Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Review: Immunotherapy Desensitization, non-injectable

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Purpose for Class Review:
Evaluate new evidence for the safety and efficacy of oral peanut allergen powder (PALFORZIA) published since the 2021 Pharmacy and Therapeutics (P & T) Committee review of this product. Review evidence for the safety and efficacy of sublingual immunotherapy (SLIT) tablets in preventing allergic rhinitis associated with an allergy to grass, ragweed, or dust mites. Develop an Oregon Health Plan (OHP) policy to assess medical appropriateness in children and adolescents up the age of 21 years for non-injectable desensitization immunotherapies that are not funded under OHP under Medicaid provisions but may be covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit. In addition, develop a policy for use of desensitization immunotherapies that are funded in the OHP population.

Plain Language Summary:
- Peanut allergies can cause a range of mild to severe symptoms when people are exposed to or consume peanuts. Mild symptoms include tingling of the tongue and lips and can progress to severe, life-threatening symptoms such as tongue swelling or difficulty breathing.
- PALFORZIA capsules and packets received Food and Drug Administration approval in 2020 for patients aged 4 to 17 years with a history of a serious reaction to peanuts and confirmed peanut allergy through testing. This product reduces the severity of symptoms someone with a peanut allergy will experience when exposed to peanuts.
- People who are allergic to grass, ragweed, or dust mites may develop long lasting hay fever symptoms including a runny nose, sneezing and red, itchy eyes. Injecting small amounts of the agents that trigger the allergy, also known as allergy shots, has proven to be an effective way to develop tolerance and reduce these symptoms over time. This is known as desensitization. Allergy shots must be given in a doctor's office so that rare, but serious side effects can be immediately treated, if they occur.
- Tablets that are dissolved under the tongue (known as sublingual tablets) are another treatment option. These tablets can be taken at home and have less risk of serious side effects than allergy shots. Four different products are approved in the United States to help prevent the severity and frequency of allergy symptoms when exposed to grass, ragweed, or dust mites. GRASTEK AND ORALAIR are used in people with a grass allergy. RAGWITEK is approved for people with allergy to ragweed and ODACTRA is used in people with a dust mite allergy.
- Some people notice mild swelling or itching of the lips when first starting allergy therapy. In most cases, these symptoms will decrease over time as people continue taking the tablets. If serious symptoms develop, such as difficulty breathing or throat swelling, medical attention should be immediately received.
- Providers must explain to the Oregon Health Authority why someone needs sublingual immunotherapy before Medicaid will pay for it. This process is called prior authorization.

Author: Deanna Moretz, PharmD, BCPS

Research Questions:

1. Is there new evidence or guidance for the prevention of serious reactions to peanuts using oral powder (PALFORZIA) in people with an allergy to peanuts?
2. What is the evidence for the efficacy of SLIT tablets in the treatment of allergic rhinitis (with or without conjunctivitis) caused by hypersensitivity to grass, ragweed, or dust mites?
3. What is the evidence for the safety of SLIT tablets in the treatment of allergic rhinitis (with or without conjunctivitis) caused by hypersensitivity to grass, ragweed, or dust mites?
4. Are there subpopulations (based on age, gender, ethnicity, or comorbidities) more at risk for efficacy or harm for treatment of allergic rhinitis with immunotherapy?

Conclusions:

Prevention Of Peanut Allergy

- The National Institute for Health And Care Excellence (NICE) published recommendations in February 2022 to guide the utilization of PALFORZIA.[1] Based on clinical trial evidence that shows PALFORZIA improves tolerance to peanut protein compared with placebo in a food challenge test, PALFORZIA is recommended as an option to treat peanut allergy in children aged 4 to 17 years.[1]

Evidence Summary for the Safety And Efficacy Of Sublingual Immunotherapy

- Evidence for the safety and efficacy of SLIT tablets in the treatment of allergic rhinitis and/or conjunctivitis is evaluated in 5 high-quality systematic reviews.[2-6] Three guidelines provide recommendations for the use of SLIT tablets in allergic rhinitis.[7-9] Data for safety of SLIT tablets in patients with asthma and allergic rhinitis are summarized in 3 systematic reviews,[10-12] and recommendations are presented in 2 guidelines.[13,14]

Sublingual Immunotherapy in Patients with Allergic Rhinitis or Conjunctivitis

- A 2010 Cochrane systematic review evaluated the safety and efficacy of SLIT tablets and oral immunotherapy drops for allergic rhinitis with or without conjunctivitis in children and adults.[2] Primary outcomes included symptom scores and use of relevant rescue medications (antihistamines and nasal corticosteroids).[2] Moderate-quality evidence showed a significant reduction in symptoms (standardized mean difference [SMD] -0.49; 95% confidence interval [CI] -0.64 to -0.34, P<0.00001) and rescue medication requirements (SMD -0.32; 95% CI -0.43 to -0.21, P<0.00001) in participants receiving SLIT compared to placebo.[2] Patients reported improved quality of life when allergic rhinitis symptoms such as red, itchy eyes, runny nose and sneezing were alleviated. None of the trials included in this review reported severe systemic reactions or anaphylaxis, and none of the reported systemic reactions required the use of epinephrine.[2]
- A 2011 Cochrane systematic review and meta-analysis of double-blind, placebo-controlled RCTs evaluated the efficacy of SLIT tablets and oral immunotherapy drops for treating allergic conjunctivitis in patients with or without rhinitis.[3] Moderate-quality evidence from 36 RCTs (n=3,399) showed SLIT significantly reduced total ocular symptom scores (SMD, -0.41; 95% CI, -0.53 to -0.28; P<0.00001) when compared with placebo in the targeted population.[3] Individual ocular symptoms scores showed a significant reduction with SLIT versus placebo in patients with allergic conjunctivitis (moderate-quality evidence for all outcomes) for red eyes (SMD, -0.34; 95% CI, -0.45 to -0.22; P<0.00001), itchy eyes (SMD, -0.31; 95% CI, -0.42 to -0.20; P<0.00001) and watery eyes (SMD, -0.23; 95% CI, -0.34 to -0.11; P=0.0001).[3]
- A 2013 Canadian Agency for Drugs and Technologies (CADTH) report evaluated evidence for the safety and efficacy of 5-grass pollen allergen extract (ORALAIR) in managing allergic rhinitis.[7] The 5-grass pollen extract was shown to be superior to placebo for alleviating allergic rhinitis symptoms in 4 double-blind randomized controlled trials (RCTs).[7] Most adverse events reported in the 4 RCTs were mild or moderate in severity.[7] Based on this report, the Canadian Drug Expert Committee (CDEC) recommended the 5-grass pollen allergen extract be listed on the Canadian drug formulary for the seasonal treatment of grass pollen allergic rhinitis if: 1) patients have not adequately responded to, or tolerated, conventional pharmacotherapy and 2) treatment is initiated by an allergist.[7]

- A 2015 CADTH systematic review evaluated evidence for the safety and efficacy of timothy grass allergenic extract (GRASTEK) in patients with allergic rhinitis, with or without conjunctivitis.[4] Seasonal treatment with timothy grass extract sublingually once daily resulted in statistically lower symptom scores and rescue medication use over one grass pollen season compared with placebo.[4] However, the clinical importance of the observed between-treatment differences in symptom and medication scores was uncertain.[4] Based on the conclusions of this systematic review, the CDEC recommended timothy grass allergenic extract not be listed on the Canadian drug formulary.[4]
- A 2020 systematic review and meta-analysis assessed the efficacy of SLIT tablets in the management of grass pollen-induced allergic rhinitis in adults.[5] The primary outcome measure was change in a 4-point symptom score (0=no symptoms and 3=severe symptoms) based on the World Allergy Organization (WAO) guidance in which 6 symptoms were evaluated (nasal obstruction, sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and tearing).[5] In the meta-analysis of 5 studies, SLIT reduced symptoms compared with placebo (SMD, -0.36; 95% CI, -0.46 to -0.25; P<0.00001; moderate-quality evidence).[5] The studies reported only mild, local adverse events related to treatment.[5] Oral pruritus and dyspepsia were the most commonly reported adverse events.[5]
- A 2017 systematic review assessed the effectiveness and safety of allergen immunotherapy in the management of allergic rhinoconjunctivitis.[6] The European Academy of Allergy and Clinical Immunology (EAACI) taskforce based their guideline recommendations on the findings from this systematic review.[8] The primary outcome was effectiveness, as assessed by symptom resolution and rescue medication scores.[6] Pooled data from 58 subcutaneous immunotherapy (SCIT) and SLIT randomized controlled trials (RCTs) suggested a moderate effect on short term (less than 2 years) improvement in symptom scores in favor of immunotherapy versus placebo (SMD, -0.53; 95% CI, -0.63 to -0.42; p<0.0001; low-quality evidence).[6] Data pooled from 15 RCTs showed a small-to-moderate effect in favor of immunotherapy versus placebo on the combined endpoint of symptom and rescue medication scores (SMD, −0.49; 95% CI, −0.69 to −0.30; p<0.001; low-quality evidence).[6] Safety data from 51 SCIT and SLIT RCTs were pooled to provide an overall risk ratio (RR) of experiencing an adverse event of 1.64 with SLIT treatment (95% CI, 1.43 to 1.89; p=0.00; low-quality evidence).[6]
- A 2017 guideline published by EAACI provides recommendations for the use of allergen immunotherapy to manage allergic rhinoconjunctivitis in adults and children.[8] Sublingual immunotherapy with grass pollen tablets or house dust mite (HDM) tablets is recommended to manage allergic rhinitis for short-term and long-term benefit (i.e., 1 year after cessation of treatment) in adults and children (Grade of Recommendation: A; Evidence Level: 1).[8]
- An allergen immunotherapy practice parameter was published by a joint task force of American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) members in 2017.[9] At the time of writing, 3 Food and Drug Administration (FDA)-approved SLIT tablets were available to alleviate allergic rhinitis symptoms associated with ragweed, timothy pollen, and 5-grass pollen.[9] Only FDA-approved SLIT tablets are recommended in this guidance for the treatment of allergic rhinitis and/or rhinoconjunctivitis and not for any other related or unrelated condition. (Strength of Recommendation: Strong; Evidence: A/B).[9]

