

Sublingual Immunotherapy

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[➔ Instructions for Use](#)

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Related Policy
None
Medicare Advantage Policy Guideline
<ul style="list-style-type: none"> Antigens Prepared for Sublingual Administration

Coverage Rationale

[➔ See Benefit Considerations](#)

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, is 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 Clarification: CPT 95115 or 95117 should not be reported when administering sublingual immunotherapy; these CPT codes are specific to subcutaneous administration. The unlisted CPT code 95199 should be used when sublingual immunotherapy is provided in the office/ambulatory setting and furnished by a physician or other qualified health care practitioner.

Note: Sublingual Immunotherapy (SLIT) is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. 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
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

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Description of Services

Subcutaneous injection of allergen-specific immunotherapy (SCIT) is the standard approach for treating allergies. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, sublingual immunotherapy (SLIT) is the most prominent.

Sublingual immunotherapy (SLIT, SIT) 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 3 times daily. This practice is thought to desensitize the patient to the allergen, as would conventional immunotherapy by injection (Hayes, 2015).

Benefit Considerations

Sublingual Immunotherapy (SLIT) is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed.

Clinical Evidence

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 have not been endorsed by the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Joint Task Force (Mahler et al., 2019).

In 2018, a consortium of healthcare providers published an International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (ICAR:AR). 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. In regard to SLIT, the reviewers examined the grades of clinical evidence on 25 studies. The group concluded with a strong recommendation for SLIT in patients with allergic rhinitis unable to obtain adequate relief from pharmacotherapy (Wise, et al.).

Scadding and colleagues (2018) conducted a randomized double-blind, placebo-controlled, 3-parallel-group study known as the GRASS trial to assess whether 2 years of treatment with grass pollen SLIT, compared with placebo, provides improved nasal response to allergen challenge at 3-year follow-up. Adults (N=106) with moderate to severe seasonal AR (interfering with usual daily activities or sleep) were included with study groups divided as follows: 36 participants received 2 years of SLIT (daily tablets containing 15 µg of major allergen Phleum p 5 and monthly placebo injections), 36 received subcutaneous immunotherapy (monthly injections containing 20 µg of Phleum p 5 and daily placebo tablets) and 34 received matched double-placebo. Nasal allergen challenge was performed before treatment, at 1 and 2 years of treatment, and at 3 years (1 year after treatment discontinuation). Primary outcome was total nasal symptom scores (TNSS) comparing SLIT vs placebo at year 3. Subcutaneous immunotherapy was included as a positive control. The study was not powered to compare SLIT with subcutaneous immunotherapy. At 3 years, 92 individuals completed the study. Researchers concluded that among patients with moderate to severe seasonal AR, 2 years of sublingual grass pollen immunotherapy was not significantly different from placebo in improving the nasal response to allergen challenge at 3-year follow-up.

A comparative 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 β 2 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 2 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.

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, 8 non-RCTs for SCIT safety, and 4 non-RCTs for SLIT safety. The authors found moderate-strength evidence that in children with allergic asthma, SCIT may reduce long-term asthma medication use, found low-strength evidence that SCIT improved asthma-related quality of life and forced expiratory volume in 1 second. There was low-strength evidence that SLIT improves medication use and force expiratory volume in 1 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 (eg, 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 2 prospective placebo RCTs was conducted by Jerzynska et al. The goal was to identify any differences in symptom-medication scores between two groups of SLIT tablets and drops, given pre-seasonally (starting 8 weeks before the pollen season) in 41 children (ages 6-18 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 (2018).

The efficacy and safety of SLIT with *D. farinae* drops along with pharmacotherapy were evaluated in 2 retrospective studies. Subjects with AR totaled 855 with ages ranging from 2-69 years. The TNSS, total medication score (TMS), and visual analogue score (VAS) were significantly improved at 2 years (Tang et al., 2018) and 3 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 4 years old.

