Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

Policy # 00263
Original Effective Date: 06/16/2010
Current Effective Date: 03/08/2021

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

Coverage eligibility for the use of Ragwitek will be considered when 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:
    - Patient has a positive skin test response to short ragweed pollen; OR
    - 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

Coverage eligibility for the use of Grastek will be considered when 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:
    - 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
    - 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

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*(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

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

- Patient is 5-65 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:
    - 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
    - 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

Coverage eligibility for the use of Odactra will be considered when 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:
    - Patient has a positive skin test response to licensed house dust mite allergen extracts; OR
    - 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) 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.***

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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 5-17, 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. In November of 2018, Oralair's age was extended to 5 years of age.
- 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

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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. Evidence and regulatory approval have progressed since the 2003 TEC Assessment.

The meta-analysis by Yang et al (2018) evaluated the use of SLIT to treat allergic conjunctivitis (AC) or allergic rhinoconjunctivitis (ARC) in patients aged 3 to 18 years, specifically looking for SLIT's effectiveness for relieving eye symptoms. Thirteen randomized clinical trials were identified, which included a total of 1,592 pediatric patients. Overall, the trials showed that AC symptoms were significantly reduced by SLIT (standardized mean difference [SMD] = -0.21; 95% CI, -0.41 to -0.01; p=0.04; I^2 = 55%). However, on a subgroup analysis of the different SLIT modalities, ocular symptoms improved with tablets (p <0.001) but not drops (p=0.47); in addition, SLIT significantly reduced pollen-induced AC (p <0.001) but not mite-induced (p=0.34). The investigators stated that the meta-analysis was limited by variations in the baseline severity of patients' AC or ARC, the ocular scoring systems used, and in the SLIT therapeutic regimens, as well as the small sample sizes (n<30) of 46% of the studies. However, their results showed that SLIT effectively reduced conjunctivitis symptoms in pediatric patients with AC and ARC.

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.

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. Results are as follows:

Trial	**N**	**Relative Difference in Combined Score % (95% CI)**
Trial 1: Phase 3, multicenter, U.S.	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 environmental exposure chamber trial	89	29 (14 to 44)

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 (FEV_1) 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 2,800 BAU or placebo. In 1 trial (trial 3), patients continued dosing for 3 years continuously. Three (trials 1-3) of 6 studies (2,480/3,501 [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. Results are as follows:

Trial	**N**	**Relative Difference in Combined Score % (95% CI)**
Trial 1: U.S. and Canada adult and pediatric trial	1,501	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)
Trial 4: German pediatric trial	253	24 (5 to 41)
Trial 5: U.S. adult trial	329	10 (4 to 24)
Trial 6: U.S. and Canada adult trial	439	21 (6 to 33)
Pooled Analysis	3,094	20 (16 to 24)

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. Results are as follows:

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)

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

See the systematic review by Yang et al (2018) summarized in Indication 1 for their assessment of SLIT for relief of AC or ARC in patients aged 3 to 18 years. They found that SLIT significantly reduced pollen-induced AC ($p<0.001$) but not house dust mite-induced AC ($p=0.34$).

Feng et al (2017) conducted a meta-analysis of 25 placebo-controlled randomized trials (published from 1990 to 2016) on the efficacy of SLIT for house dust mite-induced allergic rhinitis in adults and children. Most trials were double-blinded, deemed to be of high quality, and included 2 phase 3 trials. All studies compared the intervention with a placebo for a period of 6 to 36 months. In total, there were 3,674 randomized patients, and the largest trial included 992 participants. There were 12

pediatric trials, with ages ranging from 3 to 18 years. Of 23 studies that reported discontinuation rates, 539 (14.6%) participants dropped out due to the following: adverse events (3.0%; most commonly oral pruritis), loss to follow-up (2.0%), noncompliance (1.9%), and poor efficacy (0.9%). Primary endpoints were symptom scores and medication use. Symptom scores varied by type, including rhinitis symptoms only, rhinoconjunctivitis symptoms, or rhinoconjunctivitis and asthma symptoms. Overall, there was a significant reduction in symptoms in the SLIT group relative to placebo (SMD=1.23; 95% CI, 1.74 to 0.73; $p<0.001$). 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 were available in 18 RCTs, but the final analysis included only 15 RCTs due to substantial differences in how data were evaluated. Overall, there was a significant reduction in medication use in the SLIT group relative to the placebo group (SMD= -1.39; 95% CI, -1.90 to -0.88; $p<0.001$). 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. An SMD measure, a random-effects model, and sensitivity analysis were used to mitigate these limitations.

A second systematic review assessing the effect of SLIT on house dust mite-induced allergic rhinitis only included studies conducted in children aged 4 to 18 years. The review included 16 placebo-controlled trials (N=1,929) of SLIT drops or tablets for 6 to 24 months. Pooled outcomes included nasal symptom, medication, and ocular symptom scores. The review did not report discontinuation rates. Nasal symptom scores, reported in 16 studies, were significantly lower with SLIT versus placebo (SMD -1.73, 95% CI -2.62 to -0.84), but heterogeneity was very high (I^2=98%). Total medication scores were also significantly lower with SLIT versus placebo based on evidence from 11 studies (SMD -1.21, 95% CI -1.75 to -0.67), but again heterogeneity was high (I^2=94%). For both

outcomes, the review found evidence of publication bias, but even after adjustment for bias, SLIT was more effective than placebo for both outcomes, p=0.02 and <0.0001, respectively. Ocular symptom scores were only reported in 6 of the studies. When pooled there was no clear difference between SLIT and placebo (p=0.31), however subgroup analysis found SLIT tablets (SMD -0.28, 95% CI -0.42 to -0.14) more effective than SLIT drops (SMD 0.13, 95% CI -0.20 to 0.60), relative to placebo.