Safety And Efficacy Of Sublingual Immunotherapy In Patients With Allergic Rhinitis And Asthma

- A 2018 Agency for Healthcare Research and Quality (AHRQ) review evaluated the efficacy and safety of immunotherapy for treating allergic asthma.[10] The majority of studies that met inclusion criteria included patients with mild to moderate asthma and dust mite allergies.[10] Moderate-quality evidence shows decreased use of long-term asthma control medications (specifically inhaled corticosteroids [ICS]) and improvements in forced expiratory volume in one second (FEV_1) with SLIT therapy.[10] Low-quality evidence shows SLIT administration may decrease quick-relief medication use (i.e., short-acting beta agonists [SABAs]), and may improve quality of life.[10] Local and systemic allergic reactions were common but infrequently required changes in immunotherapy treatment.[10] Life-threatening reactions were not commonly reported, with 3 case reports of anaphylaxis and no deaths (moderate-quality evidence) reported.[10]
- A 2020 Cochrane review updated a 2015 review that assessed safety and efficacy of SLIT compared with placebo in adults and children with asthma.[11] Participants were recruited with mild or intermittent asthma, often with comorbid allergic rhinitis.[11] Primary outcomes for this review included asthma exacerbations requiring a visit to the emergency department (ED) or admission to hospital, and all-cause serious adverse events (SAEs). The pooled estimate

from 2 small studies (n=108) suggests the evidence for SLIT in reducing asthma exacerbations compared with placebo or usual care is very uncertain (odds ratio [OR] = 0.35, 95% CI 0.10 to 1.20; very low-quality evidence).[11] An analysis by risk difference (RD) suggests no more than 1 in 100 people with mild or intermittent asthma taking SLIT will have a serious adverse event (RD, −0.0004, 95% CI, −0.0072 to 0.0064; p=0.09; moderate-quality evidence).[11] The findings from this review suggests the role of SLIT for people with asthma requires further evaluation.[11]

- A 2022 systematic review evaluated the efficacy and safety of HDM SLIT tablets in people with allergic asthma.[12] Seven RCTs, 5 studies in allergic asthma (4 in adults and 1 in children), and 2 studies in patients with allergic rhinitis and asthma, met inclusion criteria.[12] Moderate-to high-quality evidence from 3 RCTs showed that dust mite SLIT effectively improved ICS use in adults and adolescents with asthma, but no treatment effect was observed in a group of pediatric patients with very mild asthma.[12] Two RCTs evaluated the efficacy of dust mite SLIT tablets in reducing asthma exacerbations in patients with partially controlled moderate-to-severe asthma, and their results were inconsistent.[12] One study in children with mild-to-moderate asthma found no benefit of SLIT.[12] The percentage of participants reporting at least 1 adverse effect ranged from 39% to 96.4% in the HDM tablet-treated group.[12] Among all adverse effects, local adverse effects were the most common.[12] Of the 7 included studies, only one RCT reported 7 subjects treated with epinephrine due to adverse effects.[12] Three subjects used epinephrine for 12 standard quality (SQ)-HDM-related adverse effects. The other 4 epinephrine administrations were considered unrelated to 12 SQ-HDM, as 3 were related to food/environmental allergies, and 1 (in the placebo group) was related to complex allergy symptoms.[12]
- In 2017 the EAACI taskforce published a guideline to provide recommendations for the use of allergen immunotherapy to prevent comorbidities in patients with allergic rhinitis.[13] In children and adolescents with allergic rhinitis and grass pollen allergy, who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-year course of SCIT or SLIT can be recommended for the short-term (i.e., less than 2 years) prevention of asthma in addition to the sustained effect on allergic rhinitis symptoms and medication use. (Grade of Recommendation: A; Level of Evidence: 1).[13] This is a moderate recommendation based on consistent significant results from 2 moderate and 2 high risk of bias (ROB) RCTs and some controlled before and after studies.[13]
- In 2019 the EAACI taskforce developed a clinical practice guideline providing evidence-based recommendations for the use of HDM allergic immunotherapy as add-on treatment for HDM-driven allergic asthma.[14] To date, only immunotherapy with HDM SLIT tablets has demonstrated a robust effect in adults for critical end points (exacerbations, asthma control, and safety) in 3 RCTs funded by the manufacturer.[14] The EEACI taskforce recommends HDM SLIT tablets as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma to decrease exacerbations and to improve asthma control (conditional recommendation; moderate-quality evidence).[14] The patient's asthma status should be carefully evaluated prior to initiating HDM SLIT-tablets and assessed regularly during immunotherapy treatment.[14]

Recommendations:

- Add GRASTEK, ORALAIR, RAGWITEK, AND ODACTRA sublingual tablets to the Preferred Drug List (PDL) class "immunotherapy desensitization, non-injectable" as non-preferred medications.
- Develop prior authorization (PA) criteria to provide an approval route for unfunded conditions that will be covered under the EPSDT program and to ensure appropriate utilization of SLIT tablets in people with allergic rhinitis caused by exposure to grass, pollen, or dust mite allergens that is complicated by a comorbidity such as asthma.
- No PDL changes recommended after evaluation of costs in the executive session.

Background:

Peanut Allergy Desensitization

Peanut allergy is estimated to affect approximately 2% of children,[15] and is an important cause of food allergy-related mortality.[16] Currently, the only Food and Drug Administration (FDA)-approved immunotherapy to mitigate severe reactions to peanut exposure is oral peanut allergen powder (PALFORZIA). This product received FDA-approval in 2020 for use in patients aged 4 through 17 years with a confirmed diagnosis of peanut allergy. The Oregon Health Plan (OHP) prioritized list includes funding for peanut allergy treatment in Guideline Note 203.[17] Funding for pharmaceutical treatment with medications to reduce severity are included on line 123 when specified criteria are met.[17] Peanut allergy must be diagnosed clinically based on history of serious reaction or anaphylaxis, with skin or serologic testing, and with a double-blind, placebo-controlled food challenge. Any treatment must be by, or in consultation with, an allergist or immunologist.[17] The P & T Committee reviewed the safety and efficacy of PALFORZIA at the February 2021 meeting. Recommendations to create a Preferred Drug List (PDL) class titled "Immunotherapy Desensitization" and designate PALFORZIA (powder capsules/packet) as non-preferred with PA criteria (**Appendix 3**) to ensure appropriate use were approved by the P & T Committee.

Pollen and Dust Mite Desensitization

Allergic rhinitis is divided into seasonal allergic rhinitis, which can be triggered by exposure to grass and ragweed pollens, and perennial allergic rhinitis in which dust mites are the primary trigger.[18] It is characterized by a type I hypersensitivity response, in which repeated allergen exposure results in histamine release by means of mast cell degranulation.[19] Symptoms of allergic rhinitis include sneezing, nasal congestion, nasal and oral pruritus, and rhinorrhea. Associated conditions, such as conjunctivitis, asthma and atopic dermatitis may contribute to the allergic response.[20] Symptom severity varies from mild to severe, with nasal congestion having the largest impact on quality of life.[20] Allergic rhinitis affects about 10% to 30% of adults and 40% of children worldwide.[21] Rhinitis is also a significant cause of decreased work productivity and absenteeism and school performance.[22] Allergic rhinitis can, by itself, introduce significant inattention, impairment of cognition, and decreased daytime school performance.[22] Quality of life issues associated with rhinitis include disturbed sleep; daytime somnolence and fatigue; irritability; depression; impairment of physical and social functioning; and attention, learning, and memory deficits.[22]

Mild-to-moderate allergic rhinitis is managed with intranasal antihistamines, while moderate-to-severe cases require intranasal corticosteroid therapy. The AAAAI 2020 rhinitis guideline suggests clinicians offer intranasal antihistamines as an initial treatment option for patients with seasonal allergic rhinitis (strength of recommendation: strong; high-quality evidence).[22] When selecting monotherapy for persistent allergic rhinitis, intranasal corticosteroids are the preferred medication (strength of recommendation: strong; high-quality evidence).[22] For the initial treatment of moderate- to severe-seasonal allergic rhinitis in patients 15 years of age and older, the clinician should use an intranasal corticosteroid over a leukotriene antagonist (strength of recommendation: strong; high-quality evidence).[22] Initial treatment with intranasal corticosteroid monotherapy in patients 12 years of age and older with symptoms of seasonal allergic rhinitis is preferred over combination therapy with an oral antihistamine and an intranasal corticosteroid (strength of recommendation: strong; moderate-quality evidence).[22]

Seasonal and perennial allergic rhinitis, are not currently funded by OHP, unless these conditions complicate a co-morbidity such as asthma. The nasal allergy inhalers were reviewed by the P & T Committee at the August 2022 meeting. The Committee approved a recommendation to remove PA criteria for preferred intranasal allergy products in children and adolescents with rhinitis up to their 21st birthday to enhance the ability to grow, develop, or participate in school per the EPSDT Medicaid benefit. All intranasal products require PA for OHP funded indications. Fluticasone propionate is the only preferred drug on the preferred drug list (PDL) and all other intranasal corticosteroids are non-preferred and use for OHP-funded conditions is restricted by PA criteria. Non-steroidal intranasal allergy drugs are non-preferred due to lack of evidence for OHP-funded conditions.

