



# CIGNA HEALTHCARE COVERAGE POSITION

Revised Date .....	8/15/2008
Original Effective Date .....	8/15/2005
Next Review Date.....	8/15/2009
Coverage Position Number .....	0405

**Subject Allergen Immunotherapy**

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## Hyperlink to Related Coverage Positions

- Allergy Testing
- Complementary and Alternative Medicine
- Omalizumab (Xolair®)

### INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), 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 Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. 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 group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Position

**CIGNA HealthCare covers allergen immunotherapy (i.e., allergy injections, desensitization, hyposensitization) with subcutaneous injections as medically necessary for ANY of the following immunoglobulin E (IgE)-mediated allergies when hypersensitivity cannot be managed by medications or allergen avoidance:**

- allergic (extrinsic) asthma
- allergic rhinitis and conjunctivitis
- Hymenoptera sensitivity (e.g., hornets, wasps, bee, fire ants)

**CIGNA HealthCare covers rapid desensitization (e.g., rush or cluster immunotherapy) as medically necessary for EITHER of the following:**

- Hymenoptera sensitivity (e.g., hornets, wasps, bee, fire ants)
- IgE antibodies to a medically necessary drug that cannot be treated with alternate medications

**CIGNA HealthCare does not cover allergen immunotherapy for any of the following because it is considered experimental, investigational or unproven for these indications:**

- angioedema
- atopic dermatitis
- chronic urticaria
- food hypersensitivity

**CIGNA HealthCare does not cover the use of any of the following allergy treatment methods because they are considered experimental, investigational or unproven (this list may not be all-inclusive):**

- acupuncture for allergies
- allergoids
- autogenous urine injections
- detoxification for allergies
- environmental chemical avoidance for idiopathic environmental intolerances
- enzyme-potentiated desensitization (EPD) immunotherapy
- high-dose sublingual-swallow immunotherapy
- homeopathic remedies for allergies
- injection of food extracts
- intranasal immunotherapy
- low-dose immunotherapy
- oral immunotherapy
- peptide therapy
- provocation-neutralization therapy
- repository emulsion therapy
- rhinophototherapy
- rotational and multiple food elimination diets (e.g., rotary diversified diet)

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## **General Background**

Allergies result from an overreaction of the immune system to foreign substances. 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) that 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. The treatment options for allergies are avoidance of the allergen(s), pharmacological therapy and immunotherapy.

### **Allergen Immunotherapy**

Allergen immunotherapy is the repeated administration of a specific allergen(s) to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to the allergen(s). Other terms that have been used for allergen immunotherapy are allergy vaccine therapy, hyposensitization, allergen-specific desensitization, and the common terms, allergy injections or shots. Evaluation of the patient with allergy symptoms includes a detailed history and physical exam. A definite diagnosis depends on results of allergy testing (in vitro tests or hypersensitivity skin tests). Immunotherapy should be considered when positive tests for specific IgE antibodies correlate with suspected triggers and patient exposure. Immunotherapy is effective for fungi (molds), pollen, animal dander, dust mite, cockroach, and Hymenoptera sensitivity. Many immunologic changes occur as a result of immunotherapy. Immunotherapy results in the generation of specific suppressor cells, decreased allergen-specific IgE, increased allergen-specific IgG, decreased inflammatory cells, decreased mediators of inflammation and decreased histamine-releasing factors. These changes result in decreased reactivity to the allergen in the target organ. Which changes are responsible for the efficacy of immunotherapy is unknown.

The current gold standard of care for allergen administration is subcutaneous immunotherapy (SCIT). Alternative routes of immunotherapy (e.g., sublingual, oral, nasal) have been evaluated in clinical studies but have not been confirmed to improve health outcome compared to SCIT. Allergen immunotherapy is indicated for patients with allergic diseases such as seasonal or perennial allergic rhinoconjunctivitis, asthma triggered by allergen exposures, or insect venom sensitivity, who have a demonstrated response to this form of therapy through testing. Evidence supporting the effectiveness of allergen immunotherapy for the treatment of atopic dermatitis, food allergy, latex allergy, or acute or chronic urticaria is lacking, and therefore allergen immunotherapy has not been recommended as a treatment for these disorders.

