Medical Coverage Policy

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Allergy Testing and Non-Pharmacologic Treatment

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Related Coverage Resources

Complementary and Alternative Medicine
Grass Pollen Sublingual Products
Odactra
Omalizumab
Peanut (arachis hypogaea) allergen powder-dnfp
Ragwitek

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers

must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses testing and non-pharmacologic treatment for allergy. Allergy testing may be in vivo (i.e., testing on or near the patient and monitoring the patient's physiological response(s)) or in vitro procedures (i.e., analyzing the individual's serum). Non-pharmacologic immunotherapy may be allergen immunotherapy by subcutaneous injection and sublingual antigen extract drop immunotherapy preparations.

Coverage Policy

Testing:

Medically Necessary

The following in vivo allergy tests are considered medically necessary:

- prick/puncture allergy testing to diagnose suspected immunoglobulin E (IgE)-mediated hypersensitivity to inhalants and foods
- intradermal allergy testing to diagnose suspected immunoglobulin E (IgE)-mediated hypersensitivity to inhalants

When in vivo allergy testing is considered medically necessary as noted in the criteria above, the following frequency limits apply (rolling 12 months):

- percutaneous (scratch, puncture, prick) testing (CPT code 95004): 80 units
- intracutaneous (intradermal) testing (CPT code 95024): 40 units

In vivo allergy testing that exceeds the following limits is not covered or reimbursable:

- percutaneous (scratch, puncture, prick) testing (CPT code 95004): 80 units
- intracutaneous (intradermal) testing (CPT code 95024): 40 units

The following in vitro allergy testing (blood serum analysis, e.g., ImmunoCAP®, radioallergosorbent test [RAST], multiple radioallergosorbent test [MAST], fluorescent allergosorbent test [FAST], paper radioimmunosorbent test [PRIST], radioimmunosorbent test [RIST], enzyme-linked immunosorbent assay [ELISA], MRT [modified RAST], and VAST) are considered medically necessary:

- for the diagnosis of suspected IgE-mediated food or inhalant allergies
- as an alternative to skin testing for the evaluation of cross-reactivity between insect venoms
- when specific IgE immunoassays are used as adjunctive testing for disease activity of allergic bronchopulmonary aspergillosis and certain parasitic diseases

When in vitro allergy testing is considered medically necessary as noted in the criteria above, the following frequency limit applies (rolling 12 months):

- allergen specific IgE; quantitative or semiquantitative testing (CPT code 86003): 80 units

Allergen specific IgE; quantitative or semiquantitative testing that exceeds 80 units is not covered or reimbursable.

Bead-based epitope assay (e.g., VeriMAP™ Peanut Dx, VeriMAP™ Peanut Sensitivity) is not covered or reimbursable.

Treatment:

Medically Necessary

Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single or multiple antigens (CPT® code 95165) that exceeds a maximum of 150 doses per year (i.e., rolling 12 months) are not covered or reimbursable.

Sublingual antigen extract drop immunotherapy preparations are not covered or reimbursable.

Note: Please refer to Drug and Biologic Coverage Policies IP0515: Grass Pollen Sublingual Products, IP0516: Odactra, IP0518: Ragwitek, and 2004: Peanut (arachis hypogaea) allergen powder-dnfp for information regarding FDA-approved non-subcutaneous allergen immunotherapy.

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Testing

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
86003	Allergen specific IgE; quantitative or semiquantitative, crude allergen extract, each
95004	Percutaneous tests (scratch, puncture, prick) with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests
95024	Intracutaneous (intradermal) tests with allergenic extracts, immediate type reaction, including test interpretation and report, specify number of tests

Not Covered or Reimbursable:

CPT®* Codes	Description
0165U	Peanut allergen-specific quantitative assessment of multiple epitopes using enzyme-linked immunosorbent assay (ELISA), blood, individual epitope results and probability of peanut allergy
0178U	Peanut allergen-specific quantitative assessment of multiple epitopes using enzyme-linked immunosorbent assay (ELISA), blood, report of minimum eliciting exposure for a clinical reaction