Immunotherapy is an alternative therapy for treatment-resistant allergic rhinitis. Allergen immunotherapy involves the repeated administration of allergen extracts to individuals who have symptoms upon allergen exposure and immunoglobulin E (IgE)-sensitization to environmental triggers.[23] Allergen immunotherapy is effective in patients with allergic rhinitis and, unlike antihistamines, leukotriene antagonists, or intranasal corticosteroid nasal sprays, has been shown to modify the underlying immunologic cause of the allergic response.[24] The OHP prioritized list includes funding guidance for allergen testing and treatment in Guideline Note 156.[17] Testing and treatment are funded when the following criteria are met: 1) the allergy affects a diagnosis that appears above the current funding line (e.g., asthma, anaphylactic shock, occupational lung disease, immune disorder); 2) symptoms are not adequately controlled by empiric conservative therapy; 3) testing correlates to the member's history, risk of exposure, and physical findings; and 4) test technique and/or tested allergens have proven efficacy demonstrated through scientifically valid medical studies published in peer-reviewed literature.[17] Treatment is funded when a skin test and/or serologic evidence of IgE-mediated antibody to a potent extract of the allergen has been obtained and hypersensitivity to the allergen cannot be adequately managed by allergen avoidance or appropriate medication therapy.[17]

For many years, subcutaneous allergen immunotherapy was the gold standard to manage allergic rhinitis induced by seasonal exposure to pollen and for perennial disease in patients with dust mite allergy.[24] Due to the risk of severe systemic reactions, SCIT must be administered by a healthcare provider.[18] To maintain immunity, the injections must be administered every 2 to 4 weeks. Sublingual immunotherapy emerged in 2014 as an effective and safe alternative to SCIT due to less risk of systemic adverse events and ease of self-administration via a tablet taken once daily.[24] Sublingual immunotherapy products are available as dissolvable tablets or liquid extracts. Liquid products are used in other parts of the world, but are not approved by the FDA. Sublingual formulations may still result in minor local side effects, such as oropharyngeal swelling and pruritus. Sublingual tablets are FDA-approved to mitigate allergic rhinitis (with or without conjunctivitis) induced by exposure to certain types of pollen or dust mites.[25-28] The allergy must be confirmed by a positive skin test or in vitro testing for pollen-specific IgE antibodies prior to initiating therapy.[25-28] The 4 FDA-approved SLIT products are described in **Table 1**.

Table 1. FDA-Approved Sublingual Immunotherapy Tablets

Product Name (BRAND NAME)	How Supplied	Approved Age Range	When to Initiate Therapy	Common Adverse Events	Notes
Timothy Grass Pollen Allergen Extract (GRASTEK)[25]	2,800 BAU tablet	5 to 65 yo	Start 12 weeks prior to expected onset of grass season and continue through grass season.	Oral, ear and tongue pruritus, throat irritation, and mouth edema	Trials did not allow people with moderate or severe asthma or those requiring daily controller therapy.
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergy Extract (ORALAIR)[27]	100 IR and 300 IR tablets		Start 16 weeks prior to expected onset of respective grass season and continue through grass season.	Oral, ear, and tongue pruritus, throat irritation, mouth edema, cough, oropharyngeal pain, tonsillitis, and oral paresthesias	
Short Ragweed Pollen Allergen Extract (RAGWITEK)[28]	12 Amb a 1-Unit tablet		Start 12 weeks prior to expected onset of ragweed season and continue through ragweed season.	Oral, ear, and tongue pruritus, throat irritation, and oral paresthesias	Trials allowed patients who required low doses of inhaled glucocorticoids to treat asthma.

House Dust Mite Allergen Extract (ODACTRA)[26]	12 SQ-HDM tablet	12 to 65 yo	Start anytime and continue daily administration until discontinued by provider.	Oral and ear pruritus, swelling of lips or tongue, and throat irritation	Trials allowed patients with mild-to-moderate asthma that required, at most, a medium daily dose of an inhaled glucocorticoid to treat asthma.
Abbreviations: Amb a = Ambrosia artemisifolia (short ragweed); BAUs = Bioequivalent Allergy Units; FDA = Food and Drug Administration; SQ-HDM = Standardized-Quality House Dust Mite units; IR = Index of Reactivity; SL = sublingual; yo = years old					

All 4 SLIT products contain a black boxed warning regarding the risk of severe allergic reactions, including anaphylaxis and severe laryngopharyngeal restriction, and are contraindicated in patients with severe, unstable, or uncontrolled asthma.[25-28] Additional contraindications are a history of eosinophilic esophagitis or any severe systemic allergic reaction. The first dose should be administered in the provider's office so the patient can be observed for any serious adverse effects for at least 30 minutes. An auto-injectable epinephrine device should be prescribed and the patient or caregiver educated on proper use of the device. None of the SLIT products are indicated for immediate relief of allergic symptoms.[25-28]

Approximately 50% of people with asthma also have environmental allergies.[10] Allergic asthma is triggered by inhaling airborne allergens.[10] Some of the SLIT clinical trials excluded patients with moderate or severe asthma as the risk of severe and fatal adverse events associated with immunotherapy in patients with severe or uncontrolled asthma is a significant contraindication.[25-28] Most of the evidence for use of SLIT in mild to moderate asthma is in patients with asthma complicated by allergic rhinitis induced by dust mite exposure.[29]

Specific allergen immunotherapy improves the control of allergic diseases but does not completely alleviate symptoms in all patients, especially when the allergen load is heavy (e.g., peak pollen season).[30] Therefore, patients should be provided with appropriate rescue medication options such as an oral second-generation H1-antihistamine (once daily), inhaled short-acting beta2 bronchodilator (SABA), ocular H1-antihistamine, intranasal antihistamine, or oral corticosteroid (for short periods in the case of unresponsive/intolerable symptoms).[30]

There are currently no validated genetic or blood biomarkers for predicting or monitoring the efficacy of allergic immunotherapy in patients.[31] In 2007, the World Allergy Organization (WAO) taskforce published recommendations for standardizing allergen immunotherapy clinical trials.[30] Ordinal scales, days free of symptoms, days free of rescue medications, and symptom scores corrected for rescue medications were used as outcome measures in different trials without standardized methodology.[30] The most frequently used approach in SLIT clinical trials is a 4-point rating scale (from 0=absent to 3=severe) applied to each symptom of rhinoconjunctivitis including: nasal obstruction, sneezing, rhinorrhea, nasal itching and ocular itching.[30] Chest tightness, shortness of breath, cough and wheezing should also be considered in patients with concomitant lower airway symptoms.[30] Studies evaluating the symptom response to perennial allergens over a long period have used a visual analogue scale (VAS) to detect changes in symptom severity.[30] A 10-cm line to grade the severity of symptoms from "no symptoms" (0 cm) to "the highest level of symptoms" (10 cm) has been used.[30] In 2009, the WAO proposed a 20% mean reduction in total combined symptom scores (nasal, ocular, and bronchial) be considered a minimal clinically important difference (MCID) in evaluation of immunotherapy efficacy.[32]

For an allergen immunotherapy product to be approved by the FDA, two statistical criteria must be met: 1) point estimate: a difference of 15% in the total combined score (TCS) between active treatment and placebo must be demonstrated and 2) confidence interval: a lower bound of the 95% CI of the difference demonstrating at least a 10% separation between the two treatment groups must be demonstrated.[30] These statistical tests were selected after internal evaluation by the FDA and were mandated to identify and define a statistically significant and clinically meaningful therapeutic effect more clearly when comparing allergen immunotherapy with placebo.[30] For drug approval, the FDA requires demonstration of a statistically significant difference between SLIT and placebo and at least a 15% improvement in the total symptom scoring compared with placebo, while the WAO recommends a 20% improvement in TCS.[30,32]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 1**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Cochrane: Sublingual Immunotherapy for Treating Allergic Rhinitis Due to Various Allergens
A 2010 Cochrane systematic review evaluated the safety and efficacy of SLIT tablets and drops for allergic rhinitis with or without conjunctivitis in children and adults with or without allergic asthma.[2] Patients' sensitivity was proven by positive skin prick tests and/or high specific IgE to a particular allergen.[2] This was an update of a 2003 Cochrane publication. Data was searched through August 14, 2009.[2] A total of 60 RCTs met inclusion critiera.[2] Forty-nine were suitable for pooling in meta-analyses (n = 4589).[2] Most trials evaluated SLIT in patients with allergy to grass pollen (23 studies).[2] Other allergens included: stinging nettle (5 trials), ragweed (2 trials), trees (9 trials), HDM (8 trials) and cat dander (one trial).[2] Thirty-four studies were performed in adults and 15 studies were in children.[2] Treatment lasted for less than 6 months in 17 studies; 6 to 12 months in 16 studies and longer than 12 months in 16 studies.[2] Sublingual tablets were used in 11 studies (n = 1881) and in 35 studies (n = 2464) patients received sublingual drops.[2]

All 60 studies were double-blind, RCTs of parallel-group design. Concealment of treatment allocation was considered adequate in all studies.[2] Blinding of study subjects and investigators was maintained by the use of identical placebo preparations.[2] However, most investigators reported high levels of minor oral side effects (tingling, itching and swelling beneath the tongue) in actively treated subjects, which could influence blinding.[2]

Primary outcomes included symptom scores and use of relevant rescue medications.[2] Overall, moderate-quality evidence from 49 RCTs (n = 4589) showed a reduction in symptoms (SMD -0.49; 95% CI -0.64 to -0.34, P<0.00001; I^2 = 81%) and rescue medication requirements (SMD -0.32; 95% CI -0.43 to -0.21, P<0.00001; I^2 = 50%), favoring SLIT over placebo.[2] In a subgroup analysis of people with seasonal allergens, 39 RCTs (n = 4084) showed symptom scores were significantly reduced with SLIT compared to placebo; the combined SMD was -0.34 (95% CI -0.44, -0.25, P<0.00001; I^2 = 45%).[2] The 10 RCTS (n = 505) in people with perennial allergen also showed a significant reduction in symptoms with immunotherapy versus placebo (SMD -0.93; 95% CI -1.69 to -0.17; P=0.02; I^2 = 92%).[2] There was significant heterogeneity between all studies.[2]

Six RCTs (n = 251) reported no adverse events with SLIT during the trials.[2] Twenty-two studies reported different reactions observed with SLIT administration including buccal pruritus, lip edema, lip swelling, throat irritation, and gastrointestinal symptoms.[2] None of the trials included in this review reported severe systemic reactions or anaphylaxis, and none of the reported systemic reactions required the use of epinephrine.[2] This 2010 review reinforces the conclusion of the original 2003 Cochrane systematic review that SLIT is effective for allergic rhinitis and is a safe route of administration.[2]

