Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

Policy # 00263
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the U.S. Food and Drug Administration (FDA) approved sublingual immunotherapy (SLIT) products Ragwitek®‡, Grastek®‡, and Oralair®‡ for the treatment of pollen induced allergic rhinitis to be eligible for coverage.

Ragwitek

Patient Selection Criteria
The use of Ragwitek will be considered for coverage eligibility when ALL of the following patient selection criteria are met:

- Patient is 18-65 years of age; AND
- Ragwitek therapy is initiated 12 weeks prior to the expected onset of the short ragweed pollen season; AND
- The diagnosis of short ragweed pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions:
  - The patient has a positive skin test response to short ragweed pollen; OR
  - The patient has a positive in vitro test (i.e., a blood test for allergen-specific IgE antibodies) for short ragweed pollen; AND
- Patient is NOT currently receiving subcutaneous allergen immunotherapy; AND
- Patient must have been unable to achieve adequate symptom control with TWO products (from different classes) from the following drug classes (over the counter products are acceptable within the drug classes when taken at prescription strength doses):
  - Intranasal corticosteroids
  - Oral antihistamines
  - Intranasal antihistamines
  - Leukotriene inhibitors

Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)

Grastek

Patient Selection Criteria
The use of Grastek will be considered for coverage eligibility when ALL of the following patient selection criteria are met:
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- Patient is 5-65 years of age; AND
- Grastek therapy is initiated 12 weeks prior to the expected onset of the grass pollen season; AND
- The diagnosis of grass pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions:
  - The patient has a positive skin test response to a grass pollen from the Pooideae subfamily of grasses (this includes, but is not limited to sweet vernal, Kentucky blue grass, Timothy grass, orchard, or perennial rye grass); OR
  - The patient has a positive in vitro test (i.e., a blood test for allergen-specific immunoglobulin E [IgE] antibodies) for a grass in the Pooideae subfamily of grasses (see examples above); AND
- Patient is NOT currently receiving subcutaneous allergen immunotherapy; AND
- Patient must have been unable to achieve adequate symptom control with TWO products (from different classes) from the following drug classes (over the counter products are acceptable within the drug classes when taken at prescription strength doses):
  - Intranasal corticosteroids
  - Oral antihistamines
  - Intranasal antihistamines
  - Leukotriene inhibitors

Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.

Oralair Patient Selection Criteria

The use of Oralair will be considered for coverage eligibility when ALL of the following patient selection criteria are met:

- Patient is 10-65 years of age; AND
- Oralair therapy is initiated 16 weeks prior to the expected onset of the grass pollen season; AND
- The diagnosis of grass pollen-induced allergic rhinitis is confirmed by meeting ONE of the following conditions:
  - The patient has a positive skin test response to a grass pollen from the Pooideae subfamily of grasses (this includes, but is not limited to sweet vernal, Kentucky blue grass, Timothy grass, orchard, or perennial rye grass); OR
  - The patient has a positive in vitro test (i.e., a blood test for allergen-specific IgE antibodies) for a grass in the Pooideae subfamily of grasses (see examples above); AND
- Patient is NOT currently receiving subcutaneous allergen immunotherapy; AND
- Patient must have been unable to achieve adequate symptom control with TWO products (from different classes) from the following drug classes (over the counter products are acceptable within the drug classes when taken at prescription strength doses):
  - Intranasal corticosteroids
  - Oral antihistamines
  - Intranasal antihistamines
  - Leukotriene inhibitors

Note: This specific patient criterion is an additional Company requirement for coverage eligibility
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(and will be denied as not medically necessary** if not met.)

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers U.S. Food and Drug Administration (FDA) approved sublingual immunotherapy (SLIT) as a technique of allergy immunotherapy for all other uses not mentioned in the specific drug’s patient selection criteria to be investigational.*

Based on review of available data, the Company considers non-U.S. Food and Drug Administration (FDA) approved sublingual immunotherapy (SLIT) to be investigational.*

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of Ragwitek, Grastek, or Oralair without first attempting symptom control of allergic rhinitis with at least TWO products from the intranasal corticosteroids, oral or intranasal antihistamines, or leukotriene inhibitors (each product coming from a different class) is considered to be not medically necessary.**

Background/Overview
Sublingual immunotherapy is a potential alternative to subcutaneous immunotherapy (SCIT) for providing allergen-specific therapy. It is proposed as a more convenient alternative delivery route for treating a variety of allergic disorders. There are now three FDA approved SLITs available. These include Ragwitek, Grastek, and Oralair. Ragwitek is approved for the treatment of short ragweed pollen-induced allergic rhinitis in adults 18-65 years of age. It is doses as one 12 Amb a 1-Unit sublingual tablet daily. Ragwitek should be initiated at least 12 weeks before the expected onset of the ragweed pollen season. Grastek is approved for the treatment of grass pollen induced allergic rhinitis in persons 5-65 years of age. Grastek is dosed as one 2800 bioequivalent allergy unit (BAU) sublingual tablet daily and should be initiated at least 12 weeks prior to the start of each grass pollen season. Oralair is approved for the treatment of grass pollen induced allergic rhinitis. It has aged based dosing. For those individuals aged 10-17, the dosing is 100 IR (index of reactivity) the first day, 200 IR the second day, and 300 IR daily thereafter. Oralair is available in 100 IR and 300 IR sublingual tablets. For those individuals 18-65, Oralair is dosed at 300 IR daily.

Allergen-specific immunotherapy involves administering well-characterized allergen extracts, the potencies of which are measured and compared with a reference standard. An initial induction or build-up phase progressively increases the allergen dose; this is followed by multiple years of maintenance injections at the highest dose. Allergen-specific immunotherapy has been used to treat a variety of conditions including insect allergy, allergic rhinitis, and asthma. Subcutaneous injection of allergen-specific immunotherapy is the standard approach. Due to the inconvenience of multiple injections, particularly in children, alternative delivery routes have been investigated; of these, SLIT is the most prominent. Sublingual immunotherapy targets absorption to the sublingual and buccal mucosa. Allergen preparations used for SLIT are held under the tongue for one to several minutes and then swallowed or spit out.

