Important Reminder

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Grastek and Oralair are allergen immunotherapy tablets (AITs) for sublingual use. They are used to prevent allergy symptoms in patients with a confirmed grass allergy. NOTE: These policy criteria apply only to grass AIT (Grastek and Oralair). They do NOT apply to the use of other allergen immunotherapy, such as subcutaneous immunotherapy (“allergy shots”) or any other forms of immunotherapy.
Policy/Criteria

I. Most contracts require prior authorization approval of grass allergen immunotherapy tablet (AIT) (Grastek, Oralair) prior to coverage. Grass AIT may be considered medically necessary in patients with persistent allergic rhinitis due to grass pollen when ALL criteria A, B, C, and D below are met.

A. Patient is currently followed by an allergy specialist (allergist, immunologist, or pulmonologist).

AND

B. Documented positive pollen-specific skin prick test or pollen-specific immunoglobulin E (IgE) test to specific grass pollen allergens (Timothy grass or cross-reactive grass pollens, as listed Appendix 1), which support the patient’s clinical history.

AND

C. At least one low-cost generic nasal corticosteroid for allergic rhinitis (as listed in Appendix 2) has been ineffective, are not tolerated or all are contraindicated.

AND

D. At least one other generic medication for allergic rhinitis (as listed in Appendix 3) has been ineffective, are not tolerated or all are contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers grass AIT to be a self-administered medication.

B. When prior authorization is approved, grass AIT may be authorized in quantities of 30 sublingual tablets per month for a maximum of:

1) Grastek: 9 months (30 tablets per month) in one calendar year

OR

2) Oralair: 10 months (30 tablets per month) in one calendar year

C. Authorization shall be reviewed annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Grass AIT is considered investigational when:

A. Used concomitantly with subcutaneous immunotherapy (SCIT, “allergy shots”).

B. Used concomitantly with other AIT (such as Ragwitek).

C. Initiated after the onset of grass pollen season.

1. Used for all other conditions, including but not limited to, perennial allergies (for year-round use).
Position Statement

- Grass AIT (Grastek) is a single-allergen, Timothy grass-specific immunotherapy that desensitizes patients to certain grasses. Desensitization leads to a decrease in allergen immune response over time, to prevent the activation of the allergic cascade and associated allergic symptoms.

- Grass AIT (Oralair) contains a mix of five grasses which are cross-reactive with Timothy grass. Therefore, grass AIT (Oralair) is also considered a “single-allergen” specific immunotherapy.

- Both are approved for treatment of children and adults with allergic rhinitis, with or without conjunctivitis, due to confirmed Timothy grass or cross-reactive grass pollen allergy. Grass AIT (Grastek) is approved for children age 5 and older and grass AIT (Oralair) is approved for children age 10 and older.

- Grass AITs (Grastek, Oralair) are effective in reducing allergy symptoms in patients with allergic rhinitis that is triggered by Timothy grass or cross-reactive grass pollens.

- Grass AITs (Grastek, Oralair) have not been proven to be safer or more effective than preferred options recommended in treatment guidelines, nor in patients with severe, unstable, or uncontrolled asthma or those receiving other immunotherapy.

  * Nasal corticosteroids are effective in the treatment of many patients with seasonal allergic rhinitis and are considered the treatment of choice, along with allergen control. Several are available as low-cost generics and over-the-counter (OTC) products.

  * Other medications used for allergic rhinitis include, antihistamines (nasal, oral), nasal anticholinergics, and leukotriene modifiers. Many are available as low-cost generics and over-the-counter (OTC) products.

  * Use of immunotherapy, such as AIT or subcutaneous (SCIT, “allergy shots”), is reserved for patients with confirmed allergen-specific IgE antibodies and allergic rhinitis despite allergen avoidance and reasonable pharmacotherapy.

- The clinical utility of single-allergen AIT, such as grass AIT (Grastek, Oralair), is uncertain, as most patients have multiple allergies, treatable by individualized SCIT.

- For safety reasons, the first dose of grass AIT (Grastek, Oralair) must be given under medical observation for hypersensitivity reactions.

