Environmental Allergen Immunotherapy

Policy Number: UMR2025T0603G
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➲ Instructions for Use

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Related Policies

None

Coverage Rationale

Home-administration/self-administration of subcutaneous allergen immunotherapy is unproven and not medically necessary due to insufficient evidence of efficacy and safety.

Sublingual liquid immunotherapy or non-Food and Drug Administration (FDA) approved sublingual allergen extract tablets for the treatment of any condition/disease, including but not limited to allergic rhinitis and allergic rhinoconjunctivitis, are unproven and not medically necessary due to insufficient evidence of efficacy and safety.

Note: This policy does not apply to FDA approved sublingual allergen extract tablets.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

Coding Clarifications:

- CPT code 95165 or 95199 should be reported within a reasonable time frame from when CPT code 95115 or 95117 is billed for the administration of subcutaneous allergen immunotherapy given in the office/ambulatory setting and furnished by a physician or other qualified health care practitioner.
- CPT code 95115 or 95117 should not be reported when administering sublingual liquid immunotherapy; these CPT codes are specific to subcutaneous administration. The unlisted CPT code 95199 should be used when sublingual liquid immunotherapy is provided in the office/ambulatory setting and furnished by a physician or other qualified health care practitioner.

Note: Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed and may be covered under the pharmacy benefit plans. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, these codes apply only used when sublingual immunotherapy is provided in the office/ambulatory setting and furnished by a physician or other qualified health care practitioner.

CPT Code	Description
95115	Professional services for allergen immunotherapy not including provision of allergenic extracts; single injection
95117	Professional services for allergen immunotherapy not including provision of allergenic extracts; 2 or more injections
95165	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses)
95199	Unlisted allergy/clinical immunologic service or procedure (when used to report sublingual liquid immunotherapy)

Description of Services

Subcutaneous injection of allergen-specific immunotherapy (SCIT) administered in a medical office setting is the standard approach for treating allergies. Treatment involves subcutaneous administration of gradually increasing quantities of a specific allergen(s) until a dose is reached that will reduce or eliminate the allergic response from exposure. (AAOA, 2020)

Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes are being investigated; of these, sublingual immunotherapy (SLIT, SIT) is the most prominent. SLIT has been studied as a treatment for patients with allergic rhinitis (AR) and asthma associated with sensitivity to seasonal allergens such as grass and pollen, and to other allergens such as dust mites, mold, pet dander, or nuts. SLIT involves the administration of a diluted dose of an allergen in the form of a liquid or a tablet under the tongue, which allows the allergen to contact the oral mucosa. Generally, patients are instructed to hold the drops or tablet under the tongue for approximately 30 seconds and to repeat this treatment up to three times daily. This practice is thought to desensitize the patient to the allergen, as would conventional immunotherapy by injection. The U.S. Food and Drug Administration (FDA) has not approved the use of any liquid sublingual immunotherapy; however, there are tablet forms that are FDA approved for the treatment of allergic rhinitis and conjunctivitis in individuals ages five years and older who have sensitization to northern grass and those ages 18 years and older with sensitization to a short ragweed and dust mite mixture. (NHLBI, 2020)

Clinical Evidence

Home-Administration/Self-Administration of Subcutaneous Immunotherapy (SCIT)

Home-administration of SCIT has been identified as a possible treatment option to improve access to allergy care; however, the safety and efficacy of this approach has only been reported in a limited number of clinical trials. While results of these studies are promising, larger randomized or other controlled studies with a broader variety of settings and populations are needed to confirm these results.

