Drug and Biologic Coverage Policy

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. 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.

Coverage Policy

This coverage policy addresses the following sublingual allergen immunotherapy tablets:
- **Grastek®** (Timothy Grass Pollen Allergen Extract)
- **Odactra™** House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract
- **Oralair®** (Sweet Vernal, Orchard, Perennial Rye, Timothy, and 6 Kentucky Blue Grass Mixed Pollens Allergen Extract)
- **Ragwitek®** (Short Ragweed Pollen Allergen Extract)

Sublingual allergen immunotherapy is considered medically necessary when the following criteria for the specified product are met:

<table>
<thead>
<tr>
<th>Product</th>
<th>Criteria for Use</th>
</tr>
</thead>
</table>
| **Grastek**  
(Timothy Grass Pollen Allergen Extract) | All of the following:  
• Individual is 5 to 65 years old.  
• Grass pollen-induced allergic rhinitis confirmed by either of the following:  
  ○ Positive skin test  
  ○ In vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens |
<table>
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<tr>
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| Odactra House Dust Mite *(Dermatophagoides farinae and Dermatophagoides pteronyssinus)* Allergen Extract | • Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for intranasal corticosteroid therapy and at least one other class of pharmacotherapy:  
  o Oral antihistamines  
  o Intranasal antihistamines  
  o Oral leukotriene receptor antagonists  
  • Treatment will be initiated at least 12 weeks before the onset of grass pollen season.  

When criteria are met, a maximum of 1 tablet per day will be covered. |
| Oralair (Sweet Vernal, Orchard, Perennial Rye, Timothy, and 6 Kentucky Blue Grass Mixed Pollens Allergen Extract) | All of the following:  
  • Individual is 5 to 65 years old.  
  • Grass pollen-induced allergic rhinitis confirmed by either of the following:  
    o Positive skin test  
    o In vitro testing for pollen-specific IgE antibodies for sweet vernal, orchard, perennial rye, Timothy, or Kentucky blue grass  
  • Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for intranasal corticosteroid therapy and at least one other class of pharmacotherapy:  
    o Oral antihistamines  
    o Intranasal antihistamines  
    o Oral leukotriene receptor antagonists  
  • Treatment will be initiated 4 months before the onset of grass pollen season.  

When criteria are met, a maximum of 1 tablet per day will be covered. |
| Ragwitek (Short Ragweed Pollen Allergen Extract) | All of the following:  
  • Individual is 18 to 65 years old.  
  • Short ragweed pollen-induced allergic rhinitis confirmed by either of the following:  
    o Positive skin test  
    o In vitro testing for pollen-specific IgE antibodies for short ragweed pollen  
  • Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for intranasal corticosteroid therapy and at least one other class of pharmacotherapy:  
    o Oral antihistamines  
    o Intranasal antihistamines  
    o Oral leukotriene receptor antagonists  
  • Treatment will be initiated at least 12 weeks before the onset of ragweed pollen season. |
<table>
<thead>
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<tbody>
<tr>
<td></td>
<td>When criteria are met, a maximum of 1 tablet per day will be covered.</td>
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</table>

Initial authorization is up to 12 months.

Sublingual allergen immunotherapy is considered medically necessary for continued use when the initial criteria are met. Reauthorization is up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Sublingual allergen immunotherapy is considered experimental, investigational or unproven for ANY other use including the following:

- Odactra or Ragwitek for pediatric individuals (less than 18 years of age)

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

### FDA Approved Indications

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Approved Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grastek</strong>&lt;br&gt;(Timothy Grass Pollen Allergen Extract)</td>
<td>Grastek is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. Grastek is approved for use in persons 5 through 65 years of age. Grastek is not indicated for the immediate relief of allergic symptoms.</td>
</tr>
<tr>
<td><strong>Odactra</strong>&lt;br&gt;House Dust Mite&lt;br&gt;(Dermatophagoides farinae and Dermatophagoides pteronyssinus) Allergen Extract</td>
<td>Odactra is an allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to <em>Dermatophagoides farinae</em> or <em>Dermatophagoides pteronyssinus</em> house dust mites, or skin testing to licensed house dust mite allergen extracts. Odactra is approved for use in adults 18 through 65 years of age. Odactra is not indicated for the immediate relief of allergic symptoms.</td>
</tr>
<tr>
<td><strong>Oralair</strong>&lt;br&gt;(Sweet Vernal, Orchard, Perennial Rye, Timothy, and 6 Kentucky Blue Grass Mixed Pollens Allergen Extract)</td>
<td>Oralair is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product. Oralair is approved for use in persons 5 through 65 years of age. Oralair is not indicated for the immediate relief of allergy symptoms.</td>
</tr>
<tr>
<td><strong>Ragwitek</strong>&lt;br&gt;(Short Ragweed Pollen Allergen Extract)</td>
<td>Ragwitek is an allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollen. Ragwitek is approved for use in adults 18 through 65 years of age. Ragwitek is not indicated for the immediate relief of allergic symptoms.</td>
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Recommended Dosing