The physician prescribing immunotherapy should be trained and experienced in prescribing and administering allergen immunotherapy. The physician selects the appropriate allergen extract based on the patient's clinical history, allergen exposure history and the results of allergy testing. The allergen extracts consist of measured and standardized potencies. To ensure patient safety, the patient should have individualized treatment vials with accompanied individualized immunotherapy schedules and forms for recording immunotherapy schedules. The treatment usually has a build-up phase and a maintenance phase. In general, the schedule to reach maintenance consists of gradually increasing doses during 14–28 weeks varying between twice weekly injections for 14 weeks and weekly injections for 28 weeks. Follow-up visits should be every 6–12 months once the patient is on maintenance therapy. The duration of allergen immunotherapy can be 3–5 years.

Since anaphylaxis is the major risk factor with immunotherapy, the setting for treatment needs to allow for immediate recognition and management of adverse reactions. The preferred location is the physician's office. As most severe reactions occur shortly after immunotherapy, patients generally remain at the physician's office at least 20–30 minutes after treatment.

### **Rush Immunotherapy**

Rush, rapid desensitization or cluster immunotherapy applies to clinical situations in which antigens are administered in a few hours in sufficient quantity to neutralize available IgE antibodies rapidly. Two or more injections are administered per visit with cluster immunotherapy. Injections are given at 30–120-minute intervals. The accelerated schedule for rush immunotherapy involves multiple injections over a few hours. Premedication to reduce systemic reactions to allergen immunotherapy has been tested in patients receiving rush or cluster immunotherapy, both of which may be associated with a higher incidence of systemic reactions than conventional dosing. Physician supervision at the clinic should continue for 2–3 hours after therapy. This type of desensitization may be necessary in treating patients with allergies to a drug and has been used to treat Hymenoptera allergies.

Some of the patient contraindications to allergen immunotherapy include:

- co-existent uncontrolled asthma
- patients taking beta blockers
- patients unable to comply with the immunotherapy protocol
- patients with other immunological/medical diseases
- pregnancy (maintenance injections may be continued during pregnancy)
- children (less than five years old)

### **Alternative Allergy Treatment Methods**

Numerous alternative allergy treatment methods have been identified in the professional society guidelines and textbook literature. These allergy treatment methods remain unproven at this time due to a lack of supporting evidence published in the peer-reviewed scientific literature. The role of these techniques in the management of allergic disease has not yet been established. Some of the alternative allergy treatment methods utilize extracts that are not FDA-approved (Nelson, 2003; Grammer, 2002).

**Acupuncture:** Acupuncture has been used by allergic patients for the relief of allergic rhinitis, asthma, allergic dermatoses and by patients who have other symptoms or medical problems that they consider to be allergic. Despite the report by some patients of temporary benefit, this is an unproven form of allergy therapy due to lack of published scientific literature.

**Allergoids:** Allergoids are allergenic proteins that are treated with formaldehyde to produce larger molecules with decreased ability to react with IgE antibodies. Allergoids are licensed and manufactured for general distribution in Europe, but not yet in the United States.

**Autogenous urine injection:** Autogenous urine injection revolves around the theory that urine produced by the patient contains unspecified chemicals during an allergic reaction and that injection of these chemicals inhibits or neutralizes future allergic reactions. There is no scientific evidence to support autogenous urine injections. Repeated injections of these antigens could induce autoimmune nephritis.