Schaffer et al. (2016) conducted a multi-center, retrospective cohort study to determine the efficacy of a self-administered SCIT protocol. The protocol, which was previously tested for safety (Schaffer, 2015), required all patient to first undergo office-based SCIT, which included education, instruction in the use of epinephrine, self-administration of SCIT under the supervision of the physician of record, and a 30-minute post-injection observation period. If a patient did not successfully meet required standards for self-administration, immunotherapy was continued only as an office-based treatment. Eligible patients included both female and male patients, aged 18 to 65 years who were diagnosed with seasonal or seasonal plus perennial allergic rhinitis (AR). All study subjects could continue oral and topical antihistamines, and nasal steroids prescribed by their physician. Subjects using systemic steroids were excluded. A total of 116 patients (from centers located in Dallas and San Antonio Texas) were included in the study. Patients who opted for SCIT (n = 60) were deemed treatment patients, and those that declined SCIT were deemed control patients (n = 56). The primary and secondary outcomes were the change (baseline vs. intervention period) in combined symptom plus medication scores (CSMS) and rhinoconjunctivitis quality of life questionnaire (RQLQ) scores, respectively. Changes in pollen counts were also considered regarding the effects on those efficacy parameters. The questionnaires were completed at the end of the baseline year and after the intervention year i.e., after another 12 months. The treatment group showed significantly improved CSMS (standardized mean difference [SMD]: -1.57; 95% confidence interval [CI], -1.97 to -1.18; $p < 0.001$) and RQLQ (SMD: -0.91; 95% CI, -1.23 to -0.59; $p < 0.001$). The treatment group outcome measures were respectively improved by 33% and 29% compared to baseline, and greater than 40% in comparison to the control group ($p < 0.0001$). Significant results were also shown when examining these outcome measures in relation to the use of either monotherapy or poly-allergen SCIT. The authors concluded that these efficacy results, with their previous safety results, show that a carefully designed and implemented self-administered SCIT protocol is efficacious and safe. There are limitations to this study and therefore, a cause-and-effect relationship (i.e., use of the self-administered SCIT protocol causes improved AR

symptoms) could not be established. For example, the study design did not include randomization, instead patients self-selected their cohort assignments, recall bias from self-reported data may be present, and the study cohorts were from two cities in Texas rather than a nationally representative sample. Additional randomized studies with larger nationally representative samples are still needed to determine the efficacy of a self-administered SCIT protocol.

Hurst et al. (1999) conducted a multi-center, prospective, case series study to assess the safety of home-based vs. office-based allergy immunotherapy. The primary goal of this study was to determine the degree of safety when immunotherapy is practiced according to American Academy of Otolaryngic Allergy (AAOA) methods, and the secondary goal was to compare the safety of treatment in both the home and office settings. This study was conducted during a 12-month period in 27 medical offices in the United States. Each office recorded data, using standardized reporting forms, on all allergy patients in their practices who were treated with SCIT at any time during the year. Participating physicians passed the fellowship examination of the AAOA, had been in practice for 5 to 15 years since completing residency training, and practiced allergy according to AAOA guidelines for diagnosis and treatment. Because of differences in patient tracking, some centers reported only the number of patient treatment encounters, and others reported only the number of separate injections given. Every treatment reaction that required medical observation or an intervention was reported separately on an incident report form. Reactions to immunotherapy were defined as immediate if they began within 20 minutes of injection; otherwise, they were termed late. A reaction was considered systemic if it produced any symptoms at a location distant from the injection site. There was a total of 635,600 patient visits, 1,144,000 injections. Sixty percent of injections were given at home. Major systemic reactions were observed after 0.005% of injections. There were no hospitalizations or deaths. Eighty-seven percent of major reactions began within 20 minutes of injection. Frequently observed risk factors for major reactions were buildup phase of immunotherapy, active asthma, and first injection from a treatment vial. Home and office injections had similar rates of total systemic reactions, but home-based immunotherapy had far fewer major reactions. The authors concluded that home-based and office allergy immunotherapy are very safe, but a low rate of systemic reactions should not lead to complacency. The authors also stated that any physician administering allergy injections must anticipate the potential of life-threatening anaphylaxis, and that appropriate precautions to prevent, and preparedness to manage, such events are critically important. A limitation of this study is that it only included otolaryngology practices with specialists who were practicing for 5 to 15 years and therefore, these results may not be generalizable to primary care practices. Additional randomized trials with more diverse practices are still needed to determine the safety and efficacy of home-based immunotherapy.

Clinical Practice Guidelines

American Academy of Allergy, Asthma, and Immunotherapy (AAAAI)

AAAAI's statement, Administration of Subcutaneous Allergen Immunotherapy during the COVID-19 outbreak, states that home administration of immunotherapy is strongly discouraged except for rare and special circumstances where withholding this therapy would result in a serious detriment to the patient's health e.g., venom immunotherapy for a patient living in a remote area. (2020)

In a 2011 practice parameter on allergen immunotherapy, AAAAI states that the preferred location for administration of allergen immunotherapy is in the office of the physician who prepared the patient's allergen immunotherapy extract, particularly for patients at a high risk of systemic reactions. Home administration should only be considered in the rare circumstance when the benefit of immunotherapy clearly outweighs the risks. Careful consideration of potential benefits and risks of at-home administration should be made on an individual basis. Frequent or routine prescription of home immunotherapy is not appropriate under any circumstances.