FDA Recommended Dosing

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Recommended Dosing</th>
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</thead>
</table>
| **Grastek** (Timothy Grass Pollen Allergen Extract) | For sublingual use only. The dose is one Grastek tablet daily.  
Administer the first dose of Grastek in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of Grastek, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home.  
Initiate treatment at least 12 weeks before the expected onset of each grass pollen season and continue treatment throughout the season. For sustained effectiveness for one grass pollen season after cessation of treatment, Grastek may be taken daily for three consecutive years (including the intervals between the grass pollen seasons). The safety and efficacy of initiating treatment in season have not been established.  
Data regarding the safety of restarting treatment after missing a dose of Grastek are limited. In the clinical trials, treatment interruptions for up to seven days were allowed.  
Prescribe auto-injectable epinephrine to patients prescribed Grastek and instruct them in the proper use of emergency self-injection of epinephrine [see Warnings and Precautions (5.2)]. |
| **Odactra** House Dust Mite *(Dermatophagoides farinae and Dermatophagoides pteronyssinus)* Allergen Extract | For sublingual use only. One Odactra tablet daily.  
Administer the first dose of Odactra in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of Odactra, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home.  
Data regarding the safety of restarting treatment after missing a dose of Odactra are limited. In the clinical studies, treatment interruptions for up to seven days were allowed.  
Prescribe auto-injectable epinephrine to patients prescribed Odactra and instruct patients in the proper use of emergency self-injection of epinephrine [see Warnings and Precautions (5.2)]. |
| **Oralair** (Sweet Vernal, Orchard, Perennial Rye, Timothy, and 6 Kentucky Blue Grass Mixed Pollens Allergen Extract) | For sublingual use only. For adults 18 through 65 years of age, the dose is 300 IR (index of reactivity) daily. For children and adolescents 5 through 17 years of age, the dose is increased over the first three days as shown in Table 1.  
**Table 1. Dosage for Adults and Children for the Days 1-3 (and following)**  
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3 and following</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-17</td>
<td>100 IR</td>
<td>2x 100 IR</td>
<td>300 IR</td>
</tr>
<tr>
<td>18-65</td>
<td>300 IR</td>
<td>300 IR</td>
<td>300 IR</td>
</tr>
</tbody>
</table>

Administer the first dose of Oralair in a healthcare setting in which acute allergic reactions can be treated under the supervision of a physician with experience in the diagnosis and treatment of severe allergic reactions. After receiving the first dose of Oralair, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home.
<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Recommended Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate treatment 4 months before the expected onset of each grass pollen season and maintain it throughout the grass pollen season.</td>
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</tr>
<tr>
<td>Data regarding the safety of starting treatment during the pollen season are not available. Data regarding the safety of restarting treatment after missing a dose of Oralair are not available.</td>
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<tr>
<td>It is recommended that auto-injectable epinephrine be made available to patients prescribed Oralair. Patients who are prescribed epinephrine while receiving immunotherapy should be instructed in the proper use of emergency self-injection of epinephrine [See Warnings and Precautions (5.2)].</td>
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</tbody>
</table>

**Ragwitek** *(Short Ragweed Pollen Allergen Extract)*

For sublingual use only. Dose is one Ragwitek tablet daily.

Administer the first dose of Ragwitek in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of Ragwitek, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home.

Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season. The safety and efficacy of initiating treatment in season have not been established.

Data regarding the safety of restarting treatment after missing a dose of Ragwitek are limited. In the clinical trials, treatment interruptions for up to seven days were allowed.

Prescribe auto-injectable epinephrine to patients prescribed Ragwitek and instruct them in the proper use of emergency self-injection of epinephrine [see Warnings and Precautions (5.2)].

