

## Medical Policy



**Title: Oral Immunotherapy Agents  
(Grastek<sup>®</sup>, Oralair<sup>®</sup>, Ragwitek<sup>™</sup>)**

- Prime Therapeutics will review Prior Authorization requests.

**Prior Authorization Form:**

*(Link for PA form will be added before the effective date)*

**For information concerning Prior Authorization Prescription Drugs:**

[http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior\\_authorization.htm](http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm)

**Link to Drug List (Formulary):**

[http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug\\_list.htm](http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.htm)

**Professional**

Original Effective Date: July 23, 2004

Revision Date(s): June 7, 2013;

August 18, 2014; November 1, 2014

Current Effective Date: November 1, 2014

**Institutional**

Original Effective Date: July 23, 2004

Revision Date(s): June 7, 2013;

August 18, 2014; November 1, 2014

Current Effective Date: November 1, 2014

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

## **DESCRIPTION**

The intent of the Oral Immunotherapy Agents Prior Authorization (PA) program is to ensure appropriate selection of patients for treatment according to product labeling and guidelines. The PA defines appropriate use based on FDA approved package information and current clinical guidelines published by the Joint Task Force on Practice Parameters for Allergy and Immunology. The PA defines appropriate use as immunotherapy of allergic rhinitis in patients who have a positive skin test or pollen specific antibodies who have tried at least two traditional allergy medications, one of which is a nasal corticosteroid or have a documented intolerance, FDA labeled contraindication, or hypersensitivity to traditional treatments. PA criteria also include documentation of provider's specialty (allergy or immunology), documentation that the patient is to receive the first dose under direct supervision (30 minutes) of that provider and that the patient has epinephrine injection available at home, initiation of therapy at the required interval before the pollen season. Appropriate dosing based on FDA labeling will be included with a quantity limit of one tablet per day. Requests for oral immunotherapy agents will be reviewed when patient-specific documentation has been provided.

### **Target Drugs**

**Grastek®** (Timothy Grass Pollen Allergen Extract)

**Oralair®** (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue grass Mixed Pollens Allergen extract)

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

### **FDA Labeled Indications<sup>1-3</sup>**

<b>Product</b>	<b>Indication(s)</b>	<b>Dosage and Administration*</b>
<b>Grastek</b> (Timothy Grass Pollen Allergen Extract)  Sublingual tablet – 2800 Bioequivalent Allergy Unit (BAU)	<ul style="list-style-type: none"> <li>▪ 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.</li> <li>▪ Grastek is approved for use in persons 5 through 65 years of age.</li> </ul>	Take one tablet daily; place tablet under the tongue and allow it to remain there until completely dissolved. Do not take with food.  Initiate treatment at least 12 weeks before the expected onset of each grass pollen season and continue throughout the season. For sustained effectiveness Grastek may be taken daily for 3 consecutive years (including intervals between grass pollen seasons).
<b>Oralair</b> (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue grass Mixed Pollens Allergen extract)  Sublingual tablet – 100 IR 300 IR (Index of Reactivity)	<ul style="list-style-type: none"> <li>▪ 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.</li> <li>▪ Oralair is approved for use in persons 10 through 65 years of age.</li> </ul>	<b>Adults (age 18-65)</b> Take one tablet (300 IR) daily  <b>Children, Adolescents (age 10-17)</b> Increase dose over the first few days: Day 1 – 100 IR Day 2 – 100 IR x 2 Day 3 and following – 300 IR  Place tablet under the tongue and allow it to remain there until completely dissolved. Do not take with food. Administer Oralair to children under adult

Product	Indication(s)	Dosage and Administration*
		supervision.  Initiate treatment at least 4 months before the expected onset of each grass pollen season and continue throughout the season.
<b>Ragwitek</b> (Short Ragweed Pollen Allergen Extract)  Sublingual tablet – 12 Amb a 1-Unit	<ul style="list-style-type: none"> <li>▪ 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.</li> <li>▪ Ragwitek is approved for use in adults 18 through 65 years of age.</li> </ul>	Take one tablet daily; place tablet under the tongue and allow it to remain there until completely dissolved. Do not take with food.  Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue throughout the season.