American Academy of Otolaryngic Allergy (AAOA)

AAOA's Clinical Care Statements, which addresses home SCIT states that the AAOA encourages the preferential practice of administering subcutaneous immunotherapy in a medical office setting with professionals trained in the recognition and management of anaphylactic reactions (2020).

Sublingual Immunotherapy (SLIT)

Off-label use of sublingual drops prepared from commercial allergen extracts is widely practiced in the United States (U.S.). Commercial aqueous extract products are not FDA approved for sublingual administration, and these have not been rigorously studied in double-blind placebo-controlled studies. Thus, effective, and safe dose ranges have not been characterized for commercial aqueous allergen extracts (marketed for SCIT) used in the preparation of nonapproved SLIT drops. Because of insufficient clinical data, use of aqueous SLIT formulations has not been endorsed by the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Joint Task Force. (Mahler et al., 2019)

Theodoropoulou and Cullen (2024) conducted a single-center retrospective study to assess the safety and efficacy of desensitization to crustaceans by means of sublingual immunotherapy. The study included 66 patients (ages six to 65 years, 68% female) who had been treated by sublingual immunotherapy for either systemic or localized reactions to shrimp. Sublingual immunotherapy with serially diluted mixtures was initiated at 64 to 320 ng/dose and was gradually escalated to 0.5 mg/dose three times a day with the course of therapy lasting from five to 72 months (average 51 months), followed by a shrimp oral challenge in 18 of the patients. The authors reported that no systemic reactions occurred upon challenge and none of the patients required epinephrine. The authors also reported that tolerance of the target does was achieved in 11 of the 18 patients (61%) and that seven patients (38%) developed one or more localized reactions (oral itching, nasal symptoms, localized perioral hives, localized hives at pressure points, nausea, vomiting, abdominal pain) with five of the seven patients placed on routine exposure to shrimp every other day. The authors reported that all five patients who had routine exposure to shrimp every other day tolerated a repeat challenge six to nine months after the original challenge. The authors concluded that desensitization to shrimp by sublingual immunotherapy appears to be safe and effective. Limitations of the study include the small sample size, retrospective, single-center design, and the lack of a comparator group.

Soller et al. (2024) conducted a prospective, single-center study to evaluate the safety of multi-food SLIT in pediatric patients aged four to 18 years and the effectiveness of bypassing oral immunotherapy (OIT) buildup with an initial phase of SLIT. The study included 188 participants (median age 11.3 years, 67.6% male) with most (61.7%) of them allergic to multiple foods. Almost half (48.4%) of the participants had atopic dermatitis, 45.2% asthma, 58.0% allergic rhinitis, and 2.66% eosinophilic esophagitis (EoE). The authors reported that 173 (92%) of the participants completed their SLIT buildup, with 15 (8%) dropping out during buildup, and 93.1% had symptoms during SLIT buildup with most having grade 1 (52.1%) or grade 2 (40.4%) reactions and one (0.60%) having had a grade 3 reaction. The authors also reported that four (0.02%) participants received epinephrine, with an overall rate of epinephrine use during SLIT of 2.10 per 10,000 doses (0.02%) with 14.5 per 10,000 doses during buildup (0.15%) and 1.64 per 10,000 doses at home (0.16%) and that all four of the participants who received epinephrine continuing with SLIT without further need for epinephrine. The authors also reported that 20 participants received 50 low-dose oral food challenges (OFCs) with 35 (70%) of the 50 being successful, and another nine patients who had unsuccessful OFCs being counseled to self-escalate at home with medical guidance as needed which resulted in 44 OFCs (88%) able to transition to OIT without the need for medically supervised buildups. Limitations of the study include the single-center design, the lack of a control group, the use of commercially available food products, the lack of data regarding ethnic diversity of the population, and the preponderance of participants receiving SLIT to peanut butter and/or tree nuts. The authors concluded that 88% of participants were able to successfully bypass supervised OIT buildup visits and 70% completed low-dose OFC without any symptoms after one to two years of daily protein SLIT.