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Conventional Pharmacotherapy of Pollen-Induced Allergic Rhinitis

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

- 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.
- 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.
- Goals of treatment are symptom reduction and improvements in functional capacity and quality of life.
- A “step-up” (if treatment is inadequate)/“step-down” (if symptom relief is achieved with other interventions, eg, avoidance) approach to treatment is recommended.
- Allergen avoidance is the first step of treatment but may be unrealistic for some patients.

Various medication classes are used to treat allergic rhinitis including antihistamines (oral and intranasal), intranasal corticosteroids, and leukotriene receptor antagonists. For patients with persistent or moderate to severe symptoms, intranasal glucocorticoids (e.g. fluticasone, mometasone) show good efficacy. If the nasal glucocorticoids aren’t desirable, then other products demonstrating efficacy in this group of patients are antihistamine sprays (e.g. azelastine) and leukotriene inhibitors (e.g. montelukast). It is recommended that if single therapy isn’t adequate, combination therapy should be utilized.

FDA or Other Governmental Regulatory Approval

FDA
In April 2014, the FDA approved the first sublingual allergen extract tablets for treatment of pollen-induced allergic rhinitis with or without conjunctivitis.

- On April 1, FDA approved Oralair allergen extract (Stallergenes S.A., Antony, France) for patients 10 to 65 years of age. Oralair contains freeze-dried pollen allergen extracts of 5 grasses: Kentucky Blue Grass, Orchard, Perennial Rye, Sweet Vernal, and Timothy.
- On April 11, FDA approved Grastek Timothy grass pollen (Phleum pretense) allergen extract (Merck, Whitehouse Station, NJ) for patients 5 to 65 years of age. Grastek is marketed in Europe as Grazax.
- On April 17, FDA approved Ragwitek short ragweed pollen allergen extract (Merck, Whitehouse Station, NJ) for patients 18 to 65 years of age.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

Allergic Rhinitis
At the time of the 2003 Technology Evaluation Assessment (TEC) Assessment, there were 21 published placebo-controlled trials suggesting that SLIT decreased one or more symptoms for patients with pollen or dust mite allergies. Systemic adverse effects occurred in only one study, and these were not life-threatening. However, whether SLIT improved health outcomes when compared with injection allergen-
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Specific immunotherapy (SCIT), the gold standard comparison, could not be determined from the available evidence. There were only 2 trials that directly compared SLIT with SCIT, and these had small sample sizes and were of small duration. Due to the paucity of studies comparing SCIT to SLIT and the lack of FDA-approved agents for use in SLIT, the use of SLIT for allergen immunotherapy was considered investigational.

Since the TEC Assessment, numerous placebo-controlled randomized, controlled trials (RCTs) and meta-analyses of RCTs have been published. Some of the representative meta-analyses and reviews of meta-analyses are discussed next, as well as some of the key individual RCTs.

Systematic Reviews:
Several reviews of systematic reviews have been published. In 2011, de Bot and colleagues evaluated the quality of systematic reviews and meta-analyses on SLIT for treating allergic rhinitis in children. The investigators used the Assessment of Multiple Systematic Reviews (AMSTAR) quality evaluation tool to rate the reviews. The maximum score on the AMSTAR is 11; a score of 0-4 = low quality, 5-8 = moderate quality, and 9-11 = high quality. The authors identified 10 systematic reviews. None of these were rated as high quality; 6 were rated as moderate quality, and 4 as low quality. This analysis indicates that while there are numerous systematic reviews on SLIT, the methodologic quality remains suboptimal. This research suggests that SLIT for children could be promising, but methodologic flaws preclude definitive conclusions.

In 2009, Compalati and colleagues evaluated meta-analyses of RCTs on specific immunotherapy for respiratory allergy. They identified 7 meta-analyses of placebo-controlled RCTs using well-defined inclusion criteria, allergens, doses, and outcome measurement; 5 were on SLIT and 2 were on SCIT. Regarding evidence on SLIT, this analysis corroborated that there is evidence of efficacy compared to placebo but that questions remain, in particular regarding the optimal dose. This review highlighted the lack of consistent relationships between treatment dose, duration, and clinical efficacy.

Numerous individual systematic reviews with meta-analyses have been published. In 2014, Devillier et al in France published a systematic review with meta-analyses of SLIT and pharmacotherapy for seasonal allergic rhinitis. Only well-powered (≥100 patients in the smaller treatment arm), placebo-controlled, randomized trials were included (28 pharmacotherapy trials and 10 SLIT trials; total number of patients =21,223). Studies evaluated children and adults. Because of methodologic heterogeneity across trials (eg, in symptom scales used), results from individual trials were standardized relative to placebo effects to permit meta-analysis. Pooled percentage improvements in symptom scores were: 30% for 5-grass pollen SLIT, 24% for nasal corticosteroids, 19% for timothy pollen SLIT, 17% for combination azelastinefluticasone, 15% for H1 antihistamines, and 7% for montelukast.

