Sublingual Immunotherapy: A focused allergen immunotherapy practice parameter update

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Disclaimer

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing “Sublingual Immunotherapy: a Practice Parameter.” This is a complete and comprehensive document at the current time. The medical environment is changing and not all recommendations will be appropriate or applicable to all patients. Because this document incorporated the efforts of many participants, no single individual, including members serving on the Joint Task Force, are authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information or interpretation of this practice parameter by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI and the ACAAI. These parameters are not designed for use by the pharmaceutical industry in drug development or promotion.

The Joint Task Force on Practice Parameters understands that the cost of diagnostic tests and therapeutic agents is an important concern that may appropriately influence the work-up and treatment chosen for a given patient. The JTFPP recognizes that the emphasis of our primary recommendations regarding a medication may vary, for example, depending on 3rd party payer issues and product patent expiration dates. However, since a given test or agent’s cost is so widely variable, and there is a paucity of pharmaco-economic data, the JTFPP generally does not consider cost when formulating Practice Parameter recommendations. In extraordinary circumstances, when the cost benefit of an intervention is prohibitive as supported by pharmaco-economic data, commentary may be provided. These parameters are not designed for use by pharmaceutical companies in drug promotion.
The Joint Task Force is committed to ensuring that the Practice Parameters are based on the best scientific evidence that is free of commercial bias. To this end, the parameter development process includes multiple layers of rigorous review. These layers include the Work Group convened to draft the parameter, the Task Force Reviewers, and peer review by members of each sponsoring society. Although the Task Force has the final responsibility for the content of the documents submitted for publication, each reviewer comment will be discussed and reviewers will receive written responses to comments when appropriate.

In order to preserve the greatest transparency regarding potential conflicts of interest, all members of the Joint Task Force and the Practice Parameters Work Groups will complete a standard potential conflict of interest disclosure form, which will be available for external review by the sponsoring organization and any other interested individual. In addition, prior to confirming the selection of a Work Group chairperson, the Joint Task Force will discuss and resolve all relevant potential conflicts of interest associated with this selection.

Finally, all members of parameter work groups will be provided a written statement regarding the importance of ensuring that the parameter development process is free of commercial bias.


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CONTRIBUTORS
The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.
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I. Classification of Recommendations and Evidence
# Classification of Recommendations and Evidence

## Recommendation Rating Scale

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<tr>
<th>Statement</th>
<th>Definition</th>
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<tr>
<td><strong>Strong recommendation (StrRec)</strong></td>
<td>A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B)*. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.</td>
<td>Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
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<tr>
<td><strong>Moderate (Mod)</strong></td>
<td>A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C)*. In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.</td>
<td>Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.</td>
</tr>
<tr>
<td><strong>Weak (Weak)</strong></td>
<td>An option means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach versus another.</td>
<td>Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.</td>
</tr>
<tr>
<td><strong>No recommendation (NoRec)</strong></td>
<td>No recommendation means there is both a lack of pertinent evidence (Grade D)* and an unclear balance between benefits and harms.</td>
<td>Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.</td>
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*Grade indications are based on the quality of evidence available at the time of publication.
**Category of evidence**

- **Ia** Evidence from meta-analysis of randomized controlled trials
- **Ib** Evidence from at least one randomized controlled trial
- **IIa** Evidence from at least one controlled study without randomization
- **IIb** Evidence from at least one other type of quasi-experimental study
- **III** Evidence from non-experimental descriptive studies, such as comparative studies
- **IV** Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

**Strength of recommendation**

- **A** Directly based on category I evidence
- **B** Directly based on category II evidence or extrapolated recommendation from category I evidence
- **C** Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- **D** Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- **LB** Laboratory Based
- **NR** Not rated

**Summary of Conflict of Interest Disclosures**

A summary of interests disclosed on Work Group members' Conflict of Interest Disclosure Statements (not including information concerning family member interests) can be found in the this article's Online Repository. Completed Conflict of Interest Disclosure Statements are available upon request. In terms of the two workgroup chairs: Linda Cox, MD served as a consultant for Greer (not ongoing), member of Data Safety Monitoring Committee for Circassia and BioMay, member of an Adjudication Committee for Medimmune and Genentech, and Michael Nelson MD, PhD had no conflict of interest.