In a prospective, single-arm, single-center study to evaluate the efficacy of non-daily dosing of sublingual immunotherapy, Abdelwahab and El-Maksoud (2023) reported short term results that showed sublingual immunotherapy (SLIT) was tolerable, safe, and effective in patients with allergic rhinitis (AR) and bronchial asthma (BA). Each of the 52 participants (65.4% female, mean age 26.9 +/-10.5 years) underwent a skin prick test and then were given sublingual drops for dosing under the tongue in the morning. Dosing was repeated every three days with gradual increasing of the number of drops and SLIT concentration, and symptoms and medication scores were assessed every two months. The authors reported that 65.8% of the participants responded partially to the symptom score, and 26.3% responded completely to the medication score at two months which showed a significant decline in the symptom and medication scores from the baseline scores. At the four- month follow-up, 95.8% of participants were reported to have responded partially to symptom scores with no participants that had not responded. The authors also reported that 81% of the study participants reported no side effects, and that the reported side effects were minor (sore throat 7%, vomiting 5%, systemic 5%, and bitter taste 2%) and were dealt with. Limitations of the study include the single-center design, the lack of a control group, the small sample size, and the short follow-up period. The authors concluded that the non-daily schedule of SLIT was tolerable, safe, and effective in patients with AR and BA.

Kim et al. (2021) conducted two meta-analyses that compared the efficacy of SLIT and SCIT for house dust mite allergy on symptom score and medication score. Their study included 26 double-blind RCTs in the meta-analysis for the symptom score and 18 for the medication score. The authors performed a direct comparison versus placebo through pairwise and network meta-analysis (NMA) and reported that the results of the analyses indicated that all modalities showed significant clinical efficacy on symptom and medication scores. They also reported a significant difference in symptom score for SLIT tablet and SCIT, but not for SLIT liquid when compared with placebo where the symptom score of SLIT liquid was not significantly different from that of placebo in sensitivity analyses from both direct pairwise comparison and NMA. They concluded that the study demonstrated that SCIT may be more effective than SLIT drops or tablets in controlling symptoms of allergic rhinitis for house dust mite allergy based on the NMA while the clinical efficacy of SLIT liquid and SLIT tablet with regard to symptom score was comparable. Limitations of the study include the heterogeneity of

the studies and of the study populations, the inclusion of both two-arm and three-arm studies in the NMA and the inconsistent scoring systems that were used among the studies for symptom and medication scores.

Baba et al. (2021) conducted a single-center, prospective, parallel-group, controlled study to compare the efficacy of SLIT tablets with pharmacotherapy in 332 patients with confirmed house dust mite (HDM)-specific allergic asthma (n = 164) and/or rhinitis (n = 168). The patients were followed for a six-month run-in period and then randomized into one of three study arms with 164 patients receiving SLIT only, 88 receiving SLIT in addition to pharmacological treatment (SLIT + PT), and 80 patients receiving PT only. All patients were seen every three months for three years to evaluate symptom and medication scores along with serum total and HDM specific immunoglobulin E (HDM sIgE) levels and had in-vivo skin prick tests performed each year for three years. The authors reported that their study demonstrated sustained clinical improvement in reduction of inhaled corticosteroid dose and duration as well as prevention from developing neosensitization to other aero allergens in HDM-allergic asthmatics and/or rhinitis patients treated who were treated with three years SLIT; however, the authors found that SLIT did not significantly change the skin reactivity to HDM at three years nor was there significant change in the ratio of serum total and HDM sIgE. The authors concluded that SLIT was an effective long-term immunomodulator in HDM-sensitized nasobronchial allergies. The findings are limited by lack of masking using placebo or comparison to office-based SCIT.