Treatment

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
95165†	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses)

†**Note: Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single or multiple antigens that exceeds a maximum of 150 doses per year (i.e., rolling 12 months) are not covered or reimbursable.**

Sublingual Antigen Extract Drop Immunotherapy Preparations

Not covered or reimbursable when used to report sublingual antigen extract drop immunotherapy preparations:

CPT®* Codes	Description
95165	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses)

General Background

Allergies result from an overreaction of the immune system to foreign substances (e.g., pollen, dust, mold, animal fur or dander, stinging insect venom, food). An allergy develops when the body is exposed to a substance that prompts the initiation of an immune response. This response involves the production of antibodies, called immunoglobulins (Igs), which are directed against proteins of the foreign substance, called allergens or antigens. While there are five classes of immunoglobulins, it is IgE that is typically involved in allergic reactions. When an allergy-prone individual is exposed to a specific antigen, B-cells produce an IgE that recognizes only that antigen. This antigen-specific IgE then binds to receptors on specific cells that reside in tissue (mast cells) or circulate in the blood (basophils). Upon re-exposure to the same antigen, the antigen-specific IgE binds to membrane receptors on tissue mast cells and blood basophils and then releases a series of chemicals (histamine, leukotrienes, cytokines and proteases) that regulate the allergic reaction. While the allergic reaction begins immediately, signs and symptoms

of the reaction may occur within seconds or minutes (immediate hypersensitivity), may be delayed for several hours (delayed hypersensitivity), or may involve both early-and late-phase reactions.

Testing

Allergy tests are performed to verify or exclude the presence of IgE-mediated hypersensitivity and to identify the causative allergen(s). Testing may involve in vivo procedures, which determine the presence of specific IgE by administering an IgE-specific allergen into, on or near the patient and monitoring the patient's physiological response(s). Allergy tests may also be in vitro procedures that determine the presence of specific IgE or elevated total IgE by analyzing patient serum.

The allergy testing methods and recommendations detailed below are based primarily on practice parameters and recommendations from the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American Academy of Otolaryngic Allergy (AAOA).

In Vivo Allergy Testing

The number/frequency of tests needed to diagnose an individual with allergies is varied. Up to 80 percutaneous skin tests may be necessary to diagnose food allergies (scratch, puncture, prick, CPT code 95004). Up to 40 intracutaneous (intradermal) tests with allergenic extracts (CPT code 95024) is considered appropriate. If allergy skin tests cannot be performed due to a skin condition, etc., up to 40 allergen-specific IgE tests may be considered appropriate (CPT code 86003). Frequency is based on a rolling 12-month basis.

In vivo allergy tests fall into two general categories: skin tests and organ challenge (or provocation) tests. Both are designed to confirm hypersensitivity and identify the antigen(s) responsible for the allergic reaction. The most common in vivo allergy tests are outlined below. The efficacy of some in vivo allergy tests has not been firmly established, due to the limited numbers of well-designed clinical trials. Few prospective studies are available, and evidence is primarily in the form of expert opinion.

Skin testing can be utilized to detect immediate hypersensitivity (IgE-dependent reactions) and delayed hypersensitivity (cell-mediated immune reactions). The two major methods of skin testing for IgE-mediated disease include the prick-puncture test and the intradermal test. A positive response to skin testing is typically indicated by the presence of a wheal and/or flare at the test site. Scratch testing is no longer a recommended allergy testing procedure, due to reproducibility issues and the high incidence of false-positive reactions.

Skin testing is contraindicated in patients with severe dermatographism (allergy in which a pale, raised wheal is produced when skin is scratched), ichthyosis (condition in which skin is dry and scaly, resembling fish skin) or generalized eczema; in patients who cannot be withdrawn from medications that interfere with skin testing (such as long-acting antihistamines and tricyclic antidepressants); and in patients who have a history of a previous systemic reaction to skin testing.

