atopic dermatitis. Five studies (total N=344 patients) were identified, but low methodologic quality limited conclusions that could be drawn. In 2013, Bae et al published a systematic review and meta-analysis of immunotherapy for children and adults with house dust mite-induced atopic dermatitis. 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 use of a nonstandard outcome measure.

Randomized Controlled Trials

Focusing on RCTs comparing SLIT with SCIT, 3 trials published in 2010, 2011, and 2012 found no statistically significant differences between treatments in overall reduction of symptoms or medication use. For example, Eifan et al (2010) evaluated findings on 48 children who had asthma or rhinitis and had been sensitized to house dust mites.21 Participants were randomized to 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 a significant reduction in rhinitis and asthma symptom scores and medication use scores.

A small 2013 RCT compared house dust mite SCIT with SLIT in children who had rhinitis and asthma and were monosensitized to house dust mites. 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.

In 2017, Feng et al also conducted a meta-analysis of 25 placebo-controlled randomized trials (published from 1990 to 2016) on the efficacy of SLIT for dust mite-induced allergic rhinitis in

adults and children. Most trials were double-blinded and deemed to be of high quality. All studies compared the intervention with placebo for a period that ranged from 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. The RCTs included participants from Europe (13 studies, n=2845 patients), Eastern Asia (5 studies, n=590 patients), Western Asia (5 studies, n=149 patients), Oceania (1 study, n=30 patients), and Africa (1 study, n=60 patients). Of 23 studies that reported discontinuation rates, 539 (14.6%) participants dropped out due to the following: adverse effects (3.0%), loss to follow-up (2.0%), noncompliance (1.9%), and poor efficacy (0.9%). Primary end points 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; $p<0.001$). 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=0.002) relative to drops (SMD = -1.06; 95% CI, -1.67 to -0.44; $p<0.001$).

Medication type also varied, including systemic and topical antihistamines, decongestants, and both systemic and topical nasal corticosteroids. Data on medication use was 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; $p<0.001$). Additionally, the significant reductions in medication use found among adults were not found in children (p=0.060), 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. A SMD measure, a random-effects model, and sensitivity analysis were used to mitigate these limitations.

In an additional subgroup analysis included in the 2017 review of placebo-controlled randomized trials, Feng et al also evaluated the efficacy and safety of SLIT use in pollen-induced allergic rhinitis in children ages 3 to 18 years. Of the 26 eligible RCTs (published 1990 to 2016), 12 studies (737

patients) studied symptom reduction, and 7 studies (359 patients) examined medication use in house dust mite-induced allergic rhinitis. 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 evidence review.

Nasal symptom and medication scores were assessed using mean differences and SMD. There was no statistically significant reduction in symptoms or medication use for children with house dust mite-induced allergic rhinitis.

Overall, oral pruritus was the most common adverse effect in children who were receiving SLIT. Although the meta-analysis addressed heterogeneity and potential of bias overall, these were not specifically reported for the studies included in the subgroup analysis.

Summary

A number of RCTs have evaluating 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. Trials comparing SLIT with SCIT tended not to find differences in efficacy, but conclusions have been limited due to small sample sizes. A 2017 meta-analysis found SLIT to be associated with a significant reduction (among adults) in house dust mite-induced allergic rhinitis symptoms and medication use relative to placebo. However, there was no statistically significant reduction for children.

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Policy History

Original Effective Date: 06/16/2010
Current Effective Date: 03/09/2020

06/03/2010	Medical Policy Committee approval
06/16/2010	Medical Policy Implementation Committee approval. New policy.
05/05/2011	Medical Policy Committee review
05/18/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/02/2014	Medical Policy Committee review
10/15/2014	Medical Policy Implementation Committee approval. Policy coverage and body extensively revised to meet Pharmacy Department requirements.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015	Medical Policy Committee review

Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

Policy # 00263
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Current Effective Date: 03/09/2020

10/21/2015	Medical Policy Implementation Committee approval. Updated rationale section (systematic reviews, house dust mite specific allergy, food allergy, SLIT vs. SCIT). No coverage changes.
10/06/2016	Medical Policy Committee review
10/19/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Added new FDA approved drug, Odactra, and associated evidence. Also updated information throughout background from Association update.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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