- Use of grass AIT (Grastek, Oralair) in combination with any other immunotherapy (including other AIT or SCIT) may increase the risk of local or systemic reactions. Therefore, combining any immunotherapy is not recommended.

- Grass AIT (Grastek, Oralair) may be covered for up to 1 tablet every day, starting prior to the expected onset of the grass pollen season (12 weeks prior for Grastek, 16 weeks for Oralair) and continued throughout the grass pollen season, the dosing at which it has been shown to be safe and effective.
**Clinical Efficacy**

- There is no evidence to support the superiority of grass AITs (Grastek, Oralair) over generically available treatment options for allergic rhinitis, such as intranasal corticosteroid, antihistamines (oral/nasal), anticholinergics and leukotriene modifiers.
- Six randomized, controlled studies compared grass AIT (Grastek) to placebo in patients with allergic rhinitis due to confirmed grass pollen allergy. \[1-6\]
  * Five of the six trials found a statistically significant improvement in allergic rhinitis symptoms scores; however, the clinical relevance of the modest change in symptoms is uncertain.
  * Significant flaws with the trials that impacted the certainty of the results included: incomplete reporting of results (greater than a 5% loss of the intent-to-treat analysis), differential loss (>5%), and high dropout rates (greater than 20% attrition).
  * The certainty in the efficacy is low due to varying primary endpoints evaluated and inconsistency in the statistical and clinical significance of the results.

- Four randomized, controlled studies compared grass AIT (Oralair) to placebo in patients with allergic rhinitis due to confirmed grass pollen allergy. \[7-10\]
  * All four trials found a statistically significant improvement in allergic rhinitis symptoms scores; however, the clinical relevance of the modest change in symptoms is uncertain.
  * Three of the trials had issues with internal validity similar to the grass AIT (Grastek) trials (lack of intent-to-treat analysis, differential loss and high attrition).

- In addition, there is insufficient evidence to establish if grass AITs (Grastek, Oralair) improve clinically meaningful outcomes, such as quality of life, missed days from work or school, or sustained effect after stopping treatment.

- Grass AIT (Grastek, Oralair) has not been compared to other treatment options in clinical trials. However, in the Grastek and Oralair clinical trials, all patients had access to use of rescue medications, for use in a stepwise fashion as needed for allergic rhinitis symptoms. \[1-10\]
- Allergic rhinitis treatment guidelines (AAAAI and BSACI) endorse the use of immunotherapy for symptomatic patients with demonstrated IgE antibodies to relevant allergens, who are refractory to maximal allergen avoidance (“trigger control”) and pharmacotherapy. Nasal corticosteroids are considered the treatment of choice for overall allergy symptom control for more severe or persistent allergic rhinitis, followed by antihistamines and anticholinergics. Leukotriene modifiers may be useful in patients with asthma or persistent rhinitis. \[11-14\]

**Confirmation of grass pollen allergy**

- In clinical trials, grass pollen allergy was confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens (Sweet Vernal, Orchard, perennial Rye, Kentucky bluegrass). \[1-10\]
Many aeroallergens have several species within a subfamily and those species show strong cross-reactivity within a group (See Appendix 1). When allergens are substantially cross-reactive, using one allergen immunotherapy extract within the cross-reactive subfamily will provide protection for the entire group. [11]

Timothy grass (*Phleum pratense*) is one of the standardized pasture grass species used for immunotherapy. The most common allergy-causing grass species include Orchard, Sweet vernal, Timothy, Kentucky bluegrass, Johnson, and Bermuda grasses. [11,15]

The Pooidae subfamily (Sweet Vernal, Orchard, Timothy grass, ryegrass, Kentucky bluegrass, fescue, and canary) are referred to as the “northern pasture grasses” and are all strongly cross-reactive. Therefore, an allergy to any one of these species will be reactive to Timothy grass and the rest of the subfamily. [11,16,17]

For the purposes of this policy, positive skin test results or presence of IgE antibodies to any cross-reactive grass species would be considered confirmatory of a Timothy grass allergy.