In 2013, Lin and colleagues conducted a comparative effectiveness review for the Agency for Healthcare Research and Quality (AHRQ) on allergen-specific therapy for treating allergic rhinoconjunctivitis and/or asthma. The authors identified 60 studies comparing SLIT to placebo or another intervention. (Studies using SCIT as the comparison intervention were evaluated separately; see section below on SLIT compared to SCIT). Over two-thirds of the studies (71%) compared SLIT to placebo, 14% compared SLIT to pharmacotherapy or rescue medication, and 15% compared SLIT to another intervention. Most of the
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studies (66%) evaluated seasonal allergens, 31% evaluated perennial allergens and the remainder addressed both types of allergens. About half of the studies used only one allergen and the other half used multiple allergens. Only 22% of the studies were rated as having a low risk of bias. Most (68%) were considered to have a moderate risk of bias and 14% to have a high risk of bias. The authors did not pool study findings because of heterogeneity among studies, i.e., in types of allergen extracts, sources of allergen extracts, doses, treatment duration, and outcome scoring systems. The review concluded that there is high-grade evidence that SLIT improves asthma symptoms compared to placebo or another intervention (13 RCTs) and moderate-grade evidence that SLIT improves rhinitis/rhinoconjunctivitis symptoms compared to placebo or another intervention (35 RCTs). There was moderate-grade evidence that SLIT improves other outcomes in this population, e.g., decreased medication use and increased quality of life. Lin and colleagues also published the findings of the systematic review in a peer-reviewed journal in 2013. The review focused on studies comparing SLIT to placebo, pharmacotherapy or another SLIT regimen and did not address SCIT. Like the AHRQ review, study findings were not pooled. The authors noted that high-quality studies are needed to determine optimal dosing strategies.

A 2013 systematic review and meta-analyses by the U.K. National Health Service evaluated the effectiveness of SCIT and SLIT for seasonal allergic rhinitis. Literature was searched to April 2011, and 28 placebo-controlled RCTs were included (17 SCIT, 11 SLIT). Statistically significant moderate effect sizes for improvements in symptom scores, medication scores, combined symptom and medication scores, and quality-of-life measures favored active treatment. However, due to substantial heterogeneity in outcome measures, standardized mean differences (SMDs) were used for meta-analyses, rendering conclusions about clinical significance of the results uncertain. Meta-analysis of 9 SLIT studies in children yielded statistically significant results for symptom scores but not for medication scores.

A 2013 systematic review with meta-analyses by researchers in China evaluated SLIT for allergic asthma. Literature was searched to May 2012, and 16 double-blind, placebo-controlled RCTs were included. Statistically significant reductions in symptom scores (SMD, 0.74, p=0.006) and medication scores (SMD=0.78, p=0.02) favored SLIT. The relative risk of adverse events (AEs) was 2.23 (p=0.01). Also in 2013, researchers from Johns Hopkins University reported a systematic review of SCIT and SLIT in pediatric asthma and rhinoconjunctivitis. Literature was searched through May 2012, and 34 RCTs were included. For SLIT, strength of evidence was high that SLIT improves asthma symptoms and moderate that SLIT improves rhinitis and conjunctivitis symptoms and decreases medication usage compared with placebo. Local adverse reactions were frequent.

A 2012 meta-analysis by Di Bona and colleagues focused on studies of immunotherapy in adults and children with seasonal allergic rhinitis. To be included in the meta-analysis, trials needed to be double-blind, placebo-controlled and evaluate natural grass pollen extracts for treating individuals with a history of grass pollen allergy. The authors identified 22 trials on SLIT versus placebo; 10 used sublingual drops and 12 used tablets. The authors also identified 14 studies on SCIT versus placebo. The investigators conducted an indirect meta-analysis, evaluating the impact of SLIT and SCIT, compared to placebo, on outcomes. The primary outcomes of the meta-analysis were reduction in symptoms and reduction in medication use. Because studies used different scoring symptoms, effect size was calculated as a SMD. Compared to placebo, both SCIT and SLIT (drops and tablets) resulted in significantly greater reductions in symptom and

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medication scores. The effect size of SCIT versus placebo for the symptom score was -0.92 (95% confidence interval [CI]: -1.26 to -0.58). The effect size for SLIT administered via drops was SMD: -0.25, 95% CI: -0.45 to -0.05 and for SLIT administered by tablets was SMD: -0.40, 95% CI: -0.54 to -0.27. Results were similar for medication use. The investigators noted the larger effect sizes in their pooled analysis of studies comparing SCIT to placebo.

A 2011 Cochrane review addressed SLIT for treating allergic conjunctivitis in adults and/or children. A total of 57 trials met inclusion criteria, and 42 of these had data available for meta-analysis. All of the trials were conducted in countries other than the United States. The primary outcome of the meta-analysis was the total ocular symptom score. In a pooled analysis of data from 36 trials with a total of 3,399 participants, there was a significantly greater reduction in total ocular symptom scores in the SLIT group compared to placebo (SMD: -0.41, 95% CI: -0.53 to -0.28, p < 0.0001). This review supports the conclusion that SLIT is moderately effective in reducing ocular symptom scores compared to placebo but that concerns about the overall quality of the evidence base remain.

In 2011, Radulovic and colleagues published a meta-analysis of double-blind, placebo-controlled RCTs on SLIT for allergic rhinitis in adults and/or children. Sixty studies met inclusion criteria, and 49 (total n = 4,589) of these had efficacy data available suitable for meta-analysis. Most of the studies (n = 23) used grass pollen; other allergens used included ragweed, house dust mites, and trees. In a pooled analysis of study findings, there was a significantly greater reduction in symptom scores with active SLIT treatment compared to placebo (SMD: -0.49, 95% CI: -0.64 to -0.34, p < 0.0001). In addition, a pooled analysis found a significantly greater reduction in medication use scores with SLIT versus placebo (SMD: -0.32, 95% CI: -0.43 to -0.21, p < 0.0001).

Individual Randomized Controlled Trials

There are dozens of RCTs in the published literature, and a comprehensive review of all RCTs is beyond the scope of this review. The key RCTs that were performed as part of the FDA approval process for specific SLIT products are reviewed next.