**Resolution of Non-disqualifying Interests**

The Joint Task Force on Practice Parameters recognizes that experts in a field are likely to have interests that could come into conflict with the development of a completely unbiased and objective practice parameter. To take advantage of that expertise, a process has been developed to prevent potential conflicts from influencing the final document in a negative way.

At the workgroup level, all of the sections are reviewed by all workgroup members to determine if the content is appropriate and without apparent bias. If a section is deemed to have apparent bias, it will be appropriately revised without the section author's involvement to remove potential bias. In addition, the entire document is then reviewed by the Joint Task Force on Practice Parameters and any apparent bias is removed at that level. In a final stage of review, the practice parameter is sent for review and comment to invited experts reviewers and the AAAAI and the ACAAI’s general membership via posting the document on their website.
Methods and Overview of the Guideline Development Process

The SLIT practice parameters contains systematically developed statements with recommendations intended to optimize patient care and assist physicians and/or other health care practitioners and patients to make decisions regarding this therapy. This guideline is based on two published systematic reviews of the literature, and publications identified by the workgroup’s comprehensive literature search and the Federal Drug Administration (FDA) -approved sublingual immunotherapy tablets’ product information (PI).

Systematic literature review and other sources

Both of the systematic reviews evaluated the efficacy and safety of SLIT and subcutaneous (SCIT) allergen immunotherapy. In addition, one of the reviews included economic evaluations of SLIT and SCIT versus standard drug treatment (SDT). Both systematic reviews include evidence tables summarizing the included studies’ strengths and weakness, which are referred to in this document and form the basis of the summary statement recommendations’ strength. Given the recent publication of these reviews and lack of new data pertaining to FDA approved SLIT formulations, the AHRQ literature search was used for this review, and an independent search was not re-run. This decision was discussed and agreed upon by the JTFPP members in conjunction with the SLIT workgroup. The keywords for these searches have been published elsewhere.

The Agency for Healthcare Research and Quality's (AHRQ) systematic review: Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review searched the databases of MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials through December 22, 2012. English-language, randomized controlled trials (RCT) were included if they compared SLIT with placebo, pharmacotherapy, or other SLIT regimens and reported clinical outcomes. SLIT studies for which a related immunotherapy product was not unavailable in the United States were excluded (e.g. SLIT tablets). Paired reviewers selected articles and extracted the data. The strength of the evidence for each outcome was graded based on the risk of bias, consistency, magnitude of effect, and the directness of the evidence.

The other systematic review's objective was to evaluate “… the comparative clinical effectiveness and cost-effectiveness of SCIT and SLIT for seasonal allergic rhinitis (SAR) by (1) undertaking a systematic review of RCTs in order to update the existing Cochrane reviews on the topic; (2) undertaking an indirect comparison of SCIT with SLIT; (3) undertaking a systematic review of existing economic evaluations (EEs); and (4) conducting an independent EE.”

The databases of MEDLINE, EMBASE, The Cochrane Library [Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Science Citation Index (Web of Knowledge) were searched through April of 2011 for RCT of SCIT and/or SLIT compared with placebo and head-to-head comparisons (SCIT vs. SLIT). Seventeen new RCTs of SCIT compared with placebo and 11 of SLIT compared with placebo were identified. The results presented were of the 11 SLIT trials published from last SLIT Cochrane review (2009 onwards), but all relevant studies were included in the meta-analyses. Fourteen economic evaluations were included; 5 studies compared SCIT with standard care, 6
studies compared SLIT with standard care and two studies compared both SCIT and SLIT with standard care and one study compared different forms of SCIT to SLIT and standard care.

This guideline also includes publications identified through a comprehensive search of the literature conducted by the workgroup members utilizing the MEDLINE database and the search terms; immunotherapy, allergen immunotherapy, sublingual immunotherapy, subcutaneous immunotherapy, allergic rhinitis, and asthma through April 2015. Information and clinical trials included in the FDA-approved SLIT tablet PI was also considered in this document.