Cochrane: Sublingual Immunotherapy for Treating Allergen-Induced Conjunctivitis

A 2011 Cochrane systematic review evaluated the efficacy of SLIT compared with placebo for treating allergic conjunctivitis, a comorbidity of allergic rhinitis.[3] Literature was searched through January 2011 to identify double-blinded RCTS of sublingual drops or tablets in children and adults with allergic conjunctivitis.[3] Forty-two trials (n = 3958) met inclusion criteria.[3] Heterogeneity among studies was around 50% or below for all endpoints.[3] Thirty-five (88%) of the included studies evaluated the efficacy of seasonal allergens (i.e., grass, pollen) while 7 (12%) trials were in people with perennial allergens (i.e., dust mites).[3] Nineteen trials used grass pollen extracts, 10 evaluated tree pollen extracts, 6 trials evaluated mites, 6 evaluated weeds and one study assessed the efficacy of a standardized cat extract.[3] All studies compared SLIT with placebo in double-blind RCTs.[3] Thirty-one (74%) studies administered the extracts as sublingual drops, 9 (21%) as tablets and 2 (5%) studies examined drops during the build-up phase and subsequently switched to tablets for the maintenance phase.[3] The median duration of therapy was 12 months (range 3 to 36 months).[3] Most studies were of moderate quality due to selection bias (unclear allocation concealment or randomization).[3]

The primary outcome was total ocular symptom scores. Thirty-six RCTs (n=3,399) showed SLIT treatment resulted in a reduction of total ocular symptom scores compared to placebo (SMD -0.41; 95% CI -0.53 to -0.28; P<0.00001; I^2 = 59%; moderate-quality evidence).[3] A subgroup assessment according to the allergen type was also analyzed. Thirty RCTs showed a reduction in total ocular symptom scores in people with seasonal allergies treated with SLIT compared to placebo (SMD -0.38; 95% CI -0.50 to -0.25; P<0.00001; I^2 = 58%; moderate-quality evidence).[3] The 6 RCTs that studied the effect of SLIT treatment on ocular symptoms in people with perennial allergies showed no difference from placebo (SMD -0.52; 95% CI -1.05 to 0.01; P=0.05; I^2 = 70%; low-quality evidence).[3]

Secondary outcomes included individual ocular symptoms scores (redness, itching, watery eyes), use of eye drops, and conjunctival allergen sensitivity. Compared with placebo, moderate-quality evidence showed that SLIT induced a significant reduction in individual ocular symptom scores compared to placebo for red eyes (SMD -0.33; 95% CI -0.45 to -0.22; P<0.00001; I^2 = 27%), itchy eyes (SMD -0.31; 95% CI -0.42 to -0.20; P<0.00001; I^2 = 46%), and watery eyes (SMD -0.23; 95% CI -0.34 to -0.11; P<0.0001; I^2 = 42%).[3] No reduction was observed in the use of ocular eye drops in the 13 RCTs that reported this outcome (SMD -0.10; 95% CI -0.22 to 0.03; P=0.13; I^2 = 34%; moderate-quality evidence).[3] Four RCTs (n=250) evaluated the effect of SLIT on conjunctival immediate allergen sensitivity using a conjunctival allergen provocation test, where topical allergen is applied to the external ocular surface to assess inflammatory response in a suspected sensitized patient.[3] Participants who received SLIT showed an increase in the threshold dose for the conjunctival allergen provocation test compared to placebo (SMD 0.35; 95% CI 0.00 to 0.69; P=0.05; I^2 = 43%; moderate-quality evidence).[3]

This systematic review provides moderate-quality evidence which confirms SLIT reduces both the total and individual ocular symptom scores for red eyes, itchy eyes, and watery eyes in patients with rhinoconjunctivitis when compared to placebo.[3] Moderate-quality evidence showed these reductions were evident with tablets and drops when the studies assessed seasonal allergens but not perennial allergens (low-quality evidence).[3] These differences could be explained by the paucity of studies evaluating perennial allergens (n=6) and the small numbers of participants analyzed for this outcome (n=219).[3] Increasing the duration of treatment beyond 12 months did not affect the treatment effect (12 months or less: SMD -0.43; P<0.0001; I^2 = 58%, and greater than 12 months: SMD -0.43; P<0.01; I^2 = 68%; moderate-quality evidence).[3]

Canadian Agency for Drugs and Technologies: Timothy Grass (Phleum pratense) Allergenic Extract

A 2015 CADTH systematic review evaluated evidence for the safety and efficacy of GRASTEK, also known as *Phleum pratense* allergenic extract (PPAE), in patients with allergic rhinitis, with or without conjunctivitis. [4] Literature was searched through February 7, 2014.[4] Eight placebo-controlled RCTs in adults and children aged 5 years and older met inclusion critieria.[4] Five RCTs involved adults, 2 studies involved pediatric patients, and one study involved a mixed population of adults and children.[4] In most of the studies, PPAE therapy was started 8 weeks before the onset of grass pollen season and continued for 24

weeks.[4] Key efficacy outcomes included symptom relief, use of rescue medications (antihistamines, corticosteroids, decongestants, eye drops, and leukotriene inhibitors), and health-related quality of life.

Daily symptom scores (DSS) were measured using a 4-point rating scale (0 to 3 points) of 6 symptoms (4 nasal symptoms and 2 ocular symptoms). The maximum total score was 18 points. Adjusted mean DSS over the entire grass pollen season were reported in all 8 studies and were lower for PPAE groups (range 2.18 to 5.69) compared with placebo groups (range 2.80 to 6.06).[4] Between-treatment mean differences ranged between –0.37 and –1.29, being statistically significant in 5 studies and non-significant in 3 studies.[4] The Daily Medication Scores (DMS) were based on the use of rescue medications. Protocol-specified rescue medications and scoring systems were different in each study.[4] The maximum possible DMS ranged from 12 to 38 across all 8 RCTs.[4] Adjusted mean DMS over the entire grass pollen season were reported in 8 eight studies and were lower with PPAE groups (range 0.78 to 2.60) compared with placebo groups (range 1.19 to 3.81).[4] Between-treatment differences ranged from –0.4 to –1.2, being statistically significant in 4 studies and non-significant in 4 studies.[4] Seasonal treatment with PPAE sublingually once daily resulted in statistically lower symptom scores and rescue medication use over one grass pollen season.[4] However, the clinical importance of the observed between-treatment differences in symptom and medication scores is uncertain.[4]

The total combined score (TCS) was a sum of the symptom and rescue medication scores. Adjusted mean TCSs over the entire pollen season were reported in 6 studies and were lower with PPAE (range 3.70 to 6.74) compared with placebo (range 4.86 to 7.53).[4] Between-treatment mean differences ranged from –0.8 to –2.3, being statistically significant in 5 studies and non-significant in one study.[4] The corresponding relative percentage differences in mean TCS ranged between –10% and –34%, being 20% or greater in 4 studies.[4] The between-treatment difference of 20% or more for the mean TCS (considered to be clinically meaningful by the WAO) was achieved in 5 of 6 studies reporting this outcome.[4] Although a between-treatment difference in the TCS of 20% or greater was achieved in a number of trials, the absolute differences in the TCS were small.[4] Small absolute differences can translate into large percentage differences when TCS scores are relatively low.[4]

Changes in health-related quality of life, as measured by the Rhinoconjunctivitis Quality Of Life Questionnaire (RQLQ), were not considered clinically meaningful.[4] Although immunotherapy was administered seasonally for several years, only one study examined the effects of PPAE over multiple seasons.[4] Despite findings of continuing efficacy over multiple treatment seasons, the findings are limited by the high (approximately 50%) and differential dropout after the first season.[4] Based on one long-term RCT, the beneficial effects of PPAE appear to be sustained over 3 subsequent years of seasonal treatment, with waning of effect in subsequent untreated years, but the validity of the long-term findings is limited by the large and differential dropout following the first grass pollen season.[4]

In all the included studies, adverse events were higher in the PPAE group compared with the placebo group and were reported as being mild or moderate in severity.[4] The most frequently reported adverse events were those associated with the mouth or throat. The treatment durations were approximately 24 weeks, in most studies, but longer-term data (seasonal treatment over three years) available from an extension study did not reveal additional safety issues.[4] Serious adverse events and withdrawals due to adverse events were few and similar in both groups across the trials.[4] Three studies reported one death each in of the PPAE groups, but these were not considered to be related to PPAE.[4]

In summary, while many of the included studies reported statistically significant improvements with PPAE compared with placebo, in terms of DSS, DMS, and TCS, these scales have not been validated and the clinical significance of the observed differences is unclear.[4] In addition, there are a number of potential sources of bias, which may affect the validity of the above reported results.[4] Potential unblinding due to the more frequent experience of oral or pharyngeal adverse events in the PPAE group may have influenced patients' assessment of symptoms, quality of life, and need for rescue medication.[4] Knowledge of

treatment allocation may also have affected the frequency of diary entries regarding symptoms and medication.[4] The extent of missing data is unclear; however, differential missing data may bias results.[4] A key gap in the evidence for PPAE is the absence of RCTs directly comparing PPAE with other SLIT products.[4] Based on the conclusions of this systematic review, the Canadian Drug Expert Committee did not recommend PPAE be listed on the Canadian drug formulary.[4]

Allergen Immunotherapy for Allergic Rhinoconjunctivitis: A Systematic Review and Meta-Analysis

A 2017 systematic review assessed the effectiveness and safety of allergen immunotherapy in the management of allergic rhinoconjunctivitis in patients of any age.[6] The EAACI taskforce based their guideline recommendations on the findings from this systematic review.[13] Literature was searched through October 31, 2015.[6] One hundred thirty-two international RCTs met inclusion criteria.[6] Sixty-one RCTs evaluated SCIT (n = 6379) and 71 RCTs assessed SLIT (n = 13636 patients).[6]The quality of the SLIT studies was assessed to be low risk of bias (ROB) in 26 studies, high ROB in 16 studies and unclear ROB in 29 studies.[6] Overall, the quality of included SCIT studies was high.[6] Thirty-seven studies were found to be at low ROB, 8 studies at high ROB, and 16 were judged at unclear ROB.[6] The majority of studies only included adults.[6] A range of allergens were assessed including weed, tree and grass pollens, molds, cat and dog dander, and dust mites. A range of protocols were utilized and the overwhelming majority of trials only reported on short-term effectiveness.[6]