\* Administer the first dose of these products 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 the product, 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.<sup>1-3</sup>

## **POLICY**

**Grastek, Oralair, or Ragwitek** will be approved when ALL of the following are met:

1. The patient has a diagnosis of allergic rhinitis, with or without conjunctivitis  
**AND**
2. The patient's diagnosis is confirmed with ONE of the following:
  - a. Positive skin test to ONE of the pollen extracts included in the requested agent  
**OR**
  - b. Pollen specific antibodies to ONE of the pollen extracts included in the requested agent
    - i. Grastek: Timothy grass or cross-reactive grass
    - ii. Oralair: Sweet vernal, orchard, perennial rye, Timothy, or Kentucky blue grass
    - iii. Ragwitek: Short Ragweed**AND**
3. The patient is within the FDA labeled age range:
  - a. Grastek: between the ages of 5 and 65
  - b. Oralair: between the ages of 10 and 65
  - c. Ragwitek: between the ages of 18 and 65**AND**
4. The prescriber has expertise in allergy or immunology or has consulted an expert in allergy or immunology  
**AND**

5. ONE of the following:
  - a. The patient has tried and failed at least two traditional allergy medications, one of which was an intranasal corticosteroid**OR**
  - b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least two standard allergy therapies, one of which was an intranasal corticosteroid**AND**
6. The patient is not currently using subcutaneous injectable immunotherapy  
**AND**
7. The patient is not taking a beta blocker (within the past 90 days)  
**AND**
8. The product will be started 3 to 4 months before the expected onset of the applicable pollen season  
**AND**
9. The first dose is given in the clinic/hospital under direct supervision from the provider for a period of at least 30 minutes  
**AND**
10. The patient has been prescribed epinephrine auto-injector for at home emergency use  
**AND**
11. The patient does not have any FDA labeled contraindications to therapy  
**AND**
12. ONE of the following:
  - a. The prescribed dosage is within the program limit (FDA approved labeled dosage)**OR**
  - b. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis

**Length of approval:** 12 months

**FDA Labeled Contraindications**

<b>Agent</b>	<b>Contraindications</b>
<b>Grastek</b>	<ol style="list-style-type: none"> <li>1. Severe, unstable or uncontrolled asthma</li> <li>2. History of any severe systemic allergic reaction</li> <li>3. History of any severe local reaction to sublingual allergen immunotherapy</li> <li>4. History of eosinophilic esophagitis</li> <li>5. Hypersensitivity to any of the inactive ingredients contained in this product</li> </ol>
<b>Oralair</b>	<ol style="list-style-type: none"> <li>1. Severe, unstable or uncontrolled asthma</li> <li>2. History of any severe systemic allergic reaction</li> <li>3. History of any severe local reaction to sublingual allergen immunotherapy</li> <li>4. Hypersensitivity to any of the inactive ingredients contained in this product</li> </ol>
<b>Ragwitek</b>	<ol style="list-style-type: none"> <li>1. Severe, unstable or uncontrolled asthma</li> <li>2. History of any severe systemic allergic reaction</li> <li>3. History of any severe local reaction to sublingual allergen immunotherapy</li> <li>4. History of eosinophilic esophagitis</li> <li>5. Hypersensitivity to any of the inactive ingredients contained in this product</li> </ol>

<b>Quantity Limits for Target Drugs</b>	
<b>Brand (generic)</b>	<b>Quantity Limit</b>
<b>Grastek</b> (Timothy Grass Pollen Allergen Extract)	
Tablet, 2800 BAUs (Bioequivalent Allergy Units)	1 tablet/day
<b>Oralair</b> (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue grass Mixed Pollens Allergen extract)	
Tablet, 300 IR (index of reactivity)	1 tablet/day
<b>Ragwitek</b> (Short Ragweed Pollen Allergen Extract)	
Tablet, 12 Amb a 1-U (Amb a 1-Unit)	1 tablet/day

**RATIONALE****Background<sup>4,5</sup>**

Allergic rhinitis (nasal passage inflammation) is characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea. Allergic rhinitis can be characterized as “seasonal” or “perennial” depending on duration and timing of the allergic response. Approximately 20-40 million people in the United States suffer from allergic rhinitis. Of these cases, 20% can be defined as seasonal allergic rhinitis, 40% are perennial allergic rhinitis, and 40% are mixed cases.<sup>4</sup>