The studies considered that were not included in the two systematic reviews or the FDA-approved SLIT tablet PIs are summarized in e-Table I, Summary of Randomized Control Trials Published since World Allergy Organization Position Paper (2009)

Description of Methods Used to Formulate the Recommendations:

The primary focus of the SLIT practice parameter is to provide guidance for effective, safe, and appropriate administration of the FDA-approved SLIT formulations. At the time of this writing, the FDA had approved three sublingual products, all of which are tablet formulations (short ragweed, timothy-pollen and 5-grass pollen). This document also considered studies of other formulations, such as European SLIT extract solutions or ‘off-label’ use of US licensed SCIT allergen extracts for SLIT, in the context of addressing some clinical questions not addressed in the systematic reviews (e.g., SLIT safety and efficacy in older adults or young children).

The workgroup evaluated the literature and formulated evidence-based recommendations. In the instances where direct evidence was lacking, the recommendations represent broadly-accepted consensus opinion. The recommendations were graded on the strength and consistency of key findings from these systematic reviews, additional literature search, and the recommendations in the FDA-approved SLIT PI to formulate evidence-linked recommendations for care (see Table 1, Classification of Strength of Evidence and Recommendations) and Evidence).

The practice parameter development process involved several stages. The process began in June 2014 with the selection of workgroup chairs, Linda Cox, MD and Michael Nelson, MD, PHD, and workgroup members; David Bernstein, MD Hal Nelson, MD Richard Lockey, MD Phil Lieberman, MD Anna Nowak-Wegrzy, MD, Anju Peters, MD, Charlotte Collins, JD, Sandra Lin, MD and ensued over 10 months. The workgroup began the process by developing a list of key clinical questions and topics to be addressed. At least two workgroup members were assigned to write each section and the entire document was reviewed and revised through several rounds of electronic review and an in-person meetings. The document was then sent to the Joint Task Force on Practice Parameter for additional review and revision. Subsequently, it was sent to the sponsoring organizations (AAAAI and ACAAI). At this stage the document was reviewed by the sponsoring organizations’ invited experts and posted to their website for membership comment. All comments were sent to the Joint Task Force and workgroup to consider for the final document. The document development and review process is outlined in the Online Repository (eTable 2- document development and review process)
Ensuring Appropriate Stakeholder Involvement: The writing group included an invited representative from the American Academy of Otolaryngology Head, Neck & Surgery (AAO-HNS) and a lay representative.

Benefits/Harms of Implementing the Guideline Recommendations Potential Benefits
The benefits/harms of a particular recommendation in the guideline was considered when the recommendation strength was assigned.

The full text guideline is available in English and can be accessed at http://www.allergyparameters.org

I. Executive Summary of FDA Approved SLIT Products

The primary focus of the SLIT Practice Parameter is to provide guidance for effective, safe and appropriate administration of the FDA approved SLIT formulations. It is crucial that the practicing allergist separate the data on FDA reviewed products that have led to approval of these products (i.e. grass and ragweed tablets) from the data in the literature with other allergens (e.g., dust mites) and other formulations (e.g., liquid formulations) that have not undergone the rigor of FDA review. Therefore, the data supporting a statement on FDA-approved products has been separated in this document from the data which supports SLIT administration of other allergens or other formulations, which it is hoped will be available in the near future. The effective dose may vary for a particular allergen depending on how it is formulated (e.g., tablet vs. extract solution). The effective SLIT dose has not been established for most of the U.S. licensed allergen products, but selected sublingual immunotherapy (grass and ragweed tablets) has been shown to be effective treatment for allergic rhinitis in both adults and children.. Sublingual immunotherapy products have been studied in children as young as 5 years and adults as old as 65 years and was found to be effective and safe in this age range.