**Detoxification:** Detoxification is a method used by individuals who believe that an allergic state can be induced by toxic damage to the immune system from exposure to environmental chemicals. It is believed that certain lipid-soluble chemicals may be stored in body fat for long periods. Detoxification consists of sauna and exercise. The individual ingests high-dose niacin to induce erythema. Body fluids are replenished with water and electrolytes and certain essential oils are consumed, presumably to help replace fat-soluble chemical contaminants. This procedure takes about five hours and is repeated daily for 20–30 days. This form of therapy has not been well-studied and is unproven.

**Environmental chemical avoidance:** Individuals with idiopathic environmental intolerances (e.g., multiple chemical sensitivities, environmental illness, ecologic illness, chemical hypersensitivity syndrome, total allergy syndrome, and 20th century disease) have been described as failing to adapt to synthetic chemicals. The 1999 American Academy of Allergy, Asthma and Immunotherapy (AAAAI) position statement on idiopathic environmental tolerance states, "A causal connection between environmental chemicals, foods, and/or drugs and the patient's symptoms continues to be speculative and cannot be based on the results of currently published scientific studies."

**Enzyme-potentiated desensitization (EPD):** EPD is a modification of conventional allergy immunotherapy. The individual is injected with a low dose of allergen that is remixed with a small quantity of  $\beta$ -glucuronidase as a single preseasonal intradermal injection. They also consume a special EPD diet. No trial has compared EPD treatment with the allergen or alone. No information is available regarding the possible chemical or biological alteration of the allergen when mixed with the enzyme.

**Homeopathic remedies:** A homeopathic remedy administers a causative agent of a disease and is administered therapeutically in small amounts. There is no scientific evidence to support homeopathic practice as a method for treating allergies.

**Injection of food extracts:** An injection of food extracts consists of a combination of foods based on skin test results or a patient's report of intolerance to foods. No clinical trials support this treatment.

**Oral immunotherapy:** Oral immunotherapy requires 20–200 times the parenteral injected dosage. Adverse effects are oral and gastrointestinal reactions.

**Peptide therapy:** The concept that the clinical response to allergen immunotherapy probably reflects the induction of nonresponsiveness in Th2 lymphocytes led to the concept of immunotherapy with allergen-derived peptides representing T cell activating epitopes that do not react with IgE antibodies.

**Provocation-neutralization therapy:** Involves the injection of substances under the skin that are suspected of triggering an allergic reaction in sufficient quantity to cause symptoms similar to the patient's complaints. This is then followed by an immediate injection of a weaker or stronger dilution of the same antigen to relieve the symptoms.

**Repository emulsion therapy:** A modification of allergen extracts widely used for several decades was termed repository immunization, which consisted of mixing allergen extracts with similar quantities of mineral oil and an emulsifier. Several injections of the repository extract were given preseasonally in one or several sessions.

**Rhinophototherapy:** Rhinophototherapy uses UV-B, UV-A, and visible light to treat allergic rhinitis.

**Rotational and multiple food elimination diets:** Proponents of the concept of multiple food allergies sometimes recommend a “rotary diversified diet,” in which the patient rotates foods so that the same food is eaten only once every 4–5 days to help identify foods that may cause allergic responses.

**Sublingual immunotherapy (SLIT):** Standardized allergen extracts can be administered under the tongue to allow absorption through the sublingual mucosa. SLIT is used in Europe, and clinical experience with this technique is growing in both children and adults. SLIT has been studied as a therapy for patients with asthma and/or allergic rhinitis for treatment of a number of allergies. Because of mixed study results, the therapy is controversial. Additionally, there is no U.S. Food and Drug Administration (FDA)-approved antigen preparation.

In Cochrane study, Calamita et al. (2006) conducted a systematic review and meta-analysis of SLIT for the treatment of asthma. A total of 25 studies with 1706 patients were included in the meta-analysis. The authors concluded that their meta-analysis did not demonstrate a definitive result regarding the efficacy of SLIT for asthma treatment. The authors stated further studies are needed to investigate the optimal maintenance doses and the length of treatment, identify whether there are subsets of patients that will respond better to treatment, and analyze the adherence to treatment.