Short ragweed pollen is prevalent during the autumn months (August through October) in most of the United States with the exception of regions west of the Rocky Mountains, where prevalence is low.<sup>22</sup> Late spring and summertime is when grass pollen reigns supreme: pollen from northern grass in colder climates, such as Timothy, rye, and blue; and southern grass pollens in the warmer climates, such as Bermuda Grass.<sup>23,24</sup> Pollination of the flowers of Timothy grass can occur during the late summer or fall. Pollen is carried by the wind, which can last well into late fall.<sup>25</sup>

Current therapy for allergic rhinitis is treated with oral antihistamines, oral corticosteroids, nasal sprays (i.e., intranasal corticosteroids, intranasal antihistamines), and leukotriene inhibitors.<sup>5</sup> The Joint Task Force on Practice Parameters on the diagnosis and management of allergic rhinitis state that intranasal corticosteroids are the most effective medications for treating allergic rhinitis.<sup>21</sup> In addition they note that intranasal antihistamines may be considered for use as first-line treatment for allergic and nonallergic rhinitis and are more efficacious and equal to or superior to oral second-generation antihistamines for the treatment of seasonal allergic rhinitis; however, they are generally less effective than intranasal corticosteroids.<sup>21</sup> In addition, inhaled nasal corticosteroids have been found to be more effective in allergy patients than leukotriene modifiers.

When conventional therapy fails (i.e., intranasal steroids, antihistamines), immunotherapy is an option. Immunotherapy is designed to restore tolerance to the allergen by reducing its tendency to induce IgE production. Upon initiation of therapy, IgE levels may increase, but overtime these levels will actually decrease upon exposure. Immunotherapy can also change the T-cell response when exposed to the allergen resulting in decreased symptoms.<sup>5</sup> Subcutaneous allergen immunotherapy (SCIT) has represented the main approach of allergen immunotherapy in the US.<sup>6</sup> SCIT may be considered for patients with evidence of symptoms based on allergen exposure, the presence of specific IgE antibodies, and whose allergic rhinitis symptoms are not well controlled by medication and/or avoidance measures.<sup>6</sup>

### **Guidelines, Reviews**

The British Society for Allergy & Clinical Immunology (BSACI) guidelines for immunotherapy for allergic rhinitis note:<sup>7</sup>

- Immunotherapy, both SCIT and sublingual (SLIT), is an effective treatment for adults and children with severe allergic rhinitis that does not respond to conventional pharmacotherapy and allergen avoidance measures.
- SCIT and SLIT have been shown to give long-lasting benefit for some years after stopping treatment.
- The safety profile of SLIT appears to be superior to SCIT in terms of severe systemic reactions although this data comes from indirect comparison not head-to-head trials. It is not yet clear from these studies whether SCIT and SLIT are of equivalent efficacy.

Allergen immunotherapy practice parameter from 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 (written before the FDA approval of SLIT, this formulation was considered investigational at the time of writing):<sup>8</sup>

- SCIT should be considered for patients who have symptoms of allergic rhinitis/conjunctivitis or asthma with natural exposure to allergens and who demonstrate specific IgE antibodies to the relevant allergen or allergens. Candidates for immunotherapy are patients whose symptoms are not controlled adequately by medications and avoidance measures or those experiencing unacceptable adverse effects of medications or who wish to reduce the long-term use of medications.

Practall-Joint position paper from Europe and the US (endorsed by both the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma, and Immunology):<sup>9</sup>

- Effective for allergic asthma and rhinitis as well as venom-induced anaphylaxis.
- Changes the course of allergic disease.

An AHRQ review found 74 RCTs (randomized controlled trials) on the efficacy and safety of SCIT, 60 RCTs on the efficacy and safety of SLIT, and 8 RCTs on head-to-head comparisons between both forms of immunotherapy.<sup>10</sup>

- There is sufficient evidence to support the overall effectiveness and safety of both SCIT and SLIT for treating allergic rhinoconjunctivitis and asthma.
- There is not enough evidence to determine if either SCIT or SLIT is superior.
- SCIT and SLIT are usually safe, although local reactions are commonly reported regardless of the mode of delivery.
- Serious, life-threatening reactions are rare, although they can occur. SLIT studies mainly include patients with allergic rhinitis and/or mild asthma. Safety outcomes for SLIT should not be extrapolated to more severely affected patients.

Most studies use a single allergen for immunotherapy. It may be difficult to extrapolate these results to the use of multiple-allergen regimens, which are commonly used in clinical practice in the US.