The age range in the product information of three FDA-approved sublingual tablets differs in terms of starting age (Grastek® ALK-Abello, Hørsholm, Denmark 5 years, Ragwitek® ALK-Abello, Hørsholm, Denmark 18 years and Oralair® Stallergenes, Anthony, France 10 years) but all list 65 years of age as the upper limit (Table 2: Comparison of FDA-approve SLIT tablets’ product information labeling). These age range recommendations reflect the ages included in the clinical trials that were considered during the SLIT tablet approval process. Sublingual immunotherapy with FDA approved grass allergen results in disease modification manifesting as persistent clinical improvement after discontinuation of treatment. Both the timothy SLIT tablet and the 5-grass tablet have demonstrated clinical benefits beginning in the first year of a 3-year treatment. 8,9 Significant improvement in the combined symptom and medication scores over placebo were observed through two additional grass pollen seasons after discontinuation of three years of continuous treatment with the timothy SLIT tablet and throughout 3 years of pre-coseasonal treatment with the 5-grass SLIT tablet. There are insufficient studies directly comparing subcutaneous and sublingual immunotherapy, precluding a definitive statement regarding efficacy of immunotherapy.

All FDA approved studies of SLIT have employed a single allergen SLIT use. As there are no studies demonstrating efficacy of multiple allergens administered as a mixture, there is a need for further investigations to determine efficacy and optimal formulations and regimens for multi-allergen SLIT. The safety of a one day ultra rush build-up and administering the maintenance dose without up-dosing in children have not been studied for FDA approved formulations. The prescribing information for Ragwitek® in adults age 18-65 years, Grastek® in children age 5 up to adults age 65 9 and Oralair® for those 18 to
65 years calls for administration of the maintenance dose tablet without build-up (Table 2). The FDA-approved prescribing information for Oralair® recommends a 3-day updosing of 100IR, 200IR and 300IR for children ages 10 to 17 years. This up-dosing recommendation reflects the Oralair® pediatric clinical trial protocol rather than documented safety issues with a no up-dosing protocol in this age group. Initiate SLIT at least 12 weeks prior to the relevant season for pre- and co-seasonal therapy to achieve optimal efficacy. Localized symptoms (e.g. oromucosal itching and swelling) are common during the first week of SLIT treatment and systemic allergic reactions can occur but are rare.

**Summary Statement 1:** SLIT should not be prescribed for nor be used in routine clinical practice for treatment of oral allergy syndrome, food allergy, latex allergy, atopic dermatitis and venom allergy since there is limited evidence that SLIT is safe or efficacious for management of these conditions. [Strength of Recommendation: Strong; Evidence: A/B]

There are no FDA approved studies indications for SLIT for the treatment of oral allergy syndrome, food allergy, latex allergy, atopic dermatitis or venom allergy. Studies evaluating indications for these conditions are ongoing.

In randomized, controlled studies, SLIT has been associated with oral pharyngeal side effects as well as systemic allergic reactions (SR). The majority of SLIT adverse events are local reactions (oral, pharyngeal, or gastro intestinal symptoms). Most SLIT adverse reactions occur outside of the medical-supervised setting and therefore these reports are dependent on patient recall and appropriate recognition of symptoms associated with a SR. This is in contrast to reaction reports related to SCIT, which tend to occur within the first 30 minutes after administration, and are highly likely to be observed directly by a physician as a 30 minute observation period is recommended after SCIT administration in guidelines (Allergen immunotherapy: a practice parameter third update). Thus, SARs to SLIT may be under-reported and mischaracterized given different post-administration procedures.

**Summary Statement 2:** The physician should be aware that SLIT may not be suitable in patients with medical conditions that reduce the patient’s ability to survive a SR or the resultant treatment. [Strength of Recommendation: Strong; Evidence: D]

The FDA-approved SLIT tablet prescribing information lists the following contraindications: severe, unstable or uncontrolled asthma, any history of a severe SR; a history of any severe local reaction to SLIT; a history of eosinophilic esophagitis (EoE); 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 SR 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, and uncontrolled hypertension. SLIT may not be suitable for patients who are taking medications that could potentiate or inhibit the effect of epinephrine.