Prick/puncture tests are used for confirmation of clinical immediate hypersensitivity induced by inhalant and food allergens. Skin prick/puncture tests are generally considered the most specific screening method for detecting the presence of IgE antibodies in patients with appropriate exposure histories. These tests may also be used in the diagnosis of drug and chemical hypersensitivity reactions. Prick/puncture tests are generally less sensitive than intradermal testing. For inhalant allergies, prick/puncture tests have been shown to correlate better with the presence of clinical allergy. Skin testing is considered the gold standard for the diagnosis of IgE-mediated allergic disease. The Joint Task Force of Allergy, Asthma, and Immunology recommends skin prick/puncture tests as the primary test for the diagnosis of IgE-mediated allergic diseases.

Intradermal or intracutaneous tests are generally used when increased sensitivity is the main goal of testing (i.e., when prick/puncture tests are negative despite a compatible history of exposure). Intradermal tests are more sensitive but less specific than prick/puncture tests for most allergens but are superior to other skin tests for assessing hypersensitivity to hymenoptera (stinging insects) and penicillin or allergens of lower potency. Intradermal testing for food allergies is not recommended because of the high rate of false positive test results and the potential for anaphylaxis.

Repeat skin testing with multiple antigens is not indicated on a regular basis (e.g., yearly). Indications for repeat testing include changing symptoms, new exposures, or 3–5 years of venom immunotherapy.

In Vitro Allergy Testing
The discovery of the role of IgE in clinical allergy testing resulted in the development of in vitro diagnostic assays to test for allergen sensitivity. The first immunoassays were developed to quantify the serum concentration of total IgE. In normal individuals, IgE is usually present at low levels; 130 ng/ml represents the upper limit of the normal range. However, a significant number of asymptomatic normal individuals, such as those with parasitic diseases or with depressed cell-mediated immunity, exceed this level. Also, some allergic patients may exhibit normal total IgE levels in the presence of elevated levels of specific IgE. Methods were therefore developed to assay allergen-specific IgE. The radioallergosorbent test (RAST) system was developed for in vitro measurement of specific IgE in a patient's serum. Other in vitro tests for specific IgE have been developed and employ the same principles as the RAST but use an enzymatic (MAST) or fluorogenic (FAST) detection system in place of a radioactive label.

In vitro tests that screen for multiple allergens in a single assay (Phadiatop®, Pharmacia Diagnostics) or that can be used in an automated system (ImmunoCAP®, Pharmacia Diagnostics) have been developed. The ImmunoCAP is designed as a "sandwich" immunoassay. The sensitivity and specificity of the ImmunoCAP compares favorably with those of the modified PhadezymRAST® system. Results from studies have indicated that, when compared to skin prick testing as the gold standard, the ImmunoCAP system has been shown to have a greater sensitivity (80–95%) than RAST and to have similar specificity (85%). Other modified versions of the RAST test include the PRIST, RIST, MRT (modified RAST) and ELISA IgE tests.

The overall sensitivity of in vitro immunoassays compared with prick/puncture skin tests has been reported to range from 50–90%, with an average of about 70–75% from most studies. Skin testing, therefore, continues to be the preferred method for the diagnosis of IgE-mediated sensitivity. According to practice parameters issued by the AAAI, selective use of in vitro tests may be justified for patients in whom skin testing is inappropriate. Situations in which specific IgE immunoassays may be appropriate include:

- testing of patients with severe dermatographism, ichthyosis or generalized eczema
- testing in patients who cannot be withdrawn from medications that interfere with skin testing (patients receiving long-acting antihistamines or tricyclic antidepressants)
- testing in patients who have a clinical history suggesting an unusually greater risk for anaphylaxis or who have had a previous systemic reaction to skin testing
- testing of patients with mental or physical impairments

When there is a clear history of sting anaphylaxis and skin test results are negative, then serum IgE antibodies should be measured, and if necessary, skin tests should be repeated after 3 to 6 months (Kowal and DuBuske, 2021; Golden, et al., 2017).

It should be noted that specific IgE immunoassays do not have sufficient sensitivity for absolute positive prediction of anaphylactic sensitization to venoms, penicillin and other drugs. This method of testing should not be used to provide definitive diagnoses, due to the potential for serious consequences resulting from a false-negative outcome. Allergen-specific IgE immunoassays provide neither diagnostic nor prognostic information when measured in the cord blood of newborn infants.