A Hayes Health Technology Assessment (2021, updated 2022) reviewed five double-blind, randomized, placebo-controlled trials evaluating liquid SLIT for the treatment of allergic rhinitis or rhinoconjunctivitis that were conducted in the United States (US). These RCTs had sample sizes of 31 to 429 patients and follow-up periods of 50 days to two years. No systematic reviews or meta-analyses specific to liquid SLIT for treatment of allergic rhinitis in the US were identified. The report noted that the studies had mixed results for patient-reported symptom and medication scores with two studies indicating SLIT therapy had better patient reported symptoms, and two studies showing no difference between SLIT and placebo. The authors stated that the body of evidence was small in size and low in quality. The report acknowledged that the evidence was limited to double-blind RCTs conducted in the US and that there currently are no FDA-approved liquid products intended for sublingual administration. The report concluded that liquid SLIT has potential but unproven benefit for adults in the US for treatment of allergic rhinitis and insufficient published evidence to assess safety and efficacy in children for treating allergic rhinitis.

A comparative cohort study by Zhong and colleagues (2018) examined the safety and efficacy of SLIT in house dust mite (HDM)-induced allergic asthma (AA) in 134 adult patients. Subjects were divided into the SLIT group (n = 85) and the control group (n = 49). All were treated with low to moderate dose of inhaled glucocorticoid and long acting β2 agonists. Patients in the SLIT group were further treated with D. farinae drops. Clinical scores including the total asthma symptom score (TASS), total asthma medicine score (TAMS), asthma control test (ACT), and peak flow percentage (PEF%) were assessed before treatment and at yearly visits. Adverse events (AEs) were recorded on a monthly basis. Before treatment, the PEF% in the SLIT group was significantly lower than that in the control group. After two years, both treatments were effective in the clinical scores when compared with baseline values. Meanwhile, the SLIT group showed significantly lower TASS and TAMS and higher ACT and PEF when compared with the control group. No severe systemic AEs were reported. Authors concluded that SLIT with D. farinae drops plus pharmacotherapy is more effective than routine drug treatment in adult patients with AA. The study is limited by lack of randomization and lack of masking.

In a systematic review, Rice et al (2018) examined the efficacy and safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in pediatric allergic asthma. Forty studies were extracted; 17 of which were SCIT trials, 11 SLIT trials, eight non-RCTs for SCIT safety, and four non-RCTs for SLIT safety. The authors found low-strength evidence that SLIT improves medication use and force expiratory volume in one second.

A systematic review of immunotherapy for asthma identified 18 randomized controlled trials on the efficacy of sublingual immunotherapy and concluded that sublingual immunotherapy is associated with improved asthma symptoms, disease-specific quality of life, medication use, and pulmonary function. The authors noted several limitations to the available data, e.g., uncertainty about whether changes in asthma symptom scores were clinically meaningful, lack of statistically significant differences in pulmonary function or quality of life between treatment and placebo arms. The authors also concluded that there was insufficient evidence about the efficacy of SLIT in children. (Lin, et al. 2018)

A retrospective, secondary analysis of pooled data from two prospective placebo RCTs was conducted by Jerzynska et al., (2018). The goal was to identify any differences in symptom-medication scores between two groups of SLIT tablets and drops, given pre-seasonally (starting eight weeks before the pollen season) in 41 children (ages six to 18 years) with AR sensitive to grass pollen. Treatment with both tablets and drops similarly and significantly reduced all symptoms (nasal, asthma, and ocular) within each group. When compared with the tablet therapy, there was a trend for drops therapy to be more effective in the reduction of combined symptom-medication score, but the difference was not statistically significant. The authors concluded that both protocols showed similar decreases in symptom-medication

scores; however, when compared with tablet therapy, there was a trend for drops therapy to be more effective in the reduction of combined symptom-medication score. The study is limited by lack of placebo comparison group, lack of randomization, and lack of masking.

The efficacy and safety of SLIT with D. farinae drops along with pharmacotherapy were evaluated in two retrospective case series. Subjects with AR totaled 855 with ages ranging from two to 69 years. The TNSS, total medication score (TMS), and visual analogue score (VAS) were significantly improved at two years (Tang et al., 2018) and three years (Lin et al., 2017), and no severe systemic AEs were reported. Researchers concluded that SLIT with D. farinae drops is clinically effective and safe in treating AR in both children and adults, including very young children less than four years old. The findings are limited by lack of comparison group.