**Drug Availability**

<table>
<thead>
<tr>
<th>Product</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Grastek</strong> <em>(Timothy Grass Pollen Allergen Extract)</em></td>
<td>Grastek is available as 2800 Bioequivalent Allergy Unit (BAU) tablets supplied as 3 blister packages of 10 tablets (30 tablets total).</td>
</tr>
<tr>
<td><strong>Odactra</strong> House Dust Mite <em>(Dermatophagoides farinae and Dermatophagoides pteronyssinus)</em> Allergen Extract</td>
<td>Odactra is available as 12 SQ-HDM tablets. SQ-HDM is the dose unit for Odactra. SQ is a method of standardization of biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite. Odactra is supplied as 3 blister packages of 10 tablets (30 tablets total).</td>
</tr>
</tbody>
</table>
| **Oralair** *(Sweet Vernal, Orchard, Perennial Rye, Timothy, and 6 Kentucky Blue Grass Mixed Pollens Allergen Extract)* | Oralair is available as a sublingual tablet equivalent to 100 IR and 300 IR of five grass mixed pollens allergen extract. It is available in the following packages:  
  - Children and Adolescents Starter Pack (5 to 17 years of age) – containing 1 blister pack of three 100 IR tablets  
  - Adult Starter Pack (18 to 65 years of age) – containing 1 blister pack of three 300 IR tablets  
  - Sample Pack – containing 1 blister pack of three 300 IR tablets  
  - Commercial Pack – containing 1 blister pack of thirty 300 IR tablets |
<table>
<thead>
<tr>
<th>Product</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ragwitek (Short Ragweed Pollen Allergen Extract)</td>
<td>Ragwitek is available as 12 Amb a 1-Unit (Amb a 1-U) tablets supplied as 3 blister packages of 10 tablets (30 tablets total) and 9 blister packages of 10 tablets (90 tablets total).</td>
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</tbody>
</table>

**General Background**

**Disease Overview**

Allergic rhinitis occurs when an allergen comes in contact with nasal mucosa and results in an immune-mediated response via IgE. Common symptoms are nasal congestion, sneezing, rhinorrhea, and mucosal itching involving the eyes, nose, and palate. (Boyce, 2014; May, 2014) Symptoms usually appear earlier in life and may diminish with age. (Boyce, 2014; Greiner, 2011) People with allergic rhinitis often also have asthma or atopic dermatitis. (Boyce, 2014; May, 2014; Seidman, 2015) Some risk factors for developing allergic rhinitis include family history, high socioeconomic status, exposure to smoke early in life, or lack of exposure to pets at a young age. (Greiner, 2011; Wang, 2005) Allergic rhinitis is precipitated by exposure to various allergens (e.g., dust mites, pollen, cockroaches, animal dander, mold). (Boyce, 2014; May, 2014; Seidman, 2015) A national health survey reported that 28% of people in the US are hypersensitive to dust mites. (Arbes, 2005)

Grass pollens and ragweed are the most common causes of seasonal allergic rhinitis in the United States. (Dipiro, 2011) Multiple grass pollen allergens from different grass pollen groups may be present within a given species of grass. Additionally, allergens may be exclusive to a grass pollen itself or may exhibit cross-reactivity through expression in other unrelated plants. (Gangl, 2011) Timothy grass is a member of the Pooideae subfamily. It is cross-reactive with other family members (rye, meadow fescue, bluegrass/June, orchard/cocksfoot, sweet vernal, and redtop/bent/velvet) and partially cross-reactive with Johnson grass. (Nelson, 2011) Cross-reactivity between ragweed species is also possible. (Nolte, 2013) The onset and duration of the grass pollen and ragweed pollen seasons vary based on region in the United States. In general, grass pollen season begins in the spring and lasts into the summer and ragweed pollen season begins in the summer and lasts into the fall. (Roth, 1978)

Classification of allergic rhinitis is determined by severity (mild or moderate-to-severe), frequency (intermittent or persistent), and timing of symptoms (seasonal, perennial, or episodic). (Seidman, 2015) These classifications as well as efficacy outcomes assessing symptom severity, medication use, and quality of life are commonly used in allergy studies. The World Allergy Organization recommends at least a 20% improvement versus placebo for an outcome assessing both symptom severity and medication use. The minimum clinically significant improvement versus placebo recommended by the FDA for the same type of outcome is 15% with at least 10% for the lower bound of the 95% confidence interval. (Canonica, 2007)

Determining the specific allergen IgE can be accomplished through either skin testing or in vitro testing for the specific IgE antibodies. The Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology prefers skin testing over in vitro testing due to skin testing’s high sensitivity, low cost, ease, and rapidity of performance. (Wallace, 2008)

**Pharmacology**

The precise mechanisms of action of allergen immunotherapy have not been fully established.