## Efficacy

### Grastek

The safety and efficacy were evaluated during the first grass pollen season in 2 trials of 24 weeks treatment duration. The sustained effect was evaluated in 1 trial conducted over 5 grass pollen seasons. All 3 trials were randomized, double-blind, parallel group, multicenter clinical trials.

- Treatment resulted in significant improvements relative to placebo in total combined score (TCS) over the entire grass pollen season ( $p < 0.001$ ), as well as for daily symptom scores (DSS) and daily medication scores (DMS) over the entire grass pollen season (GPS) ( $p = 0.001$  and  $P < 0.001$ , respectively).<sup>11</sup>
- Treatment resulted in significant improvements relative to placebo for TCS and DSS over the GPS in 345 North American pediatric or adolescent patients ( $p < 0.005$ ). Improvements were also reported with DMS for Grastek relative to placebo; although, the use of allergy medication was low in both treatment groups.<sup>12</sup>
- Grastek was superior to placebo with regard to daily DSS, DMS and TCS for all 3 treatment years ( $p < 0.001$ ) in 634 European adults. The effect of Grastek was sustained during the grass pollen season in the first year after treatment was discontinued.

### Oralair

The Center for Biologics Evaluation and Research (CBER) set criteria for success of a point difference in the CS [combined score: a measure which equally weighs allergic symptoms and concomitant rescue medication use.] between treatment and placebo groups of -15% or better, and a 95% CI upper limit of -10% or better. Such criteria were used when evaluating the efficacy of Oralair].<sup>2</sup>

- Study VO61.08 (Pivotal U.S. efficacy study in adults): In this study, 473 adults aged 18-65 years received Oralair (300 IR daily) or placebo, starting approximately four months prior to the expected onset of the grass-pollen season and continuing for the duration of

the pollen season. Oralair showed a -28.2% (95% CI: -43.4, -13) relative difference versus placebo.<sup>13</sup>

- Study V034.04 (European Study in adults):<sup>14</sup> In this published study, adults aged 18-45 years received 1 of 3 different doses of 5-grass pollen extract SL tablet or placebo. A total of 311 subjects received Oralair or placebo starting approximately 4 months prior to the expected onset of the grass pollen season and continuing for the duration of the grass pollen season. Oralair showed a -29.6% [95% CI: -43.1; -16.1] relative difference versus placebo.
- Study V052.06 (Pivotal European pediatric study):<sup>15</sup> In this study, 278 children and adolescents aged 5-17 years received Oralair (pediatric dosing regimen) or placebo starting approximately 4 months prior to the grass-pollen season and continuing for the duration of the pollen season. Oralair showed a -30.1% (-46.9; -13.2) relative difference versus placebo.
- Allergic Environmental Chamber Study (V056.07A):<sup>16</sup> In a published allergen environmental chamber study, 89 adults with grass pollen-associated allergic rhinoconjunctivitis were challenged with four of the five grass pollens contained in ORALAIR at baseline and after 4 months of treatment with ORALAIR (n=45) or placebo (n=44). The average Rhinoconjunctivitis Total Symptom Score (RTSS) of each group during the 4 hours of the allergen challenge was assessed; use of rescue medication was not permitted. Oralair showed a relative difference in average rhinoconjunctivitis total symptom score of -28.7% [95% CI: -43.7, -13.7].
- In the published long-term study, data was insufficient to demonstrate efficacy for 1 to 2 years after discontinuation of Oralair.<sup>17,18</sup>

## Ragwitek

The efficacy in the treatment of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, was investigated in two double-blind, placebo-controlled clinical trials in adults 18 through 50 years of age. Subjects received Ragwitek or placebo for approximately 12 weeks prior to the start of the ragweed pollen season and throughout the ragweed pollen season. Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS). The sums of the DSS and DMS were combined into the Total Combined Score (TCS) which was averaged over the peak ragweed pollen season. Also, in each study, the average TCS over the entire ragweed season was assessed. Other endpoints in both studies included the average DSS during the peak and entire ragweed season, and the average DMS during the peak ragweed season.