Creticos et al. (2014) conducted a phase 3, placebo RCT to determine the efficacy and tolerability of standardized glycerinated short ragweed sublingual allergen immunotherapy liquid (RW-SAIL) extract in subjects with ragweed-related allergic rhinoconjunctivitis (ARC). Subjects (ages 18-55 years) with or without asthma were selected based on ARC symptom severity and erythema skin prick reaction to short ragweed. Subjects self-administered the maximum tolerated dose of RW-SAIL (n = 218) or placebo (n = 211) daily beginning approximately eight to 16 weeks before and through the end of the ragweed pollen season. The primary end point was subject-assessed total combined daily rhinoconjunctivitis symptom and medication scores (TCS). During the entire season, there was a 43% decrease in TCS in the RW-SAIL group compared with placebo. Similar decreases were observed in TCS between the two groups during peak season (42%) and in daily symptom scores during the entire (42%) and peak (41%) seasons. Occurrences of AEs were similar between the treatment groups, and most were mild in severity. Treatment-related oromucosal local application site reactions occurred early and were transient and self-limited. No anaphylaxis occurred. Researchers concluded that once-daily SLIT-liquid administered to individuals with ragweed allergy is well tolerated and can result in highly significant clinical improvements in seasonal symptoms and rescue medication use. Further studies are needed to fully evaluate these effects.

Wahn et al. (2012) conducted a randomized, double-blind, placebo-controlled trial investigating efficacy and safety of high-dose SLIT in children allergic to grass pollen. Subjects (n = 207, ages four to 12 years) with grass pollen-AR/ARC with/without bronchial asthma (Global Initiative for Asthma I/II) received either high-dose grass pollen SLIT or placebo daily for one pre-/co-seasonal period. The primary end point was the change of the area under the curve of the symptom-medication score (SMS) from the baseline season to the first season after start of treatment. Secondary outcomes were well days, responders, immunologic changes, and safety. Mean changes in the area under the curve of the SMS as well as the number of well days were greater in the active group. Changes in allergen specific IgE and IgG levels indicated a significant immunologic effect. The treatment was well tolerated, and no serious treatment-related events were reported. The authors concluded that this SLIT preparation significantly reduced symptoms and medication use in this patient population. The preparation showed significant effects on allergen-specific antibodies, was well tolerated, and appeared to be a valid therapeutic option in children allergic to grass pollen.

Clinical Practice Guidelines

American Academy of Otolaryngic Allergy (AAOA) Foundation

In 2018 (updated 2023), a consortium of healthcare providers published an International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR) funded by the AAOA Foundation. The ICAR:AR document addressed over 100 individual topics related to AR, including diagnosis, pathophysiology, epidemiology, disease burden, risk factors for the development of AR, allergy testing modalities, treatment, and other conditions/comorbidities associated with AR. The process included a systematic review of the literature. In regard to SLIT, the reviewers examined the grades of clinical evidence on 30 studies (level 1: 17 studies, level 2: 12 studies, level 4: 1 study). The group stated that the benefit of SLIT (based on low quality evidence) is that it improves patient symptoms scores, even as an add-on treatment with rescue medications, and that the effect of SLIT lasts for at least two years after a three-year course of therapy. The group also stated that the benefit of treatment over placebo is small but tangible and occurs in addition to improvement with medication. The Statement concluded with a strong recommendation for the use of SLIT grass pollen tablet, ragweed tablet, HDM tablet, and tree pollen aqueous solution, with a recommendation for SLIT for *Alternaria* allergy, for SLIT to be an option for animal allergy and a recommendation for dual-therapy SLIT in bi-allergic patients. (Wise, et al., 2018)

American Academy of Allergy, Asthma, and Immunotherapy (AAAAI)

In a practice parameter on SLIT, the AAAAI states that alternative regimens and preparations for SLIT (e.g., liquid) have been proposed and may be used off label in the U.S. However, these products and formulations do not have FDA approval at present and have not been systematically studied in a rigorous manner in U.S. populations. Use of such products or formulations as prescribed SLIT therapy is currently off-label, at a practitioner's discretion and liability, and is without recommendation for any current particular indication in the U.S. populations. Therefore, off label use of aqueous

SLIT extracts or any other non-FDA approved SLIT formulation is not endorsed. (Strength of Recommendation: Strong; Evidence: D). (Cox et al., 2011)