Information about 3 SLIT products currently FDA-approved for the treatment of pollen-induced (ie, seasonal) allergic rhinitis with or without conjunctivitis was obtained from FDA documents and prescribing information. Published RCTs are cited when these were identified. All RCTs were placebo-controlled and double-blinded. Patients had had a minimum 2-year history of allergic rhinitis or rhinoconjunctivitis and received treatment for their symptoms during the previous pollen season. Patients with mild intermittent asthma were included (approximately 16% across all trials); all other patients with asthma were excluded. Polysensitized people were included in some trials. Precoseasonal dosing, ie, commencing before the start of the allergen pollen season and continuing throughout the season, was used in all trials. The primary efficacy end point was the combined score (CS), defined as the mean of the Rhinoconjunctivitis Total Symptom Score (RTSS) and the Rescue Medication Score (RMS).

- RTSS is the sum of 6 symptom scores: sneezing, rhinorrhea, nasal itching, nasal congestion, itchy eyes, and watery eyes, each scored on a 0 (absent) to 3 (severe) scale (range, 0-18).
- RMS measures the potency of rescue medications used. For Oralair (Grastek and presumably Ragwitek), 1 point (6 points) was assigned to antihistamine, 2 points (8 points) to intranasal...
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corticosteroid, 3 points (16 points) to oral corticosteroid, and 0 points (0 points) when no rescue medication was used. Maximum score was 3 for Oralair and 36 for Grastek (and presumably Ragwitek).

- CS was calculated by combining RTSS and RMS. For Oralair, RTSS was divided by 6 and averaged with RMS (range, 0-3). For Grastek and Ragwitek, RTSS and RMS were summed (range, 0-54).

Although the CS is not validated, minimum clinically meaningful relative differences were prespecified. The relative difference (expressed as a percentage) was calculated by dividing the least squares mean difference by the within-group least squares mean of the placebo group. For Oralair (Grastek and Ragwitek), a minimum 15 percentage point relative difference favoring the active agent, with a minimum 10 percentage point lower bound of the 95% CI, was required to demonstrate clinical efficacy. Analyses were intent-to-treat.

Oralair
Five pivotal trials were submitted to FDA in support of the biologics license application (BLA) for Oralair; 4 were natural field trials (3 European, 1 U.S.), and 1 was an environmental exposure chamber trial conducted in Europe. Trial participants had a history of seasonal rhinoconjunctivitis for at least 2 grass pollen seasons. Patients in European trials also had a positive skin prick test to 5-grass pollen extract and positive serum IgE to Timothy grass; patients in U.S. trials had a positive skin prick test to Timothy grass pollen extract. Polysensitive people exposed to additional allergens during grass pollen season (eg, who lived in areas where grass pollen season overlapped with tree or ragweed pollen season) were excluded.

The pregrass pollen season treatment duration was 4 months in most trials. All studies satisfied the FDA requirement for efficacy. A sixth pivotal trial used a 2-month preseason treatment period and did not meet FDA criteria for efficacy.

TRIAL 1: PHASE 3, MULTICENTER U.S. TRIAL
Adults (N=473) age 18 to 65 years who had baseline RTSS of 12 or greater were randomized 1:1 to Oralair 300 IR or placebo. Median duration of the grass pollen season was 43 days (range, 11-70). Median average pollen count was 32 grains/m3 (range, 4-215). Mean (SD) treatment duration was 180 (14) days, 127 (11) days before and 43 (15) days during the pollen period. Treatment adherence was 99% in both groups. Relative difference in the CS was 28% (95% CI, 13 to 43) favoring Oralair.

TRIAL 2: EUROPEAN DOSE-FINDING TRIAL
Adults (N=628) age 18 to 45 years were randomized 1:1:1:1 to 1 of 3 doses of Oralair (100 IR, 300 IR, or 500 IR) or placebo. Mean (SD) duration of the pollen season was 30 (10) days. (Pollen season was defined by the first of 3 consecutive days with a grass pollen count above 30 grains/m3 to the last of 3 consecutive days with a pollen count below 30 grains/m3.) Mean treatment duration before the pollen period was 125 days. Adherence was 88% in the Oralair 300 IR group and 96% in the placebo group. Combined score was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS for 136 patients randomized to Oralair 300 IR and 148 patients randomized to placebo was 30% (95% CI, 16 to 43) favoring Oralair.
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TRIAL 3: PHASE 3, 3-YEAR EUROPEAN TRIAL
Adults (N=633) age 18 to 50 years who had baseline RTSS of 12 or greater were randomized 1:1:1 to 1 of 3 groups: Oralair 300 IR initiated 4 months or 2 months before the grass pollen season or placebo. All patients were treated for 3 consecutive seasons, and efficacy outcomes were assessed during the third pollen season. Mean treatment duration for all 3 groups was 5.5 months per year. Treatment adherence exceeded 97%. Combined score was not the original primary end point, and FDA analyzed results post hoc. For 207 patients randomized to the 4-month Oralair pretreatment group and 219 patients randomized to placebo relative difference in the CS during the third pollen season was 38% (95% CI, 22 to 55) favoring Oralair. In years 4 and 5, patients received no treatment. Relative differences in the CS did not meet FDA’s requirement for efficacy at these time points.

TRIAL 4: PHASE 3, EUROPEAN PEDIATRIC TRIAL
Children and adolescents (N=278) age 5 to 17 years (mean [SD], 11 [3] years) who had baseline RTSS of 12 or greater were randomized 1:1 to Oralair or placebo. The Oralair group was dosed 100 IR on Day 1, 200 IR on Day 2, and 300 IR on each subsequent day. Mean (SD) duration of the pollen season was 39 (16) days. Mean (SD) treatment duration before pollen season was 113 (10) days. Treatment adherence was approximately 95% in both groups. Combined score was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS was 30% (95% CI, 13 to 47) favoring Oralair.