The primary outcome was therapy effectiveness, as assessed by symptom and medication scores.[6] Pooled data from 58 RCTS that assessed both SCIT and SLIT versus placebo showed a SMD of -0.53 (95% CI -0.63 to -0.42; p<0.0001; I^2 = 67%; low-quality of evidence) suggesting a moderate effect on short term (less than 2 years) symptom scores in favor of immunotherapy.[6] In a subgroup analysis of seasonal versus perennial allergens (SMD −0.37; 95% CI −0.45 to −0.28; p<0.159; I^2 = 22%; and SMD −0.91; 95% CI −1.47 to −0.36, p<0.0001; I^2 = 73%; respectively), low-quality evidence demonstrated benefit from both approaches.[6] Data pooled from 15 RCTs showed a small-to-moderate effect in favor of immunotherapy versus placebo on a combined endpoint of symptom and rescue medication scores (SMD −0.49; 95% CI −0.69 to −0.30; p<0.001; I^2 = 58%; low-quality evidence).[6] There is a limited body of evidence on the longer-term effectiveness of immunotherapy in improving symptom scores (2 low-quality RCTs).[6]

A secondary outcome was safety as reported by the incidence of adverse events. There was a great variation in reporting of adverse events and a number of grading scales including WAO and EAACI guidelines were used.[6] Some studies reported limited or unclear data on number of adverse events, some studies reported no data on adverse events, and others reported that no adverse events occurred at all through the duration of the trial period.[6] Conversely some studies reported all treatment emergent adverse events. Safety data for 51 SCIT and SLIT RCTs were pooled to give an overall risk ratio (RR) of experiencing an adverse event of 1.64 (95% CI 1.43 to 1.89; p=0.00; I^2 = 91%; low-quality evidence).[6] For SLIT studies (n=19 RCTs), an RR of 1.58 was calculated (95% CI 1.13 to 2.20; p=0.00; I^2 = 79%) of experiencing an adverse effect and for SLIT studies (n = 32 RCTs) an RR of 1.68 (95% CI 1.44 to 1.98 p=0.00; I^2 = 79%), suggesting a comparable safety profile for both modes of immunotherapy (low-quality evidence).[6]

Heterogeneity in outcome assessment approaches limited the effectiveness of this review as authors were unable to pool data from all trials or undertake all the planned subgroup analyses.[6] Furthermore, studies for which data was pooled also showed heterogeneity which may be related to the diverse populations studied, protocols followed, products used and duration of trial periods.[6] For the subgroup analyses, there was in some cases imprecision which impacted the ability to draw clear conclusions.[6] These subgroup analyses were indirect comparisons between SCIT and SLIT and the findings should therefore be cautiously interpreted.[6] Greater standardization of trial designs and reporting techniques would improve the research base underpinning immunotherapy.[6]

Sublingual Immunotherapy for Treating Grass Pollen-Induced Allergic Rhinitis

A 2020 systematic review and meta-analysis assessed the efficacy of SLIT in the management of adults with grass pollen-induced allergic rhinitis or allergic rhinoconjunctivitis.[5] Only sublingual tablets were included in the search; sublingual drops were excluded. Literature was searched through May 9, 2019. Of the

412 studies identified, 6 studies (n = 1971) met inclusion critiera.[5] Three studies evaluated GRASTEK and 3 studies assessed ORALAIR.[5] The risk of selection bias was high in 3 of the studies.[5] Overall, there was a low risk of bias for deviations from the intended interventions, missing outcome data and in selection of the reported result in all 6 RCTs.[5] There was some concern surrounding the method of randomization and allocation concealment process due to insufficient information in one RCT.[5] Another RCT resulted in high risk of bias due to issues with treatment adherence.[5]

The primary outcome measure was a 4-point symptom score (0 = no symptoms and 3 = severe symptoms) based on the WAO guidance on trial standardization in which 6 symptoms were evaluated (nasal obstruction, sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and tearing).[5] All studies reported an improvement in symptoms with SLIT compared to placebo, with 5 RCTs reaching statistical significance ($P<0.05$).[5] The adjusted mean difference ranged from -1.96 to -0.80 in the 5 RCTs that reported statistical significance.[5] In the meta-analysis, SLIT showed a significant reduction in symptoms compared with placebo (SMD -0.36; 95% CI -0.46 to -0.25; $P<0.00001$; $I^2 = 48\%$; moderate quality evidence).[5]

Participants in 4 studies withdrew due to adverse events in both active and placebo groups.[5] In the active group, the highest and lowest reported withdrawal was 7.2% and 0%, respectively, compared with 3.5% and 0% for the highest and lowest reported withdrawals in the control group, respectively.[5] Adverse events were limited to localized and mild pruritus and swelling of the mouth, tongue or eyes.[5] Oral pruritus was the most commonly reported adverse event.[5] Dyspepsia was reported in 22% of the active group participants.[5] Five studies reported only mild, local adverse events related to treatment.[5]
In summary, SLIT is generally safe with only minor adverse events. Meta-analysis of 5 RCTs shows that SLIT is associated with statistically significant improvement in symptom scores versus placebo.[5]

Agency for Healthcare Research and Quality: The Role of Immunotherapy in the Treatment of Asthma
A 2018 AHRQ review evaluated the efficacy and safety of SCIT and SLIT for treating allergic asthma.[10] Literature was searched through May 8, 2017.[10] Fifty-four RCTs met inclusion criteria for efficacy: 31 assessed SCIT and 18 assessed SLIT and 5 RCTS compared SCIT versus SLIT.[10] Seventy-five studies met inclusion criteria for the safety analysis: 26 RCTs and 18 non-RCTs for SCIT, 20 RCTs and 10 non-RCTs for SLIT and one non-RCT on SCIT versus SLIT.[10] The majority of studies that met inclusion criteria included adults with mild to moderate asthma with dust mite allergies.[10] The reviewers found insufficient evidence about the efficacy of SLIT in children.[10]

Moderate quality evidence shows SCIT reduces the use of long-term control medication.[10] Subcutaneous immunotherapy may improve quality of life, reduce the use of quick-relief medications (i.e., SABAs), reduce the need for systemic corticosteroids, and improve FEV_1 (low-quality evidence).[10] There was insufficient evidence regarding the effect of SCIT on asthma symptoms and health care utilization in adults.[10] There was insufficient evidence about the efficacy of SCIT in pediatric patients.[10] Local reactions to SCIT were frequent; however reactions also occurred with placebo (risk differences ranged from -0.317 to 0.4) and local reactions infrequently required a change in SCIT dosing (quality of evidence not reported).[10] Systemic allergic reactions to SCIT were frequently reported (risk differences ranged from 0 to 0.319; quality of evidence not reported).[10] The majority of systemic allergic reactions were mild, and only a small number was consistent with anaphylaxis and required treatment with epinephrine.[10] There was insufficient evidence to draw conclusions about whether SCIT increased risk of anaphylaxis, primarily because anaphylaxis was not directly measured.[10] There was one case report of a death determined possibly to be caused by SCIT.[10] High-quality evidence shows SLIT improves asthma symptoms as measured by validated instruments.[10] Moderate-quality evidence shows decreased use of long-term asthma control medication (specifically ICS) and improvements in FEV_1 with SLIT therapy.[10] Sublingual immunotherapy may decrease the use of SABAs and may improve quality of life (low-quality evidence).[10] There is insufficient evidence about the effect of SLIT on systemic corticosteroid use and health care utilization.[10] Local and systemic allergic reactions were common but infrequently required changes in treatment.[10] Life-threatening reactions were not

commonly reported, with 3 case reports of anaphylaxis and no deaths (moderate-quality evidence) reported.[10] There was insufficient evidence about the efficacy of SLIT in children.[10]

There was insufficient evidence to draw conclusions about the comparative effects of SCIT versus SLIT or for differential effects of immunotherapy based on patient age, setting of administration, or type of allergen.[10] Overall, SLIT and SCIT were beneficial for the majority of asthma-related outcomes assessed in this report.[10] Local and systemic allergic reactions were common but infrequently required changes in treatment.[10] Life-threatening events (such as anaphylaxis) were rarely reported.[10]

Cochrane: Sublingual Immunotherapy for Asthma

A 2020 Cochrane review updated a 2015 review that assessed safety and efficacy of SLIT compared with placebo in adults and children with asthma.[11] The literature search for this updated publication was conducted through October 29, 2019.[11] Trials that evaluated SLIT versus placebo, or as an add-on to standard asthma management were included in the search.[11] The target population was children and adults with asthma, rhinitis, or both, providing at least 80% of trial participants had a diagnosis of asthma.[11]

Sixty-six studies met the inclusion criteria for this update (n = 7944), including 52 studies from the original 2015 review.[11] Most studies were double-blind and placebo-controlled, varied in duration from one day to 3 years, and recruited participants with mild or intermittent asthma, often with comorbid allergic rhinitis.[11] Twenty-three studies recruited adults and teenagers; 31 studies recruited only children; 3 recruited both; and 9 did not specify the age of included population.[11] Patients with severe asthma were excluded from most of the studies, resulting in a study population consisting largely of participants with intermittent or mild symptoms.[11] Forty-seven studies examined dust mite allergy and 6 studies focused on grass pollen.[11] Other studies examined tree pollen, cockroach exposure or cat dander.

