MEDICAL POLICY

Excellus
An independent licensee of the Blue Cross Blue Shield Association

Medical Policy Title	**Allergen Immunotherapy**
Policy Number	**2.01.11**
Current Effective Date	July 17, 2025
Next Review Date	July 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Allergen immunotherapy is considered **medically appropriate** in patients:

- A. With demonstrated hypersensitivity that cannot be adequately managed by medications or avoidance, and there is a desire to avoid long-term pharmacotherapy;
- B. With coexisting allergic rhinitis and asthma, where symptoms of asthma occur after natural exposure to aeroallergens, and there is demonstrable evidence of clinically relevant, specific immunoglobulin E (IgE).

II. The following methods of immunotherapy are considered **investigational**:

- A. Acupuncture;
- B. DNA immunization/vaccination;
- C. Immunization with immunostimulatory sequences;
- D. Intranasal therapy;
- E. Mutated protein therapy;
- F. Peptide therapy;
- G. Provocative-neutralization therapy for food allergies;
- H. Repository emulsion therapy;
- I. Serial dilution endpoint titration therapy (Rinkel therapy);
- J. Sublingual-swallow, sublingual-spit, and oral immunotherapies (administration of antigen drops/tablets, or other antigens under or on the tongue) that have not been approved by the U.S. Food and Drug Administration (FDA) (e.g., Southern California Food Allergy Institute's Tolerance Induction Program);
- K. Urine auto injections, autogenous urine immunization (intramuscular injections of sterilized urine).

III. Allergy and laboratory testing for a treatment program (e.g., Southern California Food Allergy Tolerance Induction Program) is considered **investigational**. (Please refer to Corporate Medical Policy #2.01.10 Allergy Testing)

IV. Contraindications to sublingual immunotherapy (SLIT) with FDA-approved formulations include:

A. Severe, unstable, or uncontrolled asthma;

B. History of any severe local reaction or any severe systemic allergic reaction to SLIT; and

C. History of eosinophilic esophagitis for Grastek and Ragwitek.

RELATED POLICIES

Corporate Medical Policy

2.01.10 Allergy Testing

11.01.03 Experimental or Investigational Services

Pharmacy Management Drug Policy

Xolair (omalizumab)-Pharmacy-57

Palforzia (peanut [Arachis hypogaea] allergen powder-dnfp)-Pharmacy-88

POLICY GUIDELINE(S)

I. The Center for Biologics Evaluation and Research (CBER) regulates allergenic products. Currently, there are two types of licensed allergen extracts administered for allergen immunotherapy:

A. Injectable Allergen Extracts

Benefits for injections of allergens should be individualized for each patient and are considered under the medical portion of the member's subscriber contract, when medically appropriate.

B. Sublingual Allergen Extract Tablets

Benefits for sublingual immunotherapy (SLIT) formulations that have been approved for marketing by the FDA and dispensed by a pharmacist are considered under the pharmacy portion of the member's subscriber contract, when medically appropriate. The first dose of sublingual immunotherapy is administered in a healthcare setting under the supervision of a physician, for monitoring of adverse reactions.

DESCRIPTION

Allergen immunotherapy, desensitization, or hypersensitization may be appropriate in patients not adequately managed with medications or avoidance of the allergen(s), when there is a desire to avoid long-term pharmacotherapy; or in patients with coexisting allergic rhinitis and asthma, where symptoms of asthma occur after natural exposure to aeroallergens, and there is demonstrable evidence of clinically relevant, specific IgE.

Allergen injection immunotherapy involves regular injection(s) of offending allergen(s), in the form of antigen extract(s), over a period of time, with the goal of reducing symptoms. Immunotherapy begins with injection of low doses of extract(s) on a weekly or biweekly basis, to prevent untoward reactions. The doses injected are gradually increased as immunity to the antigen(s) develop. After a

maintenance antigen dose is achieved, the interval between injections may range from two to six weeks. Immunotherapy may be administered continuously for several years.