Each particular aqueous SLIT formulation must independently demonstrate a safe and effective dosing regimen for a particular indication. Despite a lack of FDA-approved aqueous SLIT formulations, an AAAAI survey suggests U.S. aqueous SLIT prescriptions among respondents increased from 5.9% to 11.4% between 2007 and 2011, and 86% of respondents reported prescribing commercially available SCIT extracts for off-label use as SLIT. (Greenhawt et al., 2017)

National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH)

In the 2020 focused updates to the Asthma Management Guidelines, the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group explored the efficacy and safety of the use of SLIT for the treatment of allergic asthma. The Expert Panel found that the evidence for SLIT provided minimal benefit for the critical outcomes of exacerbations, asthma control and quality of life. They did not find any studies that assessed the impact of SLIT on ED visits, clinic visits or hospitalizations although they did note that SLIT reduced the use of quick-relief medications and doses of inhaled corticosteroids in individuals with persistent allergic asthma.

Based on their review, the Expert Panel conditionally recommends against the use of sublingual immunotherapy in asthma treatment on the basis of currently available data for individuals with persistent allergic asthma. The Expert Panel did note that SLIT is beneficial for allergic rhinoconjunctivitis. In an individual with allergic asthma SLIT for allergic rhinoconjunctivitis might reduce the symptoms of allergic asthma as well which is why the Expert Panel made their recommendation conditional for those with persistent allergic asthma. For individuals whose allergic asthma symptoms benefit from SLIT for allergic rhinoconjunctivitis, the Expert Panel made the following two suggestions.

- Currently, only tablet SLIT formulations for short ragweed and dust mite mixture and for northern grass have FDA approval for treatment of allergic rhinitis with and without conjunctivitis. SLIT is not FDA approved specifically for asthma treatment.
- The clinician should administer the first dose of SLIT in the office, and the individual with asthma should wait in the office for at least 30 minutes after receiving the dose. If no problems develop, the individual may continue the SLIT dosing at home. Individuals receiving SLIT should ideally have an injectable epinephrine prescription and receive education on how to administer this medication.

World Allergy Organization

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

- Grass-pollen SLIT is effective in seasonal allergic rhinitis in children 5 years of age or older and probably effective in children as young as 4 years of age.
- Grass or house dust mite SLIT may be used for allergic rhinitis in children with asthma, although more large, randomized trials are needed.
- Although SLIT for latex allergy, atopic dermatitis, food allergy, and hymenoptera venom is under investigation, more evidence is needed to support the use of SLIT for these indications.
- Patients eligible for SLIT should have a history of symptoms related to allergen exposure and a documented positive allergen specific IgE test.
- SLIT may be considered as initial treatment, particularly for patients whose allergy is uncontrolled with optimal pharmacotherapy (i.e., those who have severe chronic upper airway disease); patients intolerant of injections or adverse effects of pharmacotherapy; or patients who do not want to be on constant or long-term pharmacotherapy.
- Failure of pharmacotherapy is not an essential prerequisite for SLIT.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage. The package insert should be reviewed for any Black Box Warnings prior to the administration of any allergenic extract.

There are currently no FDA-approved sublingual liquid immunotherapy formulations.

The FDA has approved several sublingual allergen extract tablets for Odactra® (dust mite), Oralair® (northern grass mix), Grastek® (timothy grass), and Ragwitek® (short ragweed). Not all sublingual allergen extract tablets are FDA-approved. To confirm FDA approval, refer to the following website for more information and search by product name: https://www.fda.gov/vaccines-blood-biologics/allergenics/allergen-extract-sublingual-tablets.
(Accessed December 31, 2024)

The FDA's general recommendation is for patients who receive SCIT to be observed in the office for at least 20 minutes following treatment and that emergency measures and personnel trained in their use should be available immediately in the event of a life-threatening reaction.

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Policy History/Revision Information

Date	Summary of Changes

05/01/2025	**Applicable Codes**
	• Revised description for CPT code 95199
	• Updated coding clarifications:
	  ○ Modified instruction to clarify CPT code 95165 or 95199 should be reported *within a reasonable time frame from when* CPT code 95115 or 95117 is *billed for the administration of* subcutaneous allergen immunotherapy given in the office/ambulatory setting and furnished by a physician or other qualified health care practitioner
	  ○ Replaced references to “sublingual immunotherapy” with “sublingual *liquid* immunotherapy”
	Supporting Information
	• Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information
	• Archived previous policy version UMR2024T0603F

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