Reporting of primary efficacy outcomes to measure the impact of SLIT on asthma exacerbations and quality of life was infrequent, and selective reporting may have had a serious effect on the completeness of the evidence; 16 studies did not contribute any data, and a further 6 studies could only be included in a post-hoc analysis of all adverse events.[11] Allocation procedures were generally not well described; about a quarter of the studies were at high risk of performance or detection bias (or both); and participant attrition was high or unknown in around half of the studies.[11] About a quarter of the studies were at high risk for blinding because they used open-label study designs.[11]

Primary outcomes were asthma exacerbations requiring a visit to the ED or admission to hospital, validated measures of quality of life, and SAEs. The primary outcome in most studies did not align with those of interest to the review (mostly asthma or rhinitis symptoms), and only 2 small studies (n = 108) reported the primary outcome of exacerbations requiring an ED or hospital visit.[11] The pooled estimate from these studies suggests the evidence for SLIT in reducing asthma exacerbations is not statistically significant and is very uncertain (OR 0.35, 95% CI 0.10 to 1.20; very low-quality evidence).[11] Nine studies reporting quality of life could not be combined in a meta-analysis and, while the direction of effect mostly favored SLIT, the effects were often uncertain and small.[11]

In total, 56 of 3,086 SLIT-treated patients and 34 of 1,724 placebo-treated patients experienced an SAE.[11] In an analysis using risk differences suggests no more than 1 in 100 people with mild or intermittent asthma taking SLIT will have a serious adverse event (RD, −0.0004, 95% CI −0.0072 to 0.0064; p=0.90; n = 4810; 29 studies; moderate-quality evidence).[11] Twenty-seven studies (n=4,251) reported all adverse events, and 17 RCTs contributed to the meta-analysis.[11] Pooled results showed increased risk of experiencing an adverse event in the SLIT group compared with the placebo group (OR 1.99, 95% CI 1.49 to 2.67; high-quality

evidence), but events were usually reported to be transient and mild and rarely led to withdrawal from the trial.[11] The most frequently reported adverse events included oral discomfort, oral pruritis, and mouth edema.[11]

Secondary outcomes were asthma symptom scores, exacerbations requiring systemic corticosteroids, response to provocation tests, and dose of inhaled steroids. Asthma symptom and medication scores were mostly measured with non-validated scales, which prevented meaningful meta-analysis or interpretation, but there was a general trend of SLIT benefit over placebo.[11] Changes in ICS use (MD, −17.13 mcg/d, 95% CI −61.19 to 26.93; n = 778; 4 studies; low-quality evidence), exacerbations requiring oral steroids (2 studies; no events), and bronchial provocation (SMD 0.99, 95% CI 0.17 to 1.82; low-quality evidence) were not often reported.[11] Results were imprecise and included the possibility of important benefit or little effect and, in some cases, potential harm from SLIT.[11]

In summary, the evidence for important outcomes such as exacerbations and quality of life remains too limited to draw clinically useful conclusions about the efficacy of SLIT for people with asthma.[11] Trials mostly recruited mixed populations with mild and intermittent asthma and/or rhinitis and focused on non-validated symptom and medication scores.[11] The findings from this review suggest the role of SLIT for people with asthma requires further evaluation.[11]

Efficacy and Safety of House Dust Mite Sublingual Immunotherapy Tablets in Allergic Asthma

A 2022 publication reviewed the efficacy and safety of HDM SLIT tablets in people with allergic asthma.[12] Literature was searched through September 30, 2021.[12] Seven RCTs, 5 studies in allergic asthma (4 in adults and 1 in children), and 2 in allergic rhinitis with asthma, met inclusion criteria.[12] Six studies were double-blinded RCTs, and one was an open-label RCT. Five studies included patients with mild-to-moderate asthma, and 2 studies included patients with moderate-to-severe asthma.[12] Six studies used standardized quality (SQ)-HDM tablets, and 1 study used index reactivity (IR)-HDM tablets. Two studies were classified as having low risk of bias, 4 studies were classified as having some concerns of bias, and one study was rated as having a high risk of bias due to suspicion of selective results reporting.[12]

The primary outcome of interest was asthma control during ICS reduction after initiating HDM tablets.[12] Secondary asthma outcomes included: asthma exacerbation, Asthma Control Questionnaire (ACQ) score, Asthma Quality of Life Questionnaire score (AQLQ), the use of SABAs during follow-up, lung function scores, nasal symptoms, and adverse effects.[12]

A high-quality, double-blinded RCT in 604 patients aged 14 years or older with mild-to-moderate asthma concomitant with HDM allergic rhinitis was conducted to evaluate the effect of 6 SQ-HDM tablets in decreasing the use of ICS while maintaining asthma control.[12] The recruited patients were treated according to steps 1 to 3 of the GINA guideline and all the patients were taking similar daily doses of inhaled budesonide.[12] The primary end point was the lowest ICS dose needed to maintain asthma control. The difference in reducing the daily ICS dose between HDM tablets and placebo was 81 mcg (95% CI, 27 to 136 mcg/day; P=0.004).[12] Mean and median reductions from baseline in ICS dose were 42% and 50% for HDM tablets and 15% and 25% for placebo, respectively.[12] No statistically significant differences were observed for the other assessed asthma parameters, reflecting the intended controlled status of the trial subjects.[29] After 1 year of treatment, 34% of the patients in the HDM tablet group could completely discontinue ICS compared with 21% of those in the placebo group.[12]

A moderate quality, 8-month, double-blinded RCT in 111 children aged 5 to 15 years with asthma evaluated the effect of 300 IR-HDM tablets versus placebo.[12] Seventy-three and 36 patients had mild and moderate asthma, respectively.[12] At baseline, 50% of the patients had no asthma symptoms, and the use of SABAs was low, indicating that most patients in this study had well-controlled mild asthma.[12] The ICS dose was stepped-down after 5 months, 9 months, and

12 months of treatment by reducing the ICS dose of 20% to 30% at each stage, based on individual asthma status.[12] There was no significant difference detected between HDM tablets and placebo in improving ICS and SABA used, asthma symptoms scores, lung function, and rhinitis symptom score.

Another high-quality, multicenter, double-blinded RCT compared the efficacy between the 6 SQ- and 12 SQ-HDM tablets and placebo in 834 partially controlled moderate-to-severe asthmatic patients 18 years or older with concomitant dust mite-induced allergic rhinitis.[12] During the last 6 months of the trial, the HDM tablets significantly reduced the risk for a moderate or severe asthma exacerbation while reducing the ICS dose by 50% with a hazard ratio (HR) of 0.72 (95% CI 0.52 to 0.99; P=0.045) for the 6 SQ-HDM group, and HR of 0.69 (95% CI 0.50–0.96; P=0.03) for the 12 SQ-HDM group.[12] There was no significant treatment effect difference between the 2 doses of HDM tablets, and no significant improvement in ACQ or AQLQ was found for either dose.[12] In a similar RCT, 826 Japanese patients with asthma not well controlled by ICS (judged by ACQ score of 1.0 to 1.5) and HDM-induced allergic rhinitis were administered 6 SQ- and 12 SQ-HDM tablets to assess asthma control.[12] No significant difference was found among the 6 SQ-HDM, 12 SQ-HDM, and placebo in all asthma outcomes, including exacerbation, ICS use, asthma symptoms, ACQ, AQLQ, and lung function.[12]

The percentage of participants reporting at least 1 AE ranged from 39% to 96.4% in the HDM tablet-treated group.[12] Among all adverse effects, local adverse effects were the most common.[12] The symptoms include local swelling of the mouth, lips, tongue, or ear along with pruritus and some degree of gastrointestinal discomfort.[12] Of the 7 included studies, only one RCT reported 7 subjects treated with epinephrine due to adverse effects.[12] Three subjects used epinephrine for 12 SQ HDM-related adverse effects. The other 4 epinephrine administrations were considered unrelated to 12 SQ-HDM, 3 related to food/environmental allergies, and 1 (in the placebo group) related to complex allergy symptoms.[12]

In summary, moderate- to high-quality evidence from 3 RCTs review showed that SLIT effectively improved ICS use in adults and adolescents with mild-to-moderate or partially controlled moderate-to-severe asthma, but had no treatment effect in pediatric patients with very mild asthma.[12] Two RCTs evaluated the efficacy of house dust mite SLIT in reducing asthma exacerbation in partly controlled moderate-to-severe asthma, and their results were inconsistent.[12] One study in children with mild-to-moderate asthma found no benefit of SLIT.[12] Adverse events were primarily local, and anaphylaxis treated with epinephrine was reported in 3 patients.[12]

This systematic review has several limitations. First, the number of high-quality RCTs addressing the clinical questions was small.[12] In addition, each RCT also focused on different primary end points or different aspects of asthma control.[12] Finally, although the contrast groups were similar and seemingly comparable across studies, the reported outcomes varied substantially.[12] Only 2 studies reported the intended primary outcome of interest.[12] The measurements of asthma outcomes, asthma severity, and level of asthma control of the recruited population differed among studies, leading to a limitation in conducting quantitative synthesis and concluding clinical benefit.[12]

After review, 5 systematic reviews were excluded due to poor quality (e.g., network meta-analyses),[33-36] wrong study design of included trials (e.g., observational),[37] comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

Peanut Allergy

National Institute for Health And Care Excellence: PALFORZIA For Treating Peanut Allergy In Children And Young People

A recommendation for the use of PALFORZIA in children with a peanut allergy was published by NICE in February 2022.[1] The goal of treatment for peanut allergy is preventive, to reduce the frequency and severity of allergic reactions and improve quality of life, reduce anxiety, and to normalize activities of daily living.[1] The main preventive strategy for peanut allergy is strictly avoiding peanuts and being ready to respond to an emergency.[1] Clinical trial evidence shows that PALFORZIA improves tolerance to peanut protein compared with placebo when precise amounts are used in a food challenge test.[1] It is uncertain how long people would continue treatment beyond 24 months and the effect of stopping treatment on maintaining clinical efficacy has not been evaluated.[1]

NICE Recommendation: PALFORZIA is recommended as an option for treating peanut allergy in children aged 4 to 17 years. It can be continued in people who turn 18 years while on treatment. PALFORZIA should be used with a peanut-avoidant diet.[1]

Grass, Pollen and House Dust Mite Allergies

Canadian Agency for Drugs and Technologies: Grass Pollen Allergen Extract

A 2013 CADTH report evaluated evidence for the safety and efficacy of 5-grass pollen allergen extract (ORALAIR) in allergic rhinitis.[7] The 5-grass pollen extract SLIT was shown to be superior to placebo for management of allergic rhinitis in 4 double-blind RCTs.[7] Most adverse events reported in the 4 RCTs were mild or moderate in severity.[7] Oral pruritus, throat irritation, and mouth edema were reported more frequently with SLIT compared with placebo.[7] Serious adverse events were rare. Compared with placebo, a larger proportion of patients treated with 5-grass pollen extract experience at least one SAE during the first year of treatment (3.4% vs. 0.%) in one RCT.[7] In the other 3 RCTs the proportion of patients with at least one SAE was similar between 5-grass pollen extract and placebo (0.6% vs 0%; 1.4% vs. 1.4%; and 0.9% vs 1.7%, respectively).[7] There is no comparative evidence to evaluate the safety and efficacy of 5-grass pollen extract tablets with SCIT. The CDEC recommended the 5-grass pollen allergen extract be listed on the Canadian drug formulary for the seasonal treatment of grass pollen allergic rhinitis if: 1) patients have not adequately responded to, or tolerated, conventional pharmacotherapy, and 2) treatment is initiated by an allergist.[7]