Bead-Based Epitope Assay (BBEA):
A bead-based epitope assay (BBEA) has been proposed to diagnose and monitor patients with food allergies. The test breaks down allergenic proteins into smaller components, called epitopes. It then measures the reactivity of a patient's IgE/IgG4 levels to each epitope to generate a detailed reactivity profile that can be used by clinicians to manage the allergy. There are several IgE epitope mapping methods based on the binding of IgE molecules to peptides that are derived from the allergen, thereby allowing for the identification of epitopes. The epitope mapping technology of such peptide arrays, by means of immobilized peptides on a surface, have been subjected to substantial development over the last decades. Typically, overlapping peptides of 10–20 amino acid residues are synthetized in parallel, for example, on a glass slide or a nitrocellulose membrane. A few years ago, standard peptide synthesis could only synthetize a few hundred peptides, but with the recent technological advances, synthesis of up to 2,100,000 peptides is now a possibility. These advances in peptide arrays have recently allowed for the identification of epitopes on the amino acid level, this being able to identify the amino acids within an epitope contributing to the binding to IgE of peanut allergic patients (Broekman, et al., 2015).

AllerGenis™ has developed technology using data-driven machine learning and multiplex immunoassay technology that is proposed to more precisely diagnose and monitor patients with food allergies. According to the manufacturer's website, diagnostic technology subdivides allergenic proteins into smaller peptides, called epitopes, and measures the reactivity of a patient's IgE to these epitopes. The platform uses a high-throughput, Luminex bead-based epitope assay (BBEA) to analyze IgE reactivity to discrete food allergen epitopes (e.g., VeriMAP™ Peanut Dx, VeriMAP™ Peanut Sensitivity).

The evidence in the published peer-reviewed medical literature evaluating the effectiveness of BBEA primarily consists of cohort studies and comparative case control studies with prospective and retrospective designs with relatively small sample sizes (Suprun, et al., 2019; Suárez-Fariñas, et al., 2019; Flinterman, et al., 2008; Shreffler, et al., 2005; Beyer, et al., 2003). More rigorous studies are needed to establish that the bead-based epitope assay improves outcomes compared to alternative testing modalities.

Treatment:

Immunotherapy has been an option for the long-term treatment of allergic diseases. It is designed to modify the immune system's response to allergens rather than simply controlling symptoms. Immunotherapy aims to induce immune tolerance by gradually exposing the body to controlled amounts of allergies compared to antihistamines and corticosteroids which provide short-term relief. Exposure of controlled amounts of allergens, shifts the immune response away from IgE-mediated hypersensitivity reaction and promotes regulatory pathways that reduce inflammation and allergic symptoms over time (Akdis and Akdis, 2011; Cox et al., 2011). There are different types of allergy immunotherapy utilized such as subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Subcutaneous immunotherapy (i.e. allergy shots) is the most established form of allergen immunotherapy. It involves administering increasing doses of allergen extracts via injection, typically over a build-up phase followed by a maintenance phase lasting 3-5 years. SCIT has demonstrated strong efficacy in treating allergic rhinitis, allergic asthma, and insect venom allergy, with evidence showing long-term symptom reduction

and prevention of new sensitizations (American Academy of Allergy, Asthma & Immunology, 2023)

SLIT delivers allergen extracts, typically in the form of a tablet, under the tongue, where they are absorbed through oral mucosa. This recently FDA approved method provides a more convenient, needle-free alternative to SCIT and has a more favorable safety profile with fewer systemic reactions (Calderón et al., 2012). SLIT is widely used for pollen allergies and dust mite sensitivity.