Grass AIT (Grastek, Oralair) has not been proven to be effective for other common allergy-causing grasses, such as Johnson, Bahia, and Bermuda grasses, which have little to no cross-reactivity with Timothy grass or the other northern pasture grasses. [11,15-17]

**Determination of grass pollen season**

Grass pollen season is May to August in the Northern states and April to September in the South Central U.S. The Southeast and Southwest can be extended from March to October, due to a later first frost. [18,19]

Pollen season (trees, grasses, weeds, and molds) are tracked continuously and reported from a variety of sources. The AAAAI runs the National Allergy Bureau (NAB) and is considered a standard source for determination of current pollen counts and allergy season.

Based on a review of NAB national pollen data from 1998 to 2009, grass pollen season lasted from 25 to 42 days per grass season (average of 35 days nationally), but up to 79 days in some regions. [20,21] Moderate or greater levels of pollen were defined as “in season.” (See Appendix 4)

Accounting for regional variability of the onset and length of the grass pollen season, up to nine months of grass AIT (Grastek), and ten months of grass AIT (Oralair) may be authorized per year.

Assuming the latest expected onset of grass pollen season in the U.S. is June 1st, initiation of grass AIT (Grastek, Oralair) after June 1st is considered investigational and cannot be covered.

**Safety** [22,23]

Grass AITs (Grastek, Oralair) have a boxed warning for severe allergic reactions, including anaphylaxis and severe laryngopharyngeal restriction.

* The first dose of grass AIT (Grastek, Oralair) is to be administered at the provider’s office and the patient should be observed for at least 30 minutes for signs and symptoms of allergic reaction.
All patients should be prescribed and instructed on the use of self-injectable epinephrine for anaphylactoid reactions.

- Use of grass AIT (Grastek, Oralair) is contraindicated in patients with eosinophilic esophagitis or severe, unstable, or uncontrolled asthma.

- Local (oropharyngeal/ear) reactions are the most frequent adverse effect reported with grass AIT (Grastek, Oralair) therapy, including pruritus, irritation and edema.

**Dosing** [22,23]

- Grass AIT (Grastek, Oralair) is for sublingual use. The tablet should be placed under the tongue to dissolve, with no swallowing for at least one minute. Food and beverage should not be consumed for at least five minutes after grass AIT (Grastek, Oralair) administration.

- Grass AIT (Grastek, Oralair) therapy should be initiated before the expected onset of grass pollen season (at least 12 weeks for Grastek, 16 weeks for Oralair) and continued treatment throughout the season.
  * The safety and efficacy of initiating treatment during the grass pollen season have not been established, or when starting with less than 12-16 weeks pre-season treatment (less than 12-16 weeks before the expected onset of grass pollen season).
  * Treatment must be used continuously, pre-season until the end of grass pollen season. In clinical trials, treatment interruptions of up to seven days were allowed. The safety and efficacy of restarting treatment after a longer treatment interruption (more than seven days) have not been established.

**Cross References**

| Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy, BlueCross BlueShield Association Medical Policy, 2.01.17, Issue 5.2014. |
| Ragweed pollen allergen immunotherapy tablet (Ragwitek), Medication Policy Manual, Policy No. dru359 |
| High cost nasal corticosteroid-containing products (Beconase AQ®, budesonide nasal (generic), DermacinRx® Azenase Pak, Dymista™, mometasone nasal (generic), Nasonex®, Omnaris®, Qnasl™, Rhinocort Aqua®, Veramyst®, Zetonna™), Medication Policy Manual, Policy No. dru448 |

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
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## Appendix 1: Seasonal Allergens – Cross-reactivity and Usual Dates of Pollen Seasons

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Cross-reactive pollens [16,17]</th>
<th>Start pre-seasonal</th>
<th>Usual start date [18,19]</th>
<th>Length of season (in clinical trials)</th>
</tr>
</thead>
</table>
| **Grastek:** Timothy grass *(Phleum pratense)* | Pooideae subfamily *(Festucoideae)*: Sweet vernal Orchard Ryegrass Kentucky bluegrass Timothy Fescue Canary | 12 weeks (3 months) | - North: May to August (3 months)  
- South Central: April to September (5 months)  
- Southeast and Southwest: can extend March to October (7 months) | 43 to 81 days (1.5 to 3 months) |
| **Oralair:** Mixed grasses  
Sweet vernal, Orchard, Perennial rye, Kentucky bluegrass, Timothy | Pooideae subfamily *(Festucoideae)* (see above) | 16 weeks (4 months) | (see above) | 30 to 60 days (1 to 2 months) |