Mortuaire et al. (2017) conducted a review based on the most recent meta-analyses and clinical studies which showed that SIT significantly reduces symptoms and medication requirements (nasal corticosteroids, H1-antihistamines) in AR. It can reduce the risk of progression to asthma and, if initiated early enough, of developing new sensitizations. Immunobiological analysis shows an altered inflammatory profile following SIT, with immune tolerance involving T-regulatory lymphocyte induction and IgG production. Standardization of trial protocols in terms of treatment response assessment and side effect grading is recommended to improve comparative studies.

Normansell et al. (2015) conducted a Cochrane review to assess the efficacy and safety of SLIT compared with placebo or standard care for adults and children with asthma. Fifty-two met inclusion criteria, randomly assigning 5077 participants to comparisons of interest. Researchers found that lack of data for important outcomes such as exacerbations and quality of life and use of different unvalidated symptom and medication scores limited their ability to draw a clinically useful conclusion. Further research using validated scales and important outcomes for patients and decision makers is needed so that SLIT can be properly assessed as clinical treatment for asthma. Very few serious AEs have been reported, but most studies have included patients with intermittent or mild asthma, so we cannot comment on the safety of SLIT for those with moderate or severe asthma.

Creticos and colleagues 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 8 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 2 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 (2014).

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 4-12 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 1 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 (NCT00841256).

Professional Societies

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).

American Academy of Otolaryngology - Head and Neck Surgeons (AAO-HNS)

In a clinical practice guideline on AR, the AAO-HNS notes that there are no U.S. practice guidelines specifically addressing the dosing of aqueous SLIT, which is not standardized (Seidman et al., 2015).

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.

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

The FDA has approved several sublingual allergen extract tablets for Odactra[®], Oralair[®], Grastek[®], and Ragwitk[®]. Not all sublingual allergen extract tablets are FDA-approved. To confirm FDA approval, see the following website for more information and search by product name: <http://www.fda.gov/BiologicsBloodVaccines/Allergenics/default.htm>. (Accessed June 17, 2020)

Centers for Medicare and Medicaid Services (CMS)

Medicare does not cover antigens if they are to be administered sublingually, i.e., by placing drops under the patient's tongue. This kind of allergy therapy has not been proven to be safe and effective. Antigens are covered only if they are administered by injection. See the National Coverage Determination (NCD) for [Antigens Prepared for Sublingual Administration \(110.9\)](#). (Accessed July 10, 2020)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2020	<p>Title Change</p> <ul style="list-style-type: none"> Previously titled <i>Sublingual Liquid Immunotherapy</i> <p>Coverage Rationale</p> <ul style="list-style-type: none"> Added language to indicate: <ul style="list-style-type: none"> <i>Non-Food and Drug Administration (FDA) approved sublingual allergen extract tablets</i> for the treatment of any condition/disease, including but not limited to allergic rhinitis and allergic rhinoconjunctivitis, is unproven and not medically necessary due to insufficient evidence of efficacy and safety This policy does not apply to FDA approved sublingual allergen extract tablets <p>Applicable Codes</p> <ul style="list-style-type: none"> Added notation to clarify: <ul style="list-style-type: none"> CPT codes 95115 and 95117 are specific to subcutaneous administration; the unlisted CPT code 95199 should be used when sublingual immunotherapy is provided in the office/ambulatory setting and furnished by a physician or other qualified health care practitioner Sublingual immunotherapy (SLIT) is typically covered under pharmacy benefit plans <ul style="list-style-type: none"> Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed 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 <p>Benefit Considerations</p> <ul style="list-style-type: none"> Added language to indicate sublingual immunotherapy (SLIT) is typically covered under pharmacy benefit plans; certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed <p>Supporting Information</p> <ul style="list-style-type: none"> Updated <i>Description of Services, Clinical Evidence, FDA, and References</i> sections to reflect the most current information Archived previous policy version 2019T0603A

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from

the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.