**Professional Societies/Organizations**

Relevant guidelines for the management of allergic rhinitis include the American Academy of Otolaryngology-Head and Neck Surgery (2015), the Allergic Rhinitis and its Impact on Asthma guideline (ARIA, 2010), and the
American Academy of Allergy, Asthma, and Immunology guideline. (AAAAI, 2011) Allergen avoidance and environmental controls (e.g., washing sheets, air filters, vacuuming) are recommended to treat all types of allergic rhinitis. Pharmacotherapy is implemented for increased symptom control. Intranasal steroids and second-generation antihistamines are consistently described as first-line treatment options. (Brozek, 2010; Seidman, 2015) Other pharmacologic treatment options include oral, intranasal, or ophthalmic decongestants, leukotriene receptor antagonists, or mast cell stabilizers. Combination therapies have varying levels of efficacy. (Brozek, 2010; Seidman, 2015) Immunotherapy, which is the only disease-modifying therapy available, involves repeated exposure to a specific allergen to produce desensitization. (Seidman, 2015) Subcutaneous immunotherapy (SCIT) or SLIT is used if other therapies are ineffective. (Brozek, 2010; Seidman, 2015)

The Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology suggests allergen immunotherapy for those with evidence of specific IgE antibodies and note the decision to begin therapy is based on multiple factors (patient preference, response and adverse effects of medications as examples). (Cox, 2011) An updated practice parameter includes recommendations regarding use of FDA-approved sublingual immunotherapy and advises against use of non-FDA approved formulations. (Greenhawt, 2017)

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:
No recommendations are available for sublingual allergen immunotherapy.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for Grastek, Odactra, Oralair, or Ragwitek.

Clinical Efficacy
Grastek and Oralair
There are no head-to-head trials comparing the safety and efficacy of Grastek and Oralair. Both were more effective than placebo for the treatment of allergic rhinitis symptoms in most published trials. (Didier, 2011; Durham, 2012; Maloney, 2014; Murphy, 2013; Nelson, 2011)

An indirect analysis was conducted comparing Grastek, Oralair, and subcutaneous immunotherapy (SCIT) for the treatment of seasonal allergic rhinitis. A total of 20 randomized, double-blind, placebo-controlled trials were included. The majority of the trials were conducted in Europe. Fifteen trials were conducted in adults, 2 trials in children, and 3 trials included both children and adults. The median preseasonal initiation of treatment was 2.1 months prior to the start of grass pollen season. The total median duration of treatment was 5.3 months. A moderate degree of heterogeneity existed between all trials included in this analysis ($I^2 = 38.2\%$, Q-statistic $p = 0.040$). Results for comparisons between agents are only reported for Oralair compared with Grastek and Oralair compared with SCIT. Study authors did not report data comparing Grastek with SCIT. Two separate analyses were conducted comparing the effect of Grastek, Oralair, and SCIT on the symptom score. The definition of symptom score was not provided. The standardized mean difference (SMD) for symptom score was lower with Oralair compared with Grastek (-0.18; 95% CI -0.32 to -0.035) and SCIT (-0.21; 95% CI -0.36 to -0.066). There was no difference between Grastek and Oralair following a univariate analysis. (Dranitsaris, 2014)

Odactra
No published trials have compared Odactra with other active agents for allergic rhinitis. Three pivotal trials evaluated the safety and efficacy of Odactra compared with placebo for confirmed house dust mite (HDM)-induced allergic rhinitis. Two trials were field studies and 1 trial used a sealed chamber where participants were only exposed to HDM allergens. The North American field trial reported a 17% improvement and the European field trial reported a 22% improvement relative to placebo for symptom relief and allergy medication use. (Nolte, 2016; Demoly, 2016) The environmental chamber trial reported a 48.6% improvement versus placebo for nasal symptom relief. (Nolte, 2015)
**Ragwitek**

Ragwitek was more effective than placebo in reducing allergic rhinitis symptoms and rescue medication use in two trials. The mean total combined score (TCS) was lower with Ragwitek 12 Amb a 1-U (6.22-6.41) compared with placebo (7.70-8.46). (Creticos, 2013; Nolte, 2013) There are no trials comparing Ragwitek and SCIT.

**Off Label Uses**

AHFS Drug Information 2019 Edition does not have a monograph for Grastek, Odactra, Oralair, or Ragwitek.

**Experimental, Investigational, Unproven Uses**

There is no published data evaluating the safety and efficacy of Ragwitek in pediatric individuals (under 18 years of age). Ragwitek is FDA approved for use in adults.

Odactra is only FDA approved for treating adults up to 65 years of age. Odactra is well-tolerated in children as young as 12 years old. (Maloney, 2016; Nolte, 2016) The efficacy of Odactra for HDM-induced allergic rhinitis was studied in off-label age groups. The North American field study included 12.8% of patients between 12 to 18 years old and 1.7% of patients older than 65 years. Post hoc analyses indicated that Odactra may be slightly more efficacious in adolescents. However, the limited number of participants in these age groups was too small to establish efficacy. (CDER, 2017)

**Coding/ Billing Information**

**Note:** Sublingual Allergen Immunotherapy is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

**References**