- The first study was a placebo-controlled trial which evaluated subjects 18 through 50 years of age comparing Ragwitek (n=187) and placebo (n=188) administered as a sublingual tablet daily. There was a significant reduction versus placebo in TCS (point estimate -26% [95% CI: -38.7, -14.6]; p<0.001).<sup>19</sup>
- The second study was a placebo-controlled trial which evaluated subjects 18 through 50 years of age comparing Ragwitek (n=194) and placebo (n=198) administered as a sublingual tablet daily. There was a significant reduction versus placebo in TCS (point estimate -24% [95% CI: -36.5, -11.3]; p<0.001).<sup>20</sup>

In both trials, subjects treated with Ragwitek also showed a decrease in the average TCS from the start of and throughout the entire ragweed pollen season. Similar decreases were observed in subjects treated with Ragwitek for DSS and DMS.<sup>19,20</sup>



**Safety<sup>1-3</sup>**

All three oral immunotherapy agents carry the same boxed warning:

- Can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema/restriction.
- Do not administer to patients with severe, unstable or uncontrolled asthma.
- Observe patients in the office for at least 30 minutes following the initial dose.
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.
- May not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction.
- May not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

Adverse reactions  $\geq 5\%$  included: oral pruritus, throat irritation, ear pruritus, mouth edema, tongue pruritus, cough, and oropharyngeal pain.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

95199 Unlisted allergy / clinical immunologic service or procedure

J3490 Unclassified drugs

There are no specific HCPCS codes for the drugs listed in this policy.

- The unlisted CPT code 95199 should be used.
- CPT codes for allergen immunotherapy are specific to parenteral administration and should not be used for sublingual immunotherapy.

**ICD-9 Diagnoses**

477.0 Allergic rhinitis; due to pollen

**ICD-10 Diagnoses (Effective October 1, 2015)**

J30.1 Allergic rhinitis due to pollen

**REVISIONS**

06-07-2013	Policy added to the bcbsks.com web site.
08-18-2014	Description section updated
	In Policy section: <ul style="list-style-type: none"> <li>▪ Revised policy from experimental / investigational to medically necessary adding,</li> </ul> "Sublingual immunotherapy using Oralair®, Grastek®, or Ragwitek® may be

considered medically necessary, when used according to FDA-labelling, for the treatment of pollen-induced allergic rhinitis when the following conditions are met:

1. Patient has a history of rhinitis or rhinoconjunctivitis symptoms related to grass or short ragweed pollen exposure.
2. Patient has a documented positive pollen-specific skin test or pollen-specific immunoglobulin E (IgE) test (see Policy Guidelines section).
3. Patient's symptoms are not adequately controlled by appropriate pharmacotherapy (see Policy Guidelines section)."

▪ Revised E/I statement adding "for all other uses" to read,  
"Sublingual immunotherapy as a technique of allergy immunotherapy is considered experimental / investigational for all other uses."

▪ Added Policy Guidelines:

"For Oralair®, Grastek®, or Ragwitek®(1-3):

#### Documentation of Allergy

Allergy must be confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies to the species contained in the product or, for Grastek®, Timothy grass pollen extract, to cross-reactive species.

#### Contraindications

Contraindications include severe, unstable or uncontrolled asthma; history of any severe local reaction, or any severe systemic allergic reaction to SLIT; and for Grastek® and Ragwitek®, history of eosinophilic esophagitis.

#### Administration and Dose

1. Prescribing information includes a black box warning for severe allergic reactions including anaphylaxis. Patients must be prescribed an epinephrine auto-injector and be trained on how to use it.
2. Treatment should begin 12 weeks (16 weeks for Oralair®) before the expected onset of the allergy-inducing pollen season. Each product is dosed once daily and continued throughout the pollen season (preseasonal dosing).
3. The first dose is administered under the supervision of a physician experienced in diagnosing and treating severe allergic reactions. Subsequent doses may be taken at home.
4. All 3 agents are dosed once daily.
5. For Oralair®, dose titration is required in patients 10 to 17 years of age. Titration can be completed over 3 days at home (after the first dose) according to the schedule in Table 1. In patients between 18 to 65 years, no dose titration is needed; treatment is initiated at the maintenance dose of 300 IR (index of reactivity).
6. Grastek® and Ragwitek® both are initiated at the maintenance dose (2800 BAU [bioequivalent allergy unit] and 12 Amb a 1 unit, respectively).

