

SUBLINGUAL LIQUID IMMUNOTHERAPY

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[Instructions for Use](#) ⓘ

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Related Policy
None

COVERAGE RATIONALE

Sublingual liquid immunotherapy 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.

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 Coverage Determination Guidelines may apply.

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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Coding Clarification: CPT 95115 or 95117 should not be reported when administering sublingual immunotherapy.

DESCRIPTION OF SERVICES

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).

Note: This policy does not apply to oral immunotherapy or FDA approved sublingual tablets.

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).

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 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 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.

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-coseasonally (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).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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

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 May 16, 2019)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
09/01/2019	<ul style="list-style-type: none"> New Medical Policy

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, 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.