Sublingual immunotherapy (SLIT) administers allergen extracts—most commonly as a tablet—under the tongue, where they are absorbed through the oral mucosa. This recently FDA-approved approach provides a convenient, needle-free alternative to subcutaneous immunotherapy (SCIT) and is associated with a more favorable safety profile, including fewer systemic reactions (Calderón et al., 2012). SLIT tablets are widely used for the treatment of pollen allergies and dust mite sensitivity, and, like SCIT, have demonstrated long-term improvement in controlling allergy symptoms (American Academy of Allergy, Asthma & Immunology, 2024).

Evidence-based clinical practice guidelines support the use of subcutaneous allergen immunotherapy for the management of allergic asthma, allergic rhinitis (with or without conjunctivitis), and stinging insect venom hypersensitivity. Clinical studies do not support the use of allergen immunotherapy for treatment of angioedema, atopic dermatitis, chronic urticaria, and food hypersensitivity. Numerous allergy treatment methods have been proposed as alternatives to subcutaneous allergen immunotherapy, as detailed above. There is insufficient evidence in the published medical literature to demonstrate the safety and efficacy of these alternative treatments.

The allergy treatment recommendations in this Coverage Policy are based primarily on practice parameters developed by a joint task force representing the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) (Cox, et al., 2011).

Sublingual Antigen Extract Drop Immunotherapy Preparations: Please refer to Pharmacy Coverage Policy: Sublingual Allergen Immunotherapy for information regarding FDA-approved sublingual allergen immunotherapy.

Standardized antigen extract drop immunotherapy preparations administered under the tongue allows absorption through the sublingual mucosa. This therapy has been proposed for the treatment of patients with asthma and/or allergic rhinitis. Questions remain about the optimal dosing, duration of treatment, and the use of multiple allergens. Because of mixed study results, the therapy is controversial. There is insufficient evidence in the published, peer-reviewed scientific literature regarding improved outcomes using this therapy. Clinical trial data comparing sublingual antigen extract drop immunotherapy with other immunotherapy treatments are also lacking (American Academy of Allergy, Asthma & Immunology, 2024).

Further, professional society support in the form of published consensus guidelines is lacking. In a Practice Parameter Update (2017) regarding the use of liquid extract drops the American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) note that although alternative regimens and preparations for liquid sublingual immunotherapy or use of specific sublingual drops have been proposed and may be used off-label, these products and formulations have not been systematically studied in a rigorous manner in US populations. Use of such products or formulations is without recommendation for any current particular indication in the US populations and is not endorsed. (Strength of Recommendation: Strong; Evidence: D: Directly based on category IV evidence or extrapolated

recommendation from categories I, II, or III evidence.) At present there are no U.S. Food and Drug Administration (FDA)-approved sublingual antigen extract drop preparations.

Several meta-analyses and systematic reviews have examined outcomes with subcutaneous antigen extract drop immunotherapy (Fortescue, et al., 2020; Calderon, et al., 2011; DiBona, et al., 2010; Calamita, et al., 2006; Wilson, et al., 2004; update Radulovic, et al., 2010). Other studies have evaluated the comparative clinical effectiveness of this immunotherapy compared with subcutaneous immunotherapy, placebo and other interventions for the treatment of allergic rhino-conjunctivitis and/or asthma (Chelladurai and Lin, 2014; de Bot, et al., 2013). Study authors noted randomized controlled trials with head-to-head direct comparisons of subcutaneous immunotherapy and sublingual antigen extract drop immunotherapy are needed to strengthen the evidence base. Indirect comparisons of treatment options have many limitations and must be taken into consideration for clinical decision making.