Table 1. Oralair® Dosing in Patients Age 10-17 Years(1)

Day 1	Day 2	Day 3 and Following
100 IR	2 × 100 IR	300 IR

IR, index of reactivity, a potency unit defined by the formation of a 7-mm wheal in 30 sensitized individuals during product development.(1)

#### Pharmacotherapy of Pollen-Induced Allergic Rhinitis

Several clinical practice guidelines describe pharmacologic treatments of pollen-induced allergic rhinitis/rhinoconjunctivitis.(4-8) There is general agreement that:

1. Treatment should be individualized based on symptom severity and duration, comorbidities, and patient age, preference (eg, route of administration, tolerance for adverse effects), and previous treatment history.
2. Measures to increase treatment adherence (eg, shared decision making, consideration of the patient's school or work schedule, use of a medication calendar

	<p>or check-off list) are encouraged.</p> <ol style="list-style-type: none"> <li>Goals of treatment are symptom reduction and improvements in functional capacity and quality of life.</li> <li>A "step-up" (if treatment is inadequate)/"step-down" (if symptom relief is achieved with other interventions, eg, avoidance) approach to treatment is recommended.</li> <li>Allergen avoidance is the first step of treatment but may be unrealistic for some patients.</li> <li>Six medication classes are used to treat allergic rhinitis: H1-antihistamines (oral and intranasal), corticosteroids (oral [short-course for severe disease] and intranasal), leukotriene receptor antagonists (oral), sympathomimetic decongestants (oral and intranasal), chromones (intranasal), and the anticholinergic, ipratropium bromide (intranasal).</li> <li>Treatment should be symptom-specific, eg, oral antihistamines may be less effective for prominent congestion than other treatments; prominent rhinorrhea may respond to intranasal ipratropium; rhinitis-only symptoms may be treated with local (intranasal) rather than systemic (oral) therapy.</li> <li>For mild or intermittent symptoms, oral or nasal antihistamine may be considered first-line treatment.</li> <li>Newer generation (selective) oral antihistamines generally are recommended over older (nonselective) antihistamines. Patients with insomnia and pregnant women may prefer older antihistamines because of their sedating effects and longer safety history, respectively.</li> <li>Intranasal corticosteroids may be effective for more severe or persistent symptoms.</li> <li>Combination treatment (eg, oral antihistamine plus intranasal corticosteroid, intranasal antihistamine and corticosteroid, antihistamine [oral or intranasal] plus sympathomimetic [oral or short-course (<math>\leq 5</math> days to avoid rebound congestion) intranasal]) may be effective for symptoms nonresponsive to single medications.</li> <li>Oral sympathomimetics may cause insomnia; their use is limited in patients with certain comorbidities (eg, diabetes mellitus, unstable hypertension).</li> <li>Oral leukotriene receptor antagonists may reduce asthma exacerbations in patients with comorbid asthma.</li> </ol>
	Rationale section updated
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>Added ICD-9 Code: 477.0</li> <li>Added ICD-10 Code: J30.1</li> <li>Removed "Experimental / Investigational on all diagnoses related to this medical policy."</li> </ul>
	References updated
11-01-2014	Policy posted 10-02-2014 and effective 11-01-2014, 30 days after posting.
	Adopted PTI policy.
	Policy title changed to: "Oral Immunotherapy Agents (Grastek®, Oralair®, Ragwitek™)" from "Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy"
	<p>Description section revised</p> <ul style="list-style-type: none"> <li>Added FDA Indications</li> </ul>
	<p>In Policy section</p> <ul style="list-style-type: none"> <li>The policy was revised to the current policy language from:             <p>"A. Sublingual immunotherapy using Oralair®, Grastek®, or Ragwitek® may be considered medically necessary, when used according to FDA-labelling, for the treatment of pollen-induced allergic rhinitis when the following conditions are met:</p> <ol style="list-style-type: none"> <li>Patient has a history of rhinitis or rhinoconjunctivitis symptoms related to grass</li> </ol> </li> </ul>

- or short ragweed pollen exposure.
- 2. Patient has a documented positive pollen-specific skin test or pollen-specific immunoglobulin E (IgE) test (see Policy Guidelines section).
- 3. Patient's symptoms are not adequately controlled by appropriate pharmacotherapy (see Policy Guidelines section).
- B. Sublingual immunotherapy as a technique of allergy immunotherapy is considered experimental / investigational for all other uses.

#### Policy Guidelines

For Oralair®, Grastek®, or Ragwitek®(1-3):

#### Documentation of Allergy

Allergy must be confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies to the species contained in the product or, for Grastek®, Timothy grass pollen extract, to cross-reactive species.