Rush, or rapid, immunotherapy involves an accelerated immunotherapy build-up schedule. Incremental doses of allergen(s) are injected at intervals varying between 15 and 60 minutes over one to three days, until the target therapeutic dose is achieved. Rush immunotherapy schedules for inhalant allergens can be associated with a greater risk of systemic reactions, particularly in high-risk patients (e.g., those with markedly positive prick/puncture test responses), and premedication with antihistamines and corticosteroids appears to reduce the risk associated with rush immunotherapy. However, rush protocols for administration of Hymenoptera (stinging insect) venom immunotherapy have not been associated with a similar high incidence of systemic reactions.

Cluster immunotherapy involves an accelerated build-up schedule in which several injections are administered at increasing doses (generally two to three per visit) sequentially over the course of a single day, on nonconsecutive days. The maintenance dose is generally achieved within four to eight weeks--more rapidly than with a conventional (single injection per visit) build-up schedule.

Oral immunotherapy is a medical treatment in which an individual who is allergic to a specific food consumes an increasing amount of the allergen with the goal of reducing the risk of allergic reactions to the food.

SUPPORTIVE LITERATURE

Allergen immunotherapy is a widely accepted medical practice to treat IgE-mediated disease by injection with specific allergenic extracts. The efficacy of immunotherapy has been demonstrated in multiple double-blind, placebo-controlled studies. Continuing efforts have been made to improve the efficacy of immunotherapy, and to reduce both the risk of reactions and the number of injections necessary through the use of adjuvants, various administration routes, by chemical alteration and modification and polymerization of allergens. However, the results of clinical trials have not proven the safety and efficacy of these methods and remain investigational.

SLIT is a potential alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy. Despite multiple placebo-controlled studies evaluating SLIT, questions remain about the optimal dosing, duration of treatment, and use of multiple allergens. Four sublingual pollen extracts - Oralair, Grastek, Ragwitek and Odactra - have been approved by the FDA. Large, well-designed, randomized, controlled trials supporting the marketing applications for these products provide consistent evidence of efficacy and safety. Although trials were placebo-controlled, rather than SCIT-controlled, minimum clinically important criteria for demonstrating efficacy were pre-specified and were met in most studies. Patients in these trials had received previous treatment for their pollen-induced rhinitis or rhino conjunctivitis symptoms.

SLIT is being investigated for other allergies (e.g., other seasonal and food allergies); however, current evidence is insufficient to form conclusions about the use of SLIT for these indications, and no allergy extracts for these uses have been FDA-approved.

In a 2017 practice parameter update 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) noted that, although alternative regimens and preparations for liquid sublingual immunotherapy or use of specific sublingual drops have been proposed, these products and formulations have not been systematically studied in a rigorous manner in U.S. populations. Use of such products or formulations, currently off-label, is at a practitioner's discretion and liability, and is not endorsed. (Strength of Recommendation: Strong; Evidence: D: Directly based on category IV evidence or extrapolated recommendation from Category I, II, or III evidence.)

In 2020, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) recommended allergen immunotherapy (either subcutaneous immunotherapy [SCIT] or sublingual immunotherapy [SLIT]) be offered to patients with moderate or severe allergic rhinitis who are not controlled with allergen avoidance or pharmacotherapy; prefer immunotherapy; or those who may benefit due to comorbid conditions such as asthma.

Several studies, including well-powered, double-blind, randomized, controlled trials versus placebo, have shown that, based on overall efficacy and side effects, the evidence for SCIT versus SLIT is equipoised (Durham and Penagos, 2016). There were no significant differences in any outcome measures between the two groups (for TNSS: $P>0.05$; for TMS: $P>0.05$; for IL-4 levels: $P>0.05$). The authors concluded that the clinical efficacy of single-allergen SLIT is comparable with that of multi-allergen SCIT in children aged six to 13 years with HDM-induced allergic rhinitis (Wang et al., 2017). In a cost-minimization analysis comparing patients with persistent moderate-to-severe HDM allergic rhinitis, using SCIT as the standard care versus SLIT, the authors concluded that it is clearly cost-saving to treat patients with SLIT compared to SCIT (Ronborg et al., 2016).

There is lack of published research showing the efficacy of Tolerance Induction Programs (e.g., Southern California Food Allergy Institute's Tolerance Induction Program) to treat food allergies. These treatment programs and the extensive testing required to participate in the treatment is considered investigational.