In a Cochrane review, Wilson et al. (2004) conducted a systematic review and meta-analysis of SLIT. The authors identified 22 randomized controlled trials involving 979 patients. Only two of the studies compared injection therapy with SLIT. The studies reported similar improvements in symptoms and medication requirements. The authors found heterogeneity in the findings, due to varying methods used to administer SLIT and different clinical response scoring systems. Overall, SLIT therapy 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 SLIT studies. The total amount of allergen delivered may be a determinant of SLIT success, but the increasing time duration of SLIT did not clearly increase efficacy. SLIT 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 for SLIT treatment in any particular patient or disease group.

### **Professional Societies/Organizations**

In 2007, the AAAAI, the American College of Allergy, Asthma and Immunotherapy (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI) Joint Task Force on Practice Parameters updated their evidence-based clinical practice guidelines for allergen immunotherapy. The guidelines state that allergen immunotherapy should be considered for patients who have demonstrable evidence of specific IgE antibodies to clinically relevant allergens. The decision to begin allergen immunotherapy depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, and the adverse effects of medications. The guidelines state that well-designed, controlled studies have proven that allergen immunotherapy is effective for the treatment of allergic rhinitis, including ocular symptoms (conjunctivitis), allergic asthma and Hymenoptera (stinging insect) hypersensitivity. Clinical studies do not support allergen immunotherapy for atopic dermatitis, angioedema, chronic urticaria, and/or food hypersensitivity. Medical conditions that reduce the patient’s ability to survive the systemic allergic reaction or the resultant treatment are relative contraindications for allergen immunotherapy. Examples include severe asthma uncontrolled by pharmacotherapy and significant cardiovascular disease.

Alternative routes of immunotherapy are discussed in the guideline. Optimal high-dose sublingual swallow and oral immunotherapies are under clinical investigation. Studies of oral immunotherapy have demonstrated conflicting results. High-dose sublingual immunotherapy has been found to be effective in many studies of adults and children with allergic rhinitis and asthma, but a consistent relationship among allergen dose, treatment duration, and clinical efficacy has not been established. Since there is no FDA-approved formulation for sublingual or oral immunotherapy, these routes of immunotherapy should be considered investigational at this time. Intranasal immunotherapy is undergoing evaluation in children and adults with allergic rhinitis, but there is no FDA-approved formulation for this modality. The guideline states that immunotherapy techniques that are not recommended include low-dose immunotherapy (including coseasonal low-dose immunotherapy for aeroallergens and the Rinkel low dose titration

techniques), enzyme-potentiated immunotherapy, and immunotherapy (parenteral or sublingual) based on provocation-neutralization testing.

The 2006 AAAAI and ACAAI task force report on sublingual immunotherapy states that SLIT has been used in Europe and is being viewed with interest by allergists in the United States. The task force concluded, “Despite clear evidence that SLIT is an effective treatment, many questions remained unanswered, including effective dose, treatment schedules, and overall duration of treatment. SLIT does appear to be associated with few serious side effects, but it has not been administered in high-risk asthmatic patients, nor in the studies reviewed has it been administered as a mixture of non-crossing reacting allergens. Furthermore, there is currently no allergy extract approved in the United States” (Cox, et al., 2006).

The 2006 AAAAI and ACAAI’s food allergy practice parameter addresses immunotherapy with food allergens. The authors state that immunotherapy with food allergens has not been shown to be consistently effective or safe in the management of patients with food allergy.

The AAAAI Diagnosis and Management of Anaphylaxis Practice Parameter states there is a small risk of near fatal anaphylactic reactions to allergen immunotherapy injections. Physicians should be trained and prepared for possible systemic reactions after immunotherapy. The authors state allergen immunotherapy with the appropriate stinging insect venom should be recommended for patients with systemic sensitivity to stinging insects because this treatment is 90–98% effective. The authors recommend that caution is needed when administering allergen immunotherapy vaccine if asthma is severe or poorly controlled. Most practitioners measure peak expiratory flow rate before administering the allergy vaccine (Lieberman, et al., 2005).