TRIAL 5: EUROPEAN ENVIRONMENTAL EXPOSURE CHAMBER (EEC) TRIAL
Adults (N=89) age 18 to 50 years were randomized 1:1 to Oralair or placebo for 4 months. Patients had pretreatment RTSS greater than 7 after challenge in an EEC with 4 of the 5 grass pollens contained in Oralair. Patients were again allergen challenged in the EEC at month 4. Because rescue medications are not permitted in the EEC, the primary efficacy end point was the mean RTSS during the 4-hour allergen challenge. Relative difference in mean RTSS was 29% (95% CI, 14 to 44) favoring Oralair.

SAFETY
In the pooled FDA safety database, 1192 patients (13% children and adolescents) received Oralair 300IR. Adverse events that occurred only at higher doses were noted as potential safety signals.

In the pooled adult sample, the most common treatment-emergent adverse events (TEAEs) reported at higher frequencies with Oralair than with placebo were oral pruritus (33% vs 7%) and throat irritation (21% vs 4%). Other TEAEs reported in more than 2.5% of Oralair recipients and more commonly than in placebo recipients included tongue and ear pruritus; edema of the mouth, lip, tongue, or pharynx; oral paresthesia; and dyspepsia. Five percent of Oralair recipients and 1% of placebo recipients withdrew from trials due to TEAEs. Serious AEs occurred in 13 Oralair recipients (1.3%) and 5 placebo recipients (0.6%). Of those occurring in Oralair recipients, 1 episode of gastroenteritis requiring hospitalization was considered “possibly related” to Oralair, and 2 episodes of laryngopharyngeal disorders occurring within 5 minutes of receiving the first dose of Oralair were considered certainly related to Oralair. (One laryngeal edema episode responded to intravenous prednisolone, and 1 severe hypersensitivity episode, characterized by violent coughing and extreme dyspnea, responded to antihistamine, beta-2 agonist, and prednisolone.) There were no reported deaths, cases of anaphylactic shock, or use of epinephrine in the pooled adult safety database.
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The pooled child and adolescent safety database comprises 312 patients age 5 to 17 years; 45% of this sample was age 5 to 11 years (n=140). Treatment-emergent AEs reported at a higher frequency with Oralair than with placebo were oral pruritus (33% vs 4%), oral edema (13% vs 0%), and throat irritation (9% vs 5%). Other TEAEs reported in more than 2.5% of Oralair recipients were tongue, lip, and ear pruritus; tongue and lip edema; upper abdominal pain; and vomiting. As in the pooled adult sample, 5% of Oralair recipients and 1% of placebo recipients withdrew from trials due to TEAEs. No serious adverse event was considered related to Oralair. There were no reported deaths, cases of anaphylaxis, use of epinephrine, or severe laryngopharyngeal disorders in the pooled child and adolescent safety database.

Based on these findings, FDA considered Oralair 300 IR safe in patients age 10 to 65 years. “Because the small diameter of the upper airway of younger children may be more easily occluded during a laryngopharyngeal allergic reaction, and because of the low number of young children who have been studied in the pediatric clinical trial with Oralair, CBER [Center for Biologics Evaluation and Research] has limited the indication of Oralair to children 10-17 years of age. The indication for children 5-9 years of age will be re-evaluated upon completion of safety studies in these children, as mandated by PREA [Pediatric Research Equity Act].”

Grastek
Six phase 3 pivotal trials were submitted to FDA in support of the BLA for Grastek. All were natural field trials; 4 were conducted in North America and 2 in Europe. Trial participants had a history of grass pollen induced rhinitis with or without conjunctivitis, positive serum IgE to Timothy grass pollen, and baseline forced expiratory volume in 1 second (FEV1) greater than 70% of predicted value. Polysensitized patients who required treatment for non-grass pollen allergies during grass pollen season were excluded. Patients were randomized 1:1 to daily Grastek 2800 BAU or placebo. In 1 trial (Trial 3), patients continued dosing for 3 years continuously. Three of 6 studies (2480/3501 [71%] of total patients) met FDA criteria for efficacy.

TRIAL 1: U.S. AND CANADA ADULT AND PEDIATRIC TRIAL
Patients (N=1501) age 5 to 65 years were randomized. Eighty-five percent of patients were polysensitized, and 25% had mild intermittent asthma. Median preseason treatment duration was 19 weeks (range, 11-27). Mean pollen season duration was 54 days. Mean pollen count was 23 grains/m3, consistent with a relatively weak pollen season. Relative difference in the CS was 23% (95% CI, 13 to 36) favoring Grastek and meeting FDA criteria for efficacy.

TRIAL 2: U.S. AND CANADA PEDIATRIC TRIAL
Children and adolescents (N=345) age 5 to 18 years (mean, 12 years) were randomized. Eighty-nine percent of patients were polysensitized, and 26% had mild intermittent asthma. Median duration of grass pollen season was 56 days. Mean grass pollen count was 28 grains/m3. Median preseason treatment duration was 16 weeks (range, 2 days-22 weeks). Relative difference in the CS was 26% (95% CI, 10 to 38) favoring Grastek and meeting FDA criteria for efficacy.

TRIAL 3: EUROPEAN SUSTAINED EFFECT TRIAL
Adults (N=634) age 18 to 65 years were randomized. Median preseasonal treatment duration was 27 weeks (range, 16-35). Patients continued treatment during 3 consecutive grass pollen seasons. Mean (SD)
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duration of the first pollen season was 58 (14) days (range, 16-86). Combined score was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS at the end of treatment years 1, 2, and 3 were 34% (95% CI, 26 to 42), 41% (95% CI, 30 to 52), and 34% (95% CI, 21 to 46), respectively, all favoring Grastek and meeting FDA criteria for efficacy. For 257 patients who remained on-study for 1 year after discontinuing Grastek, relative difference in the CS was 27% (95% CI, 12 to 40) favoring Grastek and meeting FDA criteria for efficacy. For 241 patients who remained on-study for 2 years after discontinuing Grastek, relative difference in the CS was 23% (95% CI, 6 to 37) favoring Grastek but no longer meeting FDA criteria for efficacy.