European Academy of Allergy and Clinical Immunology (EAACI): Guidelines on Allergen Immunotherapy for Allergic Rhinoconjunctivitis

A 2017 guideline published by EAACI provides recommendations for the use of allergen immunotherapy for allergic rhinoconjunctivitis in adults and children.[8] The evidence for the efficacy of immunotherapy in children younger than 5 years of age is limited.[8] A 2017 systematic review (previously summarized above) informed the recommendations developed by the taskforce.[6] Members of the EACCI taskforce represented 18 countries and a range of clinical backgrounds including pediatricians, primary care specialists, ophthalmologists, pharmacists, immunologists, nurses, and patient representatives.[8]

Most clinical studies evaluating the efficacy of immunotherapy follow participants for 1 or 2 years on therapy.[8] The European Medicine Agency currently recommends an experimental, randomized, controlled design involving 3 years of therapy with a 2-year follow-up period off treatment.[8] These studies demonstrate a sustained benefit for 3 years of SLIT-tablet grass pollen therapy for 2 years off therapy.[8] There are some data from one RCT to suggest that HDM SLIT tablets give sustained benefit for at least 1 year after 1 year of therapy.[8] More data are required for HDM, and evidence is required on the optimal duration of therapy.[8] The EAACI taskforce recommends that to achieve long-term benefits, immunotherapy should be continued for a minimum of 3 years.[8]

Recommendations for SCIT and SLIT are provided in the EAACI publication. In general, the meta-analysis suggested both SCIT and SLIT are effective to manage allergic rhinitis.[8] There is insufficient data to determine which of SCIT and SLIT are most effective.[8] Severe adverse effects with SLIT appear to be much less likely than with SCIT although the overall rate of any adverse reactions is similar in both SCIT and SLIT formulations.[8] Specific SLIT recommendations are summarized in **Table 2**. Grade A recommendations are based on Level 1 evidence (systematic reviews, meta-analysis, and RCTs).[8] Grade B recommendations are based on Level 2 evidence (two groups, non-randomized [cohort or case-control] studies) or Level 3 evidence (one group, non-randomized study).[8] Grade C recommendations are based on Level 4 evidence (descriptive studies) or extrapolation of Level 2 or 3 evidence.[8]

Table 2. EAACI Recommendations for Treatment of Allergic Rhinoconjunctivitis with SLIT[3]

Recommendation	Adults		Children and Adolescents		Strength of Recommendation
	Evidence Level	Grade of Recommendation	Evidence Level	Grade of Recommendation	
Seasonal Allergic Rhinitis					
Pre-pollen or coseasonal pollen SLIT is recommended for seasonal allergic rhinitis for short-term benefit.	1	A	1	A	Strong recommendation based on high-quality adult and pediatric studies
Continuous SLIT during pollen season can be recommended for seasonal allergic rhinitis for short-term benefit.	1	A	1	A	Moderate-to-strong recommendation based on low and high ROB adult studies plus low, moderate and unclear ROB pediatric studies. Some heterogeneity between studies particularly pediatric ones, low risk of severe systemic allergic side-effects.
SLIT with grass pollen tablets is recommended for allergic rhinitis short-term benefit.	1	A	1	A	Strong recommendation based on low ROB adult and pediatric studies. Non-important heterogeneity between studies, low risk of severe systemic allergic side-effects.
Grass pollen SLIT tablets with continuous therapy during pollen season is recommended for allergic rhinitis for long-term benefit (at least 1 year after cessation of SLIT course).	1	A	1	A	Strong recommendation for adults based on low risk of bias studies. One low risk of bias pediatric study. Effective up to 2 years after cessation in adults. One pediatric study was designed to look at prevention of asthma.
Perennial Allergic Rhinitis					
SLIT with HDM tablets is recommended for allergic rhinitis for short-term benefit.	1	A	1	A	Strong recommendation based on low ROB adults and mixed adult/pediatric studies. Nonimportant heterogeneity between studies, low risk of severe systemic allergic side-effects.
HDM SLIT tablet with continuous therapy can be recommended to manage allergic rhinitis for long- term benefit (at least 1 year after cessation of SLIT course).	1	B	-	C (no pediatric data, extrapolated from adult data)	Moderate recommendation based on one large, low ROB study. No pediatric data. One study demonstrates effectiveness for one year post-treatment; data require replication especially as 3-year therapy required for grass pollen.
Abbreviations: EAACI= European Academy of Allergy and Clinical Immunology; HDM = house dust mite; ROB = risk of bias; SLIT = sublingual immunotherapy					

General contraindications for SLIT in managing allergic rhinoconjunctivitis include patients with: uncontrolled or severe asthma; active, systemic autoimmune disorders; or active malignant neoplasia.[8] Immunotherapy initiation during pregnancy is also contraindicated; although ongoing treatment is permissible if it has been well tolerated by the patient in the past.[8]

American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology: Sublingual Immunotherapy Guidance

A focused allergen immunotherapy practice parameter update was published by a joint task force of AAAAI and ACAAI members in 2017.[9] At the time of writing, 3 FDA-approved SLIT tablets were available: short ragweed, timothy grass pollen, and 5-grass pollen.[9] The primary focus of the SLIT practice parameter is to provide guidance for effective, safe, and appropriate administration of the FDA-approved SLIT formulations.[9] Both the Timothy grass SLIT tablet and the 5-grass tablet have demonstrated clinical benefits beginning in the first year of a 3-year treatment.[9] Significant improvement in the combined symptom and medication scores over placebo were observed through 2 additional grass pollen seasons after discontinuation of 3 years of continuous treatment with the Timothy grass SLIT tablet and throughout 3 years of pre- and co-seasonal treatment with the 5-grass SLIT tablet.[9] There are insufficient studies that directly compare SCIT and SLIT, precluding a definitive statement regarding efficacy comparison of these forms of immunotherapy.[9] Immunotherapy should be initiated at least 12 to 16 weeks before the relevant season for pre-seasonal and co-seasonal therapy to achieve optimal efficacy.[9] Localized symptoms (e.g., oromucosal itching and swelling) are common during the first week of SLIT treatment, whereas systemic allergic reactions can occur but are rare.[9]

Recommendations:

- Only use FDA-approved SLIT products for the treatment of allergic rhinitis/rhinoconjunctivitis and not for any other related or unrelated condition. (Strength of Recommendation: Strong; Evidence: A/B)**.[9]** There are no FDA-approved study indications for SLIT for the treatment of oral allergy syndrome, food allergy, latex allergy, atopic dermatitis, or venom allergy.**[9]**
- The physician should be aware that SLIT may not be suitable in patients with certain medical conditions, particularly those that may reduce the patient's ability to survive a systemic reaction or the resultant treatment of the systemic reaction. (Strength of Recommendation: Strong; Evidence: D).[9] The FDA-approved SLIT tablet prescribing information lists the following contraindications: severe, unstable, or uncontrolled asthma; any history of a severe systemic reaction to any form of immunotherapy; a history of any severe local reaction to SLIT; a history of eosinophilic esophagitis; or hypersensitivity to any of the inactive ingredients of the preparation. SLIT may not be suitable in patients with medical conditions that may reduce their ability to survive a serious systemic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, or uncontrolled hypertension. SLIT may not be suitable for patients who are taking medications that could potentiate or inhibit the effect of epinephrine should it be required.[9]
- Use FDA-approved SLIT products very cautiously in the pregnant or breastfeeding patient because there are insufficient data regarding the safety of initiating or continuing SLIT during either pregnancy or breastfeeding. (Strength of Recommendation: Weak; Evidence: C).[9]
- Administer the patient's first dose of SLIT in a medical facility under the supervision of a physician or other health care professional with experience in the diagnosis and treatment of anaphylaxis. The patient should be observed in the clinic or medical facility for 30 minutes after the administration of the SLIT dose. (Strength of Recommendation: Strong; Evidence: D).[9]
- Prescribe epinephrine (either an autoinjector or other form for self-injection) to patients receiving SLIT tablets. Patients should be trained how to use the device, instructed on how to recognize and manage adverse reactions and missed doses, and advised on when to contact their physician or other health care professional. Recommendations for when to withhold the SLIT tablet dose to avoid potential situations when systemic allergic reactions may be more likely should also be provided. (Strength of Recommendation: Strong; Evidence: D).[9]

European Academy of Allergy and Clinical Immunology: Allergen Immunotherapy to Prevent Allergic Comorbidities

In 2017 the EAACI taskforce published a guideline to provide evidence-based recommendations for the use of allergen immunotherapy to prevent comorbidities in patients with established allergic conditions.[13] Heterogeneity in the populations under study, methods employed, and outcomes studied made it challenging to interpret the evidence.[13] More evidence is needed for the use of SLIT or SCIT prevention in individuals with allergic rhinitis triggered by dust mites or pollen

and for the prevention of allergic sensitization, the first allergic disease, or for the prevention of allergic comorbidities in those with other allergic conditions.[13] Evidence for the preventive potential of immunotherapy as disease-modifying treatment exists but there is a need for more high-quality clinical trials.[13]

Recommendations and strength of evidence are summarized below. The grading of evidence is described above in the initial EAACI guidance. Based on limited evidence, some of the following recommendations were downgraded to Grade D recommendations and are based on Level 5 evidence (case reports and expert opinion).[13] Recommendations:

- In children and adolescents with allergic rhinitis and grass pollen allergy, who are suboptimally controlled despite appropriate treatment with antihistamines/nasal corticosteroids, a 3-year course of SCIT or SLIT can be recommended for the short-term (i.e., less than 2 years post-treatment) prevention of asthma in addition to the sustained effect on allergic rhinitis symptoms and medication use. (Grade of Recommendation: A; Level of Evidence: 1). Moderate recommendation based on consistent significant results from 2 moderate and 2 high ROB RCTs and some controlled before and after (CBA) studies.[13]
- In children with atopic dermatitis, no recommendations can currently be made in favor of or against the use of immunotherapy for the prevention of onset of later allergic manifestations. (Grade of Recommendation: B; Level of Evidence: 1). Weak recommendation based on one small moderate ROB study.[13]
- In individuals at all ages with other early atopic manifestations, e.g., food allergy, no recommendations can currently be made in favor of or against the use of immunotherapy for the prevention of onset of other allergic manifestations. (Grade of Recommendation: D; Level of Evidence: V). Expert opinion due to the lack of studies.[13]
- In healthy individuals with or without sensitization, immunotherapy cannot currently be recommended for the prevention of onset of allergic diseases. (Grade of Recommendation: A; Level of Evidence: 1).[13] Weak recommendation: based on 1 low and 1 high ROB RCT.[13]