The AAAAI Disease Management of Atopic Dermatitis Practice Parameter states that for the treatment of the difficult-to-manage patient, there is no conclusive evidence that immunotherapy with aeroallergens is effective in the treatment of atopic dermatitis, although expert opinion suggests there are selected individuals who may benefit from this treatment (Leung, et al., 2004).

## Summary

Evidence-based clinical practice guidelines support the use of allergen immunotherapy for the management of allergic rhinitis, allergic asthma and stinging insect hypersensitivity. Clinical studies do not support allergen immunotherapy for angioedema, atopic dermatitis, chronic urticaria, and food hypersensitivity. There are many alternate allergy treatment methods (e.g., sublingual immunotherapy, oral immunotherapy, and acupuncture for allergies). These methods are unproven due to a lack of well-designed clinical trials comparing the methods to the standard method of allergen administration.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

CPT <sup>®</sup> * Codes	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; two or more injections
95120	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; single injection
95125	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; two or more injections
95130	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; single stinging insect

	venom
95131	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; two stinging insect venoms
95132	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; three stinging insect venoms
95133	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; four stinging insect venoms
95134	Professional services for allergen immunotherapy in prescribing physicians office or institution, including provision of allergenic extract; five stinging insect venoms
95144	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single dose vial(s) (specify number of vials)
95145	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); single stinging insect venom
95146	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); two stinging insect venoms
95147	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); three stinging insect venoms
95148	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); four stinging insect venoms
95149	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, (specify number of doses); five stinging insect venoms
95165	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy, single or multiple antigens (specify number of doses)
95170	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy; whole body extract of biting insect or other arthropod (specify number of doses)
95180	Rapid desensitization procedure, each hour (eg, insulin, penicillin, equine serum)
95199	Unlisted allergy/clinical immunologic service or procedure

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
372.14	Other chronic allergic conjunctivitis
477.0	Allergic rhinitis due to pollen
477.8	Allergic rhinitis due to other allergen
477.9	Allergic rhinitis cause unspecified
493.00	Extrinsic asthma unspecified
493.01	Extrinsic asthma with status asthmaticus
493.02	Extrinsic asthma with (acute) exacerbation
989.5	Toxic effect of venom
995.20- 995.29	Unspecified adverse effect of drug, medicinal and biological substance
999.4	Anaphylactic shock due to serum
V14.0-V14.9	Personal history of allergy to medicinal agents
V15.06	Personal history of allergy to insects
	Multiple/Varied

**Experimental/Investigational/Unproven/Not Covered:**

CPT* Codes	Description
97810 <sup>†</sup>	Acupuncture, 1 or more needles; without electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
97811 <sup>†</sup>	Acupuncture, 1 or more needles; without electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
97813 <sup>†</sup>	Acupuncture, 1 or more needles; with electrical stimulation, initial 15 minutes of personal one-on-one contact with the patient
97814 <sup>†</sup>	Acupuncture, 1 or more needles; with electrical stimulation, each additional 15 minutes of personal one-on-one contact with the patient, with re-insertion of needle(s) (List separately in addition to code for primary procedure)
0168T	Rhinophototherapy, intranasal application of ultraviolet and visible light, bilateral

<sup>†</sup>**Note: Experimental, investigational or unproven and not covered when used to report acupuncture for the treatment of allergies.**

ICD-9-CM Diagnosis Codes	Description
691.8	Other atopic dermatitis and related conditions
693.1	Dermatitis due to food taken internally
708.8	Other specified urticaria
995.1	Angioneurotic edema not elsewhere classified
	Multiple/Varied

\*Current Procedural Terminology (CPT®) ©2007 American Medical Association: Chicago, IL.

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