TRIAL 4: GERMAN PEDIATRIC TRIAL
Children and adolescents (N=253) age 5 and 16 years were randomized. Patients initiated treatment with approximately 17 weeks (range, 8 to 23) before grass pollen season. Combined score was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS was 24% (95% CI, 5 to 41) favoring Grastek but failing to meet FDA criteria for efficacy.

TRIAL 5: U.S. ADULT TRIAL
Adults (N=329) age 18 to 65 years were randomized. Median preseason treatment duration was 16 weeks (range, 6-24). Combined score was not the original primary end point, and FDA analyzed results post hoc. Relative difference in the CS was 10% (95% CI, 4 to 24) favoring Grastek but failing to meet FDA criteria for efficacy. Post-hoc analyses suggested that baseline symptom scores and overlapping pollen seasons may have affected results.

TRIAL 6: U.S. AND CANADA ADULT TRIAL
Adults (N=439) age 18 to 63 years were randomized. Median preseason treatment duration was 17 weeks (range, 7-24). Relative difference in the CS was 21% (95% CI, 6 to 33) favoring Grastek but failing to meet FDA criteria for efficacy.

SAFETY
The pooled FDA safety database comprises 2389 patients who received Grastek (20% children and adolescents), 2116 (86%) of whom received Grastek 2800 BAU. The pattern of AEs observed in the FDA safety database was similar to that in post-European registration market support trials of Grazax (total N=1666).

The most common TEAEs that led to trial discontinuation were oral pruritus (n=12), oral edema (n=7), and swollen tongue (n=6) among Grastek-treated adults, and throat irritation (n=6) and oral edema (n=5) among Grastek-treated children or adolescents. One adult patient who had severe swollen tongue required treatment with epinephrine. Systemic treatment-related allergic reactions (eg, angioedema, dysphagia, cough) developed in 6 Grastek-treated adults and 1 Grastek-treated adolescent. All were considered nonserious and not severe, although epinephrine was administered for 3 of the systemic reactions; onset ranged from immediate to Day 42 of treatment. Among adults, 2 deaths were considered unrelated to Grastek. In pediatric studies, there were no reported deaths. Based on these data, FDA estimated a 0.1% to 0.5% risk of severe or serious laryngopharyngeal or systemic reactions with Grastek. Based on these
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data, FDA estimated a 0.1% to 0.5% risk of severe or serious laryngopharyngeal or systemic reactions with Grastek.

Ragwitek
FDA documents for Ragwitek currently are unavailable; 2 pivotal trials are included in the prescribing information. Both natural field trials that enrolled adults age 18 to 50 years who had ragweed pollen-induced allergic rhinitis with or without conjunctivitis, positive serum IgE to ragweed pollen, and baseline FEV1 at least 70% of predicted. Both trials met FDA criteria for efficacy.

TRIAL 1: PHASE 2/3 U.S. AND CANADA DOSE-FINDING TRIAL
Adults (N=565) were randomized 1:1:1 to daily Ragwitek 6 or 12 Amb a 1 units or placebo. (Amb a 1 units are FDA reference units; 1 Amb a 1 unit equals 1 mcg of the major short ragweed allergen, Ambrosia artemisiifolia). Patients began treatment approximately 12 weeks before short ragweed pollen season and continued treatment during and after the season, for a total treatment duration of 52 weeks. Approximately 85% of patients were polysensitized, and 22% had mild intermittent asthma. Mean ragweed season duration was 44 days. Mean pollen count was 122 grains/m3. For 187 patients in the Ragwitek 12 Amb a 1 unit group and 188 patients in the placebo group, relative difference in CS was 26% (95% CI, 14 to 38) favoring Ragwitek and meeting FDA criteria for efficacy.

TRIAL 2: TRIAL 2: PHASE 3 U.S., CANADA, AND EASTERN EUROPE TRIAL
Adults (N=784) were randomized 1:1:1:1 to Ragwitek 1.5, 6, or 12 Amb a 1 unit or placebo. Patients began treatment approximately 16 weeks before short ragweed pollen season and continued treatment during and after the season, for a total treatment duration of 52 weeks. Approximately 78% of patients were polysensitized, and 17% had mild intermittent asthma. The short ragweed pollen season lasted approximately 46 days. Mean pollen count was approximately 127 grains/m3. For 194 patients in the Ragwitek 12 Amb a 1 unit group and 198 patients in the placebo group, relative difference in CS was 27% (95% CI, 14 to 39) favoring Ragwitek and meeting FDA criteria for efficacy.

SAFETY
The pooled FDA safety database comprises 1057 adults who received at least 1 dose of Ragwitek. The most common TEAEs in this group were throat irritation (17% vs 3% in the placebo group), oral pruritus (11% vs 2%), ear pruritus (10% vs 1%), and oral paresthesia (10% vs 4%). Four percent and 0.8% of Ragwitek-treated and placebo-treated patients, respectively, discontinued treatment due to adverse reactions. Among Ragwitek-treated patients, the most common adverse reactions that led to study discontinuation were oral edema, swollen tongue, and dysphagia.

In trial 1 and trial 2 (total N=962 Ragwitek-treated patients), no deaths, systemic allergic reactions, or life-threatening events occurred. Treatment-emergent AEs tended to occur early in the treatment course (within the first week or weeks). Most (82% in trial 1 and 96% in trial 2) TEAEs were mild to moderate in severity. In trial 2, the most frequently reported adverse event leading to discontinuation was swollen tongue (n=10), all assessed as mild or moderate in severity. One patient required epinephrine for what was considered a progression of treatment-related local reactions.
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House Dust Mite Specific Allergy
Several placebo-controlled RCTs published in 2013 and 2014 assessed house dust mite (HDM)-SLIT in children and adults sensitized to HDM (primarily Dermatophagoides species) who have rhinitis and/or asthma. HDM-SLIT generally showed statistically significant reductions in rhinitis symptom scores in these trials, with reductions of approximately 20% in 1 study, and a statistically significant decrease in daily dose of inhaled corticosteroid in HDM-sensitized patients with mild-to-moderate asthma.