#### Contraindications

Contraindications include severe, unstable or uncontrolled asthma; history of any severe local reaction, or any severe systemic allergic reaction to SLIT; and for Grastek® and Ragwitek®, history of eosinophilic esophagitis.

#### Administration and Dose

1. Prescribing information includes a black box warning for severe allergic reactions including anaphylaxis. Patients must be prescribed an epinephrine auto-injector and be trained on how to use it.
2. Treatment should begin 12 weeks (16 weeks for Oralair®) before the expected onset of the allergy-inducing pollen season. Each product is dosed once daily and continued throughout the pollen season (preseasonal dosing).
3. The first dose is administered under the supervision of a physician experienced in diagnosing and treating severe allergic reactions. Subsequent doses may be taken at home.
4. All 3 agents are dosed once daily.
5. For Oralair®, dose titration is required in patients 10 to 17 years of age. Titration can be completed over 3 days at home (after the first dose) according to the schedule in Table 1. In patients between 18 to 65 years, no dose titration is needed; treatment is initiated at the maintenance dose of 300 IR (index of reactivity).
6. Grastek® and Ragwitek® both are initiated at the maintenance dose (2800 BAU [bioequivalent allergy unit] and 12 Amb a 1 unit, respectively).

Table 1. Oralair® Dosing in Patients Age 10-17 Years(1)

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100 IR	2 x 100 IR	300 IR

IR, index of reactivity, a potency unit defined by the formation of a 7-mm wheal in 30 sensitized individuals during product development.(1)

#### Pharmacotherapy of Pollen-Induced Allergic Rhinitis

Several clinical practice guidelines describe pharmacologic treatments of pollen-induced allergic rhinitis/rhinoconjunctivitis.(4-8) There is general agreement that:

1. Treatment should be individualized based on symptom severity and duration, comorbidities, and patient age, preference (eg, route of administration, tolerance for adverse effects), and previous treatment history.
2. Measures to increase treatment adherence (eg, shared decision making, consideration of the patient's school or work schedule, use of a medication calendar or check-off list) are encouraged.
3. Goals of treatment are symptom reduction and improvements in functional capacity and quality of life.
4. A "step-up" (if treatment is inadequate)/"step-down" (if symptom relief is achieved with other interventions, eg, avoidance) approach to treatment is recommended.
5. Allergen avoidance is the first step of treatment but may be unrealistic for some

	<p>patients.</p> <ol style="list-style-type: none"> <li>6. Six medication classes are used to treat allergic rhinitis: H1-antihistamines (oral and intranasal), corticosteroids (oral [short-course for severe disease] and intranasal), leukotriene receptor antagonists (oral), sympathomimetic decongestants (oral and intranasal), chromones (intranasal), and the anticholinergic, ipratropium bromide (intranasal).</li> <li>7. Treatment should be symptom-specific, eg, oral antihistamines may be less effective for prominent congestion than other treatments; prominent rhinorrhea may respond to intranasal ipratropium; rhinitis-only symptoms may be treated with local (intranasal) rather than systemic (oral) therapy.</li> <li>8. For mild or intermittent symptoms, oral or nasal antihistamine may be considered first-line treatment.</li> <li>9. Newer generation (selective) oral antihistamines generally are recommended over older (nonselective) antihistamines. Patients with insomnia and pregnant women may prefer older antihistamines because of their sedating effects and longer safety history, respectively.</li> <li>10. Intranasal corticosteroids may be effective for more severe or persistent symptoms.</li> <li>11. Combination treatment (eg, oral antihistamine plus intranasal corticosteroid, intranasal antihistamine and corticosteroid, antihistamine [oral or intranasal] plus sympathomimetic [oral or short-course (<math>\leq 5</math> days to avoid rebound congestion) intranasal]) may be effective for symptoms nonresponsive to single medications.</li> <li>12. Oral sympathomimetics may cause insomnia; their use is limited in patients with certain comorbidities (eg, diabetes mellitus, unstable hypertension).</li> <li>13. Oral leukotriene receptor antagonists may reduce asthma exacerbations in patients with comorbid asthma."</li> </ol> <ul style="list-style-type: none"> <li>▪ Added Contraindications chart</li> <li>▪ Added Quantity Limits chart</li> </ul>
	Rationale section updated
	Coding section reviewed with no changes
	References updated

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