Liu et al. (2019) conducted a multi-center, double-blind, randomized placebo-controlled trial with four parallel groups to evaluate the efficacy and safety of sublingual immunotherapy (SLIT) with Dermatophagoides farinae (D. farina) drops on patients with house dust mites (HDM) induced atopic dermatitis (AD). The study included patients (n=239) aged 18–60 years, a severity score of atopic dermatitis between 10 and 40 on the scoring atopic dermatitis (SOCRAD) scale, and a positive skin prick test results to D. farinae stimulation. Patients were randomly divided into four groups: placebo (n=60), high-dose sublingual D. farinae drops (n=60), medium-dose sublingual D. farinae drops (n=60) and low-dose sublingual D. farinae drops (n=59). Treatment was conducted by two phases: up-dosing phase (1st–10th weeks) and maintenance phase (11th–36th weeks). In up-doing phase, patients received low to high dose of sublingual D. farinae drops or placebo treatment. In the maintenance phase, patients took a high dose of sublingual D. farinae drops or placebo daily. The primary outcome assessed the therapeutic efficacy and safety of SLIT drops. Patients were assigned to receive relevant treatment for 36 weeks with follow-ups at four, 10, 16, 24 and 36 weeks. The therapeutic efficacy of SLIT with D. farinae drops was assessed using the SCORAD scale, the use of concomitant drugs to relieve clinical symptoms in maintenance phase, the dermatology life quality index (DLQI) and the skin lesion area. The safety was evaluated by adverse events (AE) and general clinical laboratory evaluations. 48 cases withdrew before the end of study. There were no significant differences in withdraw rates between the placebo group and D. farinae Drops groups. There was significant decreases in scoring atopic dermatitis and total medication score in the medium-dose and high-dose D. farinae drops groups. At the sixth visit, the skin lesion area showed a statistically significant difference between high-dose/medium-dose D. farinae drops group and placebo group ($p<0.05$). Most adverse events were minimal, and no life-threatening adverse drug reactions occurred. Author noted limitations included short term follow-up and children were not included as test subjects. The authors concluded that the study demonstrated the beneficial effect of SLIT with high or medium dose D. farinae drops on AD, and the treatment was well tolerated. However, further studies should include a longer time frames and a more suitable D. farina drops dosage.

Pfaar et al. (2019) conducted a parallel-group, multicenter, double-blind, randomized placebo-controlled trial to investigate the efficacy and safety of sublingual high-dose liquid birch pollen extract (40,000 allergy units native [AUN]/mL) in adults with birch pollen allergy. The study included adult patients (n=406) aged 18-65 years with moderate-to-severe birch pollen-induced allergic rhinoconjunctivitis with or without mild-to-moderate controlled asthma. Patients were randomized into the active treatment group (n=208) or the placebo group (n=198). Treatment was started three to six months before the birch pollen season and continued co-seasonally during the pollen season followed by an open-label safety extension period over six months that included 343 patients treated exclusively with the active product (n=169/active treatment group and n=174/placebo group). The primary outcome measured the difference in mean combined symptom and medication score (CSMS) between the active and placebo treatment groups. The

CSMS is the European Academy of Allergy and Clinical Immunology (EAACI) recommended end point for pivotal studies. Primary outcome analysis was carried out in the intention-to-treat (ITT) population (n=357), with 179 patients in the active treatment group and 178 patients in the placebo group. The Secondary outcomes assessed quality-of-life, immunologic parameters, and safety. Thirty-two patients were lost to follow-up primarily due to the development of adverse events (AEs). Primary efficacy results demonstrated a significant ($p<0.0001$) and clinically relevant (32%) reduction in the combined symptom and medication score compared with placebo after three to six months of sublingual allergen immunotherapy (SLIT) in the intention to treat (ITT) population. Significantly better rhinoconjunctivitis quality-of-life scores ($p<0.0001$) and the patient's own overall assessment of his or her health status, including the visual analog scale score (Euro Quality of Life Visual Analogue Scale; $p=0.0025$), were also demonstrated. In total, a good safety profile of SLIT was observed. The local and systemic treatment-emergent adverse events (TEAEs) in the double blind period of the study totaled 342 local reactions in 165 (40.6%) patients and 83.0% of all reactions were mild. Four (1.9%) patients of the active treatment group experienced at least one severe local reaction. Local and systemic adverse reactions were mainly of mild intensity and well controlled in the open label extension, 123 of 343 patients reported a local reaction, 88 of whom belonged to the former placebo group. Most local reactions were of mild-to-moderate intensity (> 97%). Regarding clinical and laboratory safety parameters, no safety issues were observed.