In 2014, Gendelman and Lang published a systematic review of HDM-SLIT in atop dermatitis. Five studies (N=344) were identified, but low methodologic quality limited conclusions that could be drawn. In 2013, Bae et al published a systematic review and meta-analysis of HDM immunotherapy for children and adults with HDM-induced atop dermatitis. Literature was searched through November 2012, and 8 placebo-controlled RCTs were included (6 SCIT [N=307], 2 SLIT [N=90]). Using a dichotomous variable for treatment success, defined as the proportion of patients whose condition improved as assessed by investigators or patients, regardless of evaluation method used, the odds ratio was 5.35 (95% CI, 1.61 to 17.77). The significance of this finding is uncertain given the heterogeneity of treatments administered and use of a nonstandard outcome measure.

Food Allergy
Several authors have examined the role of SLIT in desensitizing people with food allergies. Two studies suggested that SLIT may be safely used to desensitize children and adolescents with peanut allergy in comparison with oral immunotherapy49 or placebo, but these studies were small (total N=90) and results are preliminary. Three-year follow-up of a placebo-controlled RCT50 showed a high rate of dropout (>50%) and sustained responsiveness in only 4 (11%) of 37 SLIT-treated patients. A 2014 systematic review of the literature through September 2012 identified 5 randomized trials of SLIT in patients with food allergies, 4 of which showed symptom improvement compared with placebo. However, all trials were considered low quality; for example, most did not include symptom assessments off treatment. In a subsequently published, small, double-blind RCT, Narisety et al (2014) showed greater efficacy of oral immunotherapy compared with SLIT in 21 patients with peanut allergy.

In 2014, Romantsik et al reported on a Cochrane review of oral immunotherapy and SLIT for egg allergy. No RCTs of SLIT were identified through November 2013.

Sublingual Immunotherapy Compared to Subcutaneous Immunotherapy
Few published randomized trials have compared SLIT and SCIT head-to-head. A 2012 review by Bahceciler and Galip listed 8 RCTs comparing SLIT and SCIT. Sample sizes in individual studies ranged from 20 to 58 participants. Three of the studies were published in the 1990s and the other 5 were published between 2004 and 2012. Pipet and colleagues reported that none of the studies from the 1990s found a statistically significant difference in efficacy between the 2 routes of administration.

Allergic Rhinoconjunctivitis and Asthma
Two indirect comparative effectiveness analyses published in 2014 and 2015 reached similar conclusions regarding relative efficacy of SLIT and SCIT for grass pollen allergies. Both studies showed comparable
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reductions in allergic rhinitis symptoms with SLIT and SCIT, and 1 study showed comparable reductions in medication use. Both studies found evidence for publication bias.

The 2013 AHRQ comparative effectiveness review, discussed above, identified 8 RCTs comparing sublingual and SCIT. The report stated that only 1 study was considered to be at low risk of bias and most of the studies had biases related to improper concealment of allocation to the interventions, unblinded interventions and incomplete reporting of missing data. The authors were unable to pool study findings because of heterogeneity. Regarding the question of comparative effectiveness of SLIT and SCIT, the report concluded that there was low-grade evidence that SCIT is more effective than SLIT at controlling allergy symptoms and dust mite allergy symptoms. Moreover, the report concluded that there was moderate-grade evidence that SCIT provides better symptom control for allergic nasal and/or eye symptoms than SLIT.

Also in 2013, Dretzke and colleagues published a systematic review that included an indirect comparison of SCIT and SLIT using data from placebo-controlled trials. Several outcomes were examined. For symptom score, the overall standardized score difference (SSD) was 0.35 (95% CI: 0.13 to 0.59), a statistically significant result that favored SCIT. The overall SSD for medication score was 0.27 (95% CI: 0.03 to 0.53) which was statistically significant in favor of SCIT. The authors noted that there was substantial heterogeneity among trials and that it is difficult to draw conclusions about the clinical significance of the difference in outcomes between SCIT and SLIT.

A 2013 systematic review by researchers at Johns Hopkins University reviewed SCIT and SLIT for pediatric asthma and rhinoconjunctivitis. Three head-to-head studies published before June 2012 were identified. Low strength of evidence supported SCIT over SLIT for improving asthma and rhinitis symptoms and for decreasing medication usage. This same group subsequently reviewed head-to-head RCTs comparing SCIT and SLIT in adults and children. Literature was searched through November 2012, and 8 RCTs were included. Moderate-grade evidence supported the greater effectiveness of SCIT compared with SLIT for improving nasal and eye symptoms. Low-grade evidence supported greater effectiveness of SCIT compared with SLIT for improving asthma symptoms and combined rhinitis symptom and medication scores.

In 2011, Sieber and colleagues published a meta-analysis of individual patient data from 4 observational studies on treatment of allergic rhinitis. A total of 665 patients were treated with SLIT and 182 with SCIT. The median rhinitis symptom score decreased from 3.00 to 2.00 (range 1.00 to 4.00) in both treatment groups; p < 0.001 for changes within-group. The median conjunctivitis symptom score decreased from 2.00 to 1.00 (range 0.00-3.00) in each group; p < 0.001 for changes within-group. In addition, the median asthma symptom score decreased from 3.00 to 2.00 (range 1.00-4.00) in each group; p < 0.001 for changes within-group. There were no significant differences in symptom scores when the SLIT group was compared to the SCIT group.