## Appendix 2: Low-Cost Generic Nasal Corticosteroids a

- budesonide (generic Rhinocort®)  
- flunisolide (generic Nasarel®)  
- fluticasone propionate (generic Flonase®, OTC Flonase® Allergy Relief)  
- triamcinolone (generic Nasacort AQ®, OTC Nasacort Allergy 24 hour®)

a Including over-the-counter (OTC) options
### Appendix 3: Other Generic Treatment Options for Allergic Rhinitis

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic/Over-the-Counter (OTC) Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihistamines</strong></td>
<td></td>
</tr>
<tr>
<td>oral</td>
<td>cetirizine (generic Zyrtec, OTC)</td>
</tr>
<tr>
<td></td>
<td>desloratadine (generic Clarinex)</td>
</tr>
<tr>
<td></td>
<td>fexofenadine (generic Allegra, OTC)</td>
</tr>
<tr>
<td></td>
<td>levocetirizine (generic Xyzal)</td>
</tr>
<tr>
<td></td>
<td>loratadine (generic Claritin, OTC)</td>
</tr>
<tr>
<td>nasal</td>
<td>azelastine (generic Astelin)</td>
</tr>
<tr>
<td><strong>Anticholinergics, nasal</strong></td>
<td>ipratropium (generic Atrovent Nasal)</td>
</tr>
<tr>
<td><strong>Leukotriene modifiers, oral</strong></td>
<td>montelukast (generic Singulair)</td>
</tr>
<tr>
<td></td>
<td>zafirlukast (generic Accolate)</td>
</tr>
<tr>
<td><strong>Mast cell stabilizers, nasal</strong></td>
<td>cromolyn (generic NasalCrom)</td>
</tr>
</tbody>
</table>

### Appendix 4: NAB Ranges for Tree, Grass and Weed Pollen (Grains per Cubic Meter)

<table>
<thead>
<tr>
<th></th>
<th>Low &lt;50&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>Moderate 50&lt;sup&gt;th&lt;/sup&gt;-75&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>High 75&lt;sup&gt;th&lt;/sup&gt;-99&lt;sup&gt;th&lt;/sup&gt; percentile</th>
<th>Very high &gt;99&lt;sup&gt;th&lt;/sup&gt; percentile</th>
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<tbody>
<tr>
<td><strong>Trees</strong></td>
<td>0-14</td>
<td>15-89</td>
<td>90-1,499</td>
<td>&gt;1500</td>
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<tr>
<td><strong>Grasses</strong></td>
<td>0-4</td>
<td>5-19</td>
<td>20-199</td>
<td>&gt;200</td>
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<tr>
<td><strong>Weeds</strong></td>
<td>0-9</td>
<td>10-49</td>
<td>50-499</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>

### References


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6. Murphy, K, Gawchik, S, Bernstein, D, Andersen, J, Rud Pedersen, M. A phase 3 trial assessing the efficacy and safety of grass allergy immunotherapy tablet in subjects with grass pollen-induced allergic rhinitis with or without conjunctivitis, with or without asthma. Journal of negative results in biomedicine. 2013 Jun 1;12(1):10. PMID: 23725348
20. Kosisky, SE, Marks, MS, Yacovone, MA, Nelson, MR. Determination of ranges for reporting pollen aeroallergen levels in the Washington, DC, metropolitan area. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2011 Sep;107(3):244-50. PMID: 21875544


Revision History

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<th>Revision Summary</th>
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<tbody>
<tr>
<td>8/12/2016</td>
<td>Clarify “low-cost” generic nasal corticosteroid in coverage criteria, for consistency with cross-referenced coverage policies.</td>
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