On behalf of the Agency for Healthcare Research and Quality, Lin et al. (2013) and colleagues reported results of a comparative effectiveness review of 60 studies comparing sublingual antigen extract drop therapy to placebo or another intervention for the treatment of allergic rhinoconjunctivitis and/or asthma. Authors note overall quality of evidence is assessed to be low to moderate due in part to limitations with the description of allocation concealment in some studies, moderate statistical heterogeneity and possible publication bias. Large definitive trials are required as well as head-to-head comparative studies with currently available anti-allergic drugs. Further studies evaluating the mechanisms of sublingual antigen extract drop immunotherapy preparations are needed as is a need to develop and validate standard instruments, such as questionnaires with adequate psychometrical properties. There is need for further large rigorously designed studies that examine long-term effectiveness after discontinuation of treatment and establish the cost-effectiveness of sublingual antigen extract drop immunotherapy preparations.

In a Cochrane review, Wilson et al. (2004; update Radulovic, et al., 2010), conducted a systematic review and meta-analysis of sublingual antigen extract drop immunotherapy for the treatment for allergic rhinitis. The authors identified 22 randomized controlled trials involving 979 patients. Only two of the studies compared injection therapy with sublingual extract drop therapy. The studies reported similar improvements in symptoms and medication requirements. The authors found heterogeneity in the findings, due to varying methods used to administer sublingual extract drop therapy and different clinical response scoring systems. Overall, sublingual antigen extract drop immunotherapy was followed by a significant reduction in mean symptom scores ($p=0.002$) and medication use ($p=0.0003$) when compared to placebo therapy. There were no significant variations in response to the use of different allergens in the studies. The authors noted total amount of allergen delivered may be a determinant of success, but the increasing time duration of sublingual extract drop therapy did not clearly increase efficacy. Sublingual extract drop therapy did not appear to be effective in studies limited to allergic children; however, the numbers of children in such studies were too small to draw definitive conclusions. The subgroup analyses did not suggest a benefit of treatment in any particular patient or disease group. The updated review of 2010 resulted in no change to the conclusions.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

The American Academy of Allergy, Asthma and Immunology (AAAAI) published a workgroup report on health disparities in allergic and immunologic conditions in racial and ethnic underserved populations. Allergic rhinitis (AR) is underdiagnosed and underappreciated in certain racial and ethnic populations. Black children without a personal or family history of atopy had higher odds of sensitization to any allergen as well as discrete sensitization to mold, cockroach, grass, weed and tree pollen compared to white children. Latino populations are also significantly affected by AR and under diagnosed in Puerto Rican and urban populations. Clinical studies have demonstrated that low-income and minority groups are less likely to receive allergen immunotherapy (AIT) and Medicaid insurance is associated with more emergency room care for acute nasal symptoms compared to private insurance. The studies highlight that additional burdens faced by lower income families can contribute to a lack of resources necessary to adhere to AIT rigorous schedules. Disparities in food allergies (FA) are predominately seen among under-represented racial and ethnic groups and lower income populations in the United States, with higher rates of FA-related anaphylaxis and ED visits. Black children have higher odds of wheat, soy, corn, fish, and shellfish allergy, and Hispanic children have higher odds of corn, fish, and shellfish allergy. Children belonging to under-represented racial and ethnic groups are less likely to have prescribed FA action plans, have a shorter duration of specialist follow-up, and have higher rates of FA related anaphylaxis and ED visits. Food insecurity is a risk factor in milk and egg allergy and was associated with lower health literacy (Davis, et al., 2021).

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Revision Details

Type of Revision	Summary of Changes	Date
Annual Review	• No clinical policy statement changes.	4/15/2026
Annual Review	• Removed policy statements related to: in vitro metal LTT for joint replacement surgery, and LHR in vitro allergy testing.	04/15/2025

Annual Review	• No changes to coverage.	05/15/2024
Focused Review	• Added policy statements regarding testing limits on allergy testing and preparation of allergen immunotherapy. • Removed the not medically necessary policy statement for in vitro allergy testing and subcutaneous allergen immunotherapy. • Updated the experimental/investigational or unproven policy statement for allergy testing.	12/03/2023