PROFESSIONAL GUIDELINE(S)

Not Applicable

REGULATORY STATUS

Sublingual allergen immunotherapy involves the administration of an allergenic extract tablet, placed under the tongue, which rapidly dissolves. To date, four formulations of SLIT have been approved for marketing in the U.S. by the FDA:

I. On April 1, 2014, the FDA approved Oralair for treatment of certain grass pollen-induced allergic rhinitis, with or without conjunctivitis, in patients aged 10 to 65 years, who have grass pollen allergy to Kentucky Blue grass, Orchard grass, Perennial Rye grass, Sweet Vernal grass, and/or Timothy grass. Treatment with Oralair is commenced four months before the start of the grass pollen season and continues throughout the season.

II. On April 14, 2014, the FDA approved Grastek for the treatment of Timothy grass pollen-induced allergic rhinitis, with or without conjunctivitis, in patients aged five to 65 years. Treatment with

Grastek is commenced 12 weeks before the start of the grass pollen season and continued throughout the season.

III. On April 17, 2014, the FDA approved Ragwitek for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, in patients aged 18 to 65 years. Treatment with Ragwitek is commenced 12 weeks before the start of the ragweed pollen season and continues throughout the season.

IV. On March 1, 2017, the FDA approved Odactra, the first allergen extract to be administered under the tongue (sublingually) to treat house dust mite (HDM)-induced nasal inflammation (allergic rhinitis), with or without eye inflammation (conjunctivitis), in patients aged 18 to 65 years of age.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
95115	Professional services for allergen immunotherapy, not including provision of allergenic extracts; single injection
95117	two or more injections
95120	Professional services for allergen immunotherapy in the office or institution of the prescribing physician or other qualified health care professional, including provision of allergenic extract; single injection
95125	two or more injections
95130	single stinging insect venom
95131	two stinging insect venoms
95132	three stinging insect venoms
95133	four stinging insect venoms
95134	five stinging insect venoms
95144	Professional services for the supervision and provision of antigens for allergen immunotherapy, single dose vials (specify number of vials)
95145	Professional services for the supervision and provision of antigens for allergen immunotherapy (specify the number of doses); single stinging insect venom

Code	Description
95146	two single stinging insect venoms
95147	three single stinging insect venoms
95148	four single stinging insect venoms
95149	five single stinging insect venoms
95165	Professional services for the supervision and provision of antigens for allergen immunotherapy; single or multiple antigens (specify number of doses), Note: Not appropriate for sublingual immunotherapy.
95170	whole body extract of biting insect or other arthropod (specify number of doses)
95180	Rapid desensitization procedure, each hour (e.g., insulin, penicillin, horse serum)
95199	Unlisted allergy/clinical immunologic service or procedure Note: Used for FDA approved formulations of sublingual immunotherapy.

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
H10.411-H10.419	Chronic giant papillary conjunctivitis (code range)
H10.45	Other chronic allergic conjunctivitis
J30.0-J30.9	Vasomotor and allergic rhinitis (code range)
J45.20-J45.998	Asthma (code range)
L50.0	Allergic urticaria
L50.3	Dermatographic urticaria
Z51.6	Encounter for desensitization to allergens
Z91.010-Z91.09	Allergy status, other than to drugs and biological substances (code range)

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SEARCH TERMS

Allergy shots, Allergen/Allergy Immunotherapy, Grastek, Oralair, Ragwitek, Sublingual immunotherapy (SLIT).

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

NCD - Food Allergy Testing and Treatment (110.11) [accessed 2025 Jun 2]

NCD - Antigens Prepared for Sublingual Administration (110.9) [accessed 2025 Jun 2]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
01/20/00, 12/20/01, 10/16/02, 10/15/03, 02/19/04, 12/16/04, 11/17/05, 09/21/06, 09/20/07, 09/18/08, 09/17/09, 09/16/10, 09/15/11, 09/20/12, 09/19/13, 08/21/14, 09/17/15, 09/15/16, 09/21/17, 09/20/18, 09/19/19, 09/17/20, 09/16/21, 09/15/22, 06/22/23, 07/18/24, 07/17/25	
Date	**Summary of Changes**
07/17/25	• Annual review; policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
01/20/00	• Original effective date