In terms of the relative safety of SCIT and SLIT, the 2009 Pipet review cites reports of fatalities after SCIT, although subsequent examination of 13 deaths occurring between 1992 and 1996 suggested that unstable asthma was a major risk factor. It is generally believed that SCIT is safe when performed with proper patient

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selection and established security principles. A 2012 review of SLIT for allergic rhinitis stated that no SLIT-related fatalities have been reported. There may be a larger number of mild-to-moderate adverse effects with SLIT than SCIT. The 2012 meta-analysis by Di Bona and colleagues included 22 placebo-controlled studies on SLIT and 14 on SCIT. The investigators identified a total of 960 AEs in patients who received SCIT (0.86 AE per patient) and 4,046 AEs in patients who received SLIT (2.13 AEs per patient). Most of the AEs were modest in severity. The authors did not report the total number of serious AEs. However, they stated that there were 12 episodes of anaphylaxis requiring epinephrine treatment in patients treated with SCIT and only 1 in patients treated with SLIT. There were also 2 reported episodes of anaphylaxis in patients treated with placebo in the SCIT studies.

A 2013 systematic review and meta-analyses by the U.K. National Health Service reviewed studies of seasonal allergic rhinitis published before April 2011. AEs were common with both SCIT and SLIT, but most were local reactions at the point of administration and resolved spontaneously without treatment. Systemic reactions were less common, occurring with approximately 4% of injections for SCIT, and most were mild or moderate in severity. Of all systemic reactions, 19% were considered severe in patients taking SCIT compared with 2% in patients taking SLIT. Three percent of patients in both group discontinued treatment due to AEs. No deaths occurred in any of the trials.

HDM-Specific Allergy
Three RCTs published in 2010 and 2011 compared the efficacy of dust-mite specific SLIT and SCIT and were published by investigators in Turkey. Similar to older studies, none found statistically significant differences between treatment with SLIT and SCIT in overall reduction of symptoms or medication use. For example, Eifan et al published findings on 48 children who had asthma or rhinitis and had been sensitized to HDMs. Participants were randomized to receive treatment with SLIT (n=16), SCIT (n=16), or usual pharmacotherapy alone (n=16). There was no significant difference in efficacy between the SLIT and SCIT groups. Compared with pharmacotherapy alone, both immunotherapy groups demonstrated significant reduction in rhinitis and asthma symptom scores and medication use scores.

A small 2013 RCT compared HDM-SCIT and HDM-SLIT in children with rhinitis and asthma who were monosensitized to HDM. Thirty children were randomized to receive 1 or 2 years of SCIT or SLIT. Symptom scores were improved after 1 year of SCIT.

Ongoing Clinical Trials
A search of the online database, ClinicalTrials.gov, found 9 active trials of SLIT for allergies. One of the trials compares SLIT with SCIT using a double placebo design in patients with seasonal allergic rhinitis. Several studies investigate HDM SLIT, and 1 (NCT02052934) investigates SLIT for enterotoxigenic Escherichia Coli (ETEC). Long-Term Effects of Sublingual Grass Therapy (NCT01335139): This double-blind trial is randomizing adults with seasonal allergic rhinitis to treatment with SCIT and placebo SLIT or SLIT and placebo SCIT. The primary outcome is nasal response to an allergen challenge and secondary outcomes include use of rescue medication, quality of life and hay fever severity.
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Summary
Sublingual immunotherapy is a potential alternative to SCIT for providing allergen-specific therapy. Three new sublingual pollen extracts (1 multiple-allergen product [Oralair], 2 single-allergen products [Grastek and Ragwitek]) were FDA-approved for treatment of pollen-induced allergic rhinitis with or without conjunctivitis. Large, well-designed, RCTs supporting the marketing applications for these products provide consistent evidence of efficacy and safety. Although trials were placebo-controlled, rather than SCIT-controlled, minimum clinically important criteria for demonstrating efficacy were prespecified and were met in most studies. Patients in these trials had received previous treatment for their pollen-induced rhinitis or rhinoconjunctivitis symptoms. Therefore, SLIT using Oralair, Grastek, or Ragwitek may be considered medically necessary in patients with pollen-induced allergic rhinitis or rhinoconjunctivitis who have symptoms uncontrolled by pharmacologic treatment.

Sublingual immunotherapy is being investigated for other allergies, eg, other seasonal allergies, food allergies, and in patients sensitized to HDMs. Current evidence is insufficient to form any conclusion about the use of SLIT for these indications, and FDA-approved allergy extracts for these uses are lacking. Therefore, SLIT is investigational for all other uses.

Some evidence from clinical trials has been published on the comparative effectiveness of SLIT versus SCIT, but the quantity and quality of evidence is less than that for efficacy versus placebo. Several 2013 systematic reviews tended to find better outcomes with SCIT than with SLIT, but findings were inconclusive due to small numbers of trials and variability in study design. There also are insufficient data to draw firm conclusions about the relative safety of SLIT versus SCIT. A 2012 meta-analysis of placebo controlled trials suggested that there may be more mild-to-moderate AEs with SLIT than with SCIT, but there are data only on a few serious AEs.

References

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06/03/2010 Medical Policy Committee approval
06/16/2010 Medical Policy Implementation Committee approval. New policy.
05/05/2011 Medical Policy Committee review
05/18/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2012 Medical Policy Committee review
05/16/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013 Medical Policy Committee review
05/22/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/02/2014 Medical Policy Committee review
10/15/2014 Medical Policy Implementation Committee approval. Policy coverage and body extensively revised to meet Pharmacy Department requirements.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/08/2015 Medical Policy Committee review
10/21/2015 Medical Policy Implementation Committee approval. Updated rationale section (systematic reviews, house dust mite specific allergy, food allergy, SLIT vs. SCIT). No coverage changes.
10/06/2016 Medical Policy Committee review
10/19/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Next Scheduled Review Date: 10/2017

Coding

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  B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
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