Liao et al (2015) published a meta-analysis of studies on dust mite SLIT for treating children with asthma. 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.

Gendelman and Lang (2015) 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. Bae et al (2013) also published a systematic review and meta-analysis of immunotherapy for children and adults with house dust mite-induced atopic dermatitis. Literature was searched through November 2012, and 8 placebo-controlled randomized trials were included (6 SCIT [n=307], 2 SLIT [n=90]). Using a dichotomous variable for treatment success, defined as the proportion of patients whose condition improved as assessed by investigators or patients, regardless of evaluation method used, the odds ratio was 5.35 (95% CI, 1.61 to 17.77). The significance of this finding is uncertain given the heterogeneity of treatments administered and the use of a nonstandard outcome measure.

Randomized Controlled Trials

Included in the Feng et al (2017) meta-analysis was a phase 3 double-blind RCT by Demoly et al (2016) of Odactra as a treatment for moderate-to-severe house dust mite-induced allergic rhinitis despite pharmacotherapy. Adults were randomized to daily Odactra 6 SQ-house dust mite (HDM)

(n=336), Odactra 12 SQ-HDM (n=318), or placebo (n=338) for 52 weeks. Total Combined Rhinitis Score (TCRS), which integrated patient-reported symptoms of rhinitis or conjunctivitis and use of pharmacotherapy, met the prespecified threshold of clinical relevance (TCRS >1) after 14 weeks of treatment and at all subsequent time points, for both dosages of Odactra. The primary endpoint of TCRS in the efficacy period (8 weeks after completing 52 weeks of treatment) showed an absolute reduction from placebo for both 6 SQ-HDM (1.18; p=0.002) and 12 SQ-HDM (1.22; p=0.001). The most common adverse events were oral pruritus, throat irritation, and mouth edema. Serious adverse events were noted in the placebo (n=8) and 6 SQ-HDM (n=4) treatment groups; none were deemed to be related to treatment. One patient required adrenaline on the first dose of 12 SQ-HDM Odactra to treat laryngeal edema.

Since the publication of the Feng et al (2017) meta-analysis, 2 significant RCTs comparing SLIT with placebo have been published. Zieglmayer et al (2016) published a phase 2 trial of Odactra as a treatment for house dust mite-induced rhinitis, with or without conjunctivitis, and with or without asthma. Adults were randomized to daily Odactra 6 SQ-HDM (n=41), Odactra 12 SQ-HDM (n=42), or placebo (n=41) for 24 weeks. Patients received a precisely defined and monitored exposure to house dust mite antigen in an environmental exposure chamber at baseline, weeks 8, 16, and 24 during treatment, and at 1 year posttreatment. At 24 weeks of treatment (n=106), mean Total Nasal Symptom Score improved from baseline by 51% with 12 SQ-HDM treatment, 31% with 6 SQ-HDM treatment, and 0% with placebo. The mean Total Ocular Symptom Score improved from baseline by treatment with 12 SQ-HDM (72%), 6 SQ-HDM (50%), and placebo (11%). Among those tested a year posttreatment with 12 SQ-HDM (n=16), the mean Total Nasal Symptom Score improved by 2.5 points, and the mean Total Ocular Symptom Score improved by 0.5 points. The most common adverse event was throat irritation.

Nolte et al (2016) published a phase 3 double-blind, RCT evaluating Odactra (12 SQ-HDM) and placebo for treatment of house dust mite-induced allergic rhinitis, with or without conjunctivitis, and with or without asthma. Patients ages 12 years and older (n=1,482) were randomized to Odactra or placebo once daily for 52 weeks. Improvement in the average TCRS after treatment, compared with placebo, was 17% (95% CI, 10% to 25%). This primary efficacy endpoint, which integrated symptoms and medication use, met prespecified targets for clinical significance. Patients also demonstrated improvement in average conjunctivitis scores, with improvement over placebo of 33% (95% CI, 19% to 47%). Seven patients were treated with epinephrine for adverse events; 1 patient experienced severe “throat tightness” after the first dose. Adverse events were typically mild to

moderate in severity, with most events consisting of throat irritation, oral pruritus, and ear pruritus. No treatment-related serious adverse events were reported.

A small RCT by Yukselen et al (2013) compared house dust mite SCIT with SLIT in children who had rhinitis and asthma and were monosensitized to house dust mites.27, Thirty children were randomized to 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. Focusing on RCTs comparing SLIT with SCIT, 3 trials published in 2010, 2011, and 2012 found no statistically significant differences between treatments in an 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. Participants were randomized to 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

Summary

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

References

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Policy History

Original Effective Date: 06/16/2010
Current Effective Date: 03/08/2021

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.

Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

Policy # 00263
Original Effective Date: 06/16/2010
Current Effective Date: 03/08/2021

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
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.
02/04/2021	Medical Policy Committee review

Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

Policy # 00263
Original Effective Date: 06/16/2010
Current Effective Date: 03/08/2021

02/10/2021 Medical Policy Implementation Committee approval. Updated lower age of Oralair from 10 to 5 years in accordance with the FDA label. Updated background/rationale with the most recent and relevant information.
Next Scheduled Review Date: 02/2022

*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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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.