European Academy of Allergy and Clinical Immunology: House Dust Mite-Driven Allergic Asthma

In 2019 the EAACI taskforce developed a clinical practice guideline providing evidence-based recommendations for the use of HDM allergic immunotherapy as add-on treatment for HDM-driven allergic asthma.[14] The proportion of asthmatic patients with allergen sensitization varies between 30% and 79% in children and from 30% to 60% in adults, depending on the end points evaluated (sensitization or symptomatic allergic disease).[14] Dust mite immunotherapy was separately evaluated by route of administration (SCIT, SLIT drops and SLIT tablets) in pediatric and adult populations.[14] The important prerequisites for successful treatment with HDM immunotherapy are: 1) selection of patients most likely to respond to treatment and 2) use of allergen extracts and desensitization protocols of proven efficacy.[14] To date, only immunotherapy with HDM SLIT-tablet has demonstrated a robust effect in adults for critical endpoints (exacerbations, asthma control, and safety) in 3 RCTs funded by the manufacturer.[14] Most of the safety data are derived from allergic rhinitis studies enrolling patients with controlled asthma and with FEV_1 greater 70% predicted.[14] Limited data for adverse events are available for patients only with allergic asthma or for patients with moderate or severe asthma.[14] Thus, it is recommended as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma to decrease exacerbations and to improve asthma control (conditional recommendation, moderate-quality evidence).[14] The patient's asthma status should be carefully evaluated prior to initiating HDM SLIT tablets and assessed regularly during immunotherapy treatment.[14] Due to lack of evidence, no recommendation could be provided for the use of HDM SLIT tablets in children.[14] Uncontrolled asthma is the major independent risk factor for both severe and fatal adverse reactions and is therefore a major contraindication for HDM SLIT tablets.[14]

Additional Guidelines for Clinical Context:

Global Initiative for Asthma Strategy

The 2021 GINA report provides guidance for asthma management and prevention.[38] Personalized asthma management includes guidance for adding HDM SLIT if asthma is not well-controlled.

Recommendation:

- For adult patients with allergic rhinitis and sensitized to dust mites, with suboptimally controlled asthma despite low to high dose ICS, consider adding SLIT provided FEV_1 is greater than 70% of predicted value (evidence level B: limited body of data from RCTs and systematic reviews).[38]

Randomized Controlled Trials:

A total of 168 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alert[39]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Peanut (*Arachis hypogaea*) Allergen Powder-dnfp	PALFORZIA	5/2021	REMS Document	Modified the REMS document and materials to allow the first dose of each Up-Dosing level to be dispensed from either the Office Dose Kit or the Daily Dose Pack and require prescribers and healthcare settings to report anaphylaxis including suspected cases managed as anaphylaxis to the REMS Program using the Anaphylaxis Adverse Event Reporting Form.

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Appendix 1: Medline Search Strategy

A. Environmental Allergens

Ovid MEDLINE(R) <1996 to March Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to March 24, 2023>

1	exp Desensitization, Immunologic/	7897
2	Rhinitis, Allergic/	5008
3	Administration, Sublingual/ or Sublingual Immunotherapy/	3144
4	1 and 2 and 3	302
5	ragweed.mp. or Ambrosia/	1391
6	house dust mite.mp. or Pyroglyphidae/	5313
7	grass.mp. or Poaceae/	28874
8	5 or 6 or 7	34823
9	4 and 8	165
10	limit 9 to (english language and humans)	144

B. Food Allergens

Ovid MEDLINE(R) 1996 to March Week 3 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to March 24, 2023

1	Administration, Sublingual/ or Sublingual Immunotherapy/	3144
2	Peanut Hypersensitivity/	1699
3	1 and 2	25
4	limit 3 to (english language and humans)	24

Appendix 2: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
peanut allergen powder-dnfp	PALFORZIA	ORAL	CAP SPRINK	N
peanut allergen powder-dnfp	PALFORZIA	ORAL	POWD PACK	N
grass pollen-timothy, standard	GRASTEK	SUBLINGUAL	TAB SUBL	
mite,D.farinae-D.pteronyssinus	ODACTRA	SUBLINGUAL	TAB SUBL	
gr pol-orc/sw ver/rye/Kent/tim	ORALAIR	SUBLINGUAL	TAB SUBL	
weed pollen-short ragweed	RAGWITEK	SUBLINGUAL	TAB SUBL	

Peanut (arachis hypogaea) Allergen Powder-dnfp (Palforzia)

Goal(s):

- To ensure appropriate use of desensitization products in patients with peanut allergies

Length of Authorization:

- 12 months

Requires PA:

- Peanut (arachis hypogaea) allergen powder-dnfp (Palforzia) (both pharmacy and physician administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request by, or in consultation with, an allergist or immunologist?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for continuation of current therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for an FDA-approved indication and age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a history of serious peanut allergy or anaphylaxis?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical necessity

Approval Criteria		
6. Is there baseline documentation of number of epinephrine administrations and hospital/emergency department visits (if any) in past 12 months which were caused by presumed peanut exposure.	**Yes:** Go to #7 Epi administrations:_____ Hospital/ED visits:_____	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have a history of severe peanut reaction that included circulatory shock or need for mechanical ventilation?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the patient have a peanut-specific positive IgE of ≥ 0.35 kU_a/L OR a skin prick test wheal of ≥ 3 mm?	**Yes**: Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have a peanut allergy confirmed with a double-blind, placebo-controlled food challenge?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the patient have uncontrolled asthma, history of eosinophilic esophagitis, or other eosinophilic gastrointestinal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Are the healthcare setting and the prescriber certified in the Palforzia REMS program AND will the patient be enrolled in the REMS program upon PA approval?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for the full 300 mg daily maintenance dose of peanut allergen powder?	**Yes**: Go to #3	**No:** Go to #2

Renewal Criteria		
2. Is the patient new to OHA FFS and has the patient not yet completed the initial dose titration prior to FFS enrollment?	**Yes:** Approve for 12 months; Document baseline epinephrine use and hospital/emergency department visits	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient had a reduced number of allergic attacks since beginning peanut allergen powder as evidenced by either: • Absence of, or reduction in the number of needed epinephrine administrations due to presumed peanut exposure OR • Absence of, or reduction in the number of hospital/emergency department visits due to presumed peanut exposure	**Yes**: Approval for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 8/23 (DM); 2/21 (SF)
Implementation: 3/1/21

Sublingual Immunotherapy Tablets

Goal(s):

- Restrict use of sublingual immunotherapy tablets for conditions funded by the OHP and where there is evidence of benefit. Treatment for allergic rhinitis is funded by the Oregon Health Plan only if there is a comorbidity such as asthma.
- Allow case-by-case review for members covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program.

Length of Authorization:

- Up to 12 months

Requires PA:

- All FDA-approved sublingual immunotherapy tablets (physician administered and pharmacy claims).

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Sublingual Immunotherapy Tablets

Product Name (BRAND NAME)	How Supplied	Approved Age Range	When to Initiate Therapy
Timothy Grass Pollen Allergen Extract (GRASTEK)	2,800 BAU tablet	5 to 65 yo	Start 12 weeks prior to expected onset of grass season and continue through grass season.
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergy Extract (ORALAIR)	100 IR and 300 IR tablets		Start 16 weeks prior to expected onset of respective grass season and continue through grass season.
Short Ragweed Pollen Allergen Extract (RAGWITEK)	12 Amb a 1-Unit tablet		Start 12 weeks prior to expected onset of ragweed season and continue through ragweed season.
House Dust Mite Allergen Extract (ODACTRA)	12 SQ-HDM tablet	12 to 65 yo	Start anytime and once daily administration until discontinued by provider.

Abbreviations: Amb a = Ambrosia artemisiifolia (short ragweed); BAUs = Bioequivalent Allergy Units; FDA = Food and Drug Administration; SQ-HDM = Standardized-Quality House Dust Mite units; IR = Index of Reactivity; SL = sublingual; yo = years old

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication ?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for continuation of current therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4

Approval Criteria		
4. Is the request for house dust mite immunotherapy (e.g., Odactra) and does the patient have co-morbid conditions funded by the OHP and listed in HERC guidance? • Uncontrolled Mild to Moderate Asthma Note: sublingual immunotherapy for grass and ragweed have insufficient evidence of benefit in allergic rhinitis and comorbid asthma	**Yes:** Go to #6	**No: For current age ≥ 21 years:** Pass to RPh. Deny; not funded by the OHP. **For current age < 21 years:** Go to #5
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes**: Go to #7	**No**: Pass to RPh. Deny; medical necessity.
6. If the patient has asthma, have they tried and failed to receive adequate benefit from or have a contradiction to a low to high dose orally inhaled corticosteroid treatment?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient tried and failed to receive adequate benefit from or have a contraindication to oral antihistamines and/or nasal corticosteroids to manage allergic rhinitis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical necessity.
8. Does the patient meet the FDA-approved age range outlined in **Table 1**?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the request by, or in consultation with, an allergist or immunologist?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Does the patient have severe, unstable, or uncontrolled asthma, a history of eosinophilic esophagitis, or other severe systemic allergic reaction?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Has the patient undergone a properly performed skin test and/or is there serologic evidence of IgE-mediated antibody to a potent extract of the allergen?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a prescription on file for an epinephrine autoinjector in case of an adverse event?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Will the first dose be administered under medical supervision?	**Yes**: Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Does the provider attest that patient's symptoms have improved with sublingual immunotherapy treatment and not experienced any adverse effects?	**Yes**: Approve for 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 8/23 (DM)
Implementation: 9/1/23