Although the SLIT tablets have not been studied in patients with severe, unstable or uncontrolled asthma, these are known risks for severe and even fatal reactions to SCIT, and are relative contraindications for initiating or continuing allergen immunotherapy. There is no published basis for
withholding SLIT to patients with a history of a severe systemic reaction to agents other than AIT, but this was an exclusion criteria used in the studies of the timothy, 5-grass pollen and short ragweed SLIT tablets. There are also no published data that indicates that a patient, who has had a severe SLIT local reaction to one allergen is at increased risk for a severe LR or SR to another allergen. The inactive ingredients of the USA FDA-approved sublingual tablets (Table: Comparison of US Licensed Sublingual Immunotherapy Tablet per FDA approved Product Information Insert) have rarely been associated with anaphylaxis or other significant adverse effects.12,13

A history of eosinophilic esophagitis (EoE) is considered a contraindication to initiation of treatment in the FDA-approved SLIT tablets’ product prescribing information.3-5 Development of EoE while taking SLIT is also a risk. It is not well established if SLIT can exacerbate already present EoE in a patient initiating SLIT, though it is presumed this is of potential risk to occur. There is a case report of a patient who twice developed retrosternal pain and dysphagia accompanied by eosinophilia on esophageal biopsy while taking timothy SLIT tablets, with both symptoms and esophageal eosinophilic infiltration clearing on stopping the tablets.14 An additional patient treated with tree pollen SLIT developed dysphagia within 4 weeks of starting SLIT. Esophageal biopsy revealed inflammation with peak 164 eosinophils per high power field. Symptoms and esophageal hypereosinophilia resolved without treatment within 4 weeks after discontinuation of SLIT.15

It is recommended in European guidelines and ‘mandated’ in the FDA-approved SLIT tablet PIs that, in cases of oral inflammation, such as mouth ulcers, lichen planus or dental extractions, administration of SLIT be temporarily discontinued until there is “…complete healing of the oral cavity.”3-5 However, further data are needed to better substantiate the degree to which this is a risk.

Summary Statement 3: There are no controlled data regarding the safety of SLIT immunotherapy during pregnancy or during breast-feeding. Therefore, FDA approved SLIT products should be used cautiously in the pregnant or breast-feeding patient. [Strength of Recommendation: Weak; Evidence: C]

There is little data on the safety or efficacy of allergen immunotherapy (SLIT or SCIT) in pregnancy. However, observational retrospective SCIT studies and case reports provide reassuring safety data.

It is not known if any of the FDA approved SLIT products are secreted in breast milk and no specific recommendations can be made about the safety of SLIT during breastfeeding. The 5-grass pollen and the timothy sublingual tablets are assigned a category B rating. The FDA PI for these products states “Because systemic and local adverse reactions with immunotherapy may be poorly tolerated during pregnancy, Oralair®/ Grastek® should be used during pregnancy only if clearly needed.” The ragweed tablet (Ragwitek®) is assigned a category C rating, which the pregnancy rating status of all of the USA licensed allergen extracts.16

The current AIT practice parameters state that AIT “…can be continued but is usually not initiated in the pregnant patient.”11 Although these recommendations were directed at SCIT, the only FDA-approved formulation at the time of publication, safety data supports extending this recommendation to SLIT.11
Summary Statement 4: There are no direct comparisons between the same allergen extract administered as a SLIT tablet versus a liquid. Therefore, it is unknown if there is equal efficacy and/or safety with similar doses of the two preparations. Each formulation needs to establish its own safety regulation. [Strength of Recommendation: Weak; Evidence: C]

There are no FDA approved SLIT liquid formulations and thus no basis for comparison. The effective doses with grass\textsuperscript{17,18} and ragweed SLIT tablets\textsuperscript{19} have been carefully defined in large, multi-dose studies. As there are no studies demonstrating efficacy of multiple allergens administered as a mixture, there is a need for further investigations to determine efficacy and optimal formulations and regimens for multi-allergen SLIT.

Summary Statement 5: Know that the first dose of SLIT should be administered 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]

It is a recommendation in the FDA-approved SLIT tablets’ PI that the first SLIT dose be administered in a medically-supervised setting, and is the general practice in Europe. In Phase III studies of SLIT tablets the majority of systemic reactions and administrations of epinephrine have been with the first dose.\textsuperscript{4,5,10} In SCIT the first dose is always administered in a medically-supervised setting.\textsuperscript{11} This recommendation, while based mainly on expert opinion of where one can most safely accomplish introduction of new allergen in immunotherapy, also reflects that the safety of first dose initiation of SLIT at home has not been studied to determine if this may be feasible. Future studies are needed to demonstrate this is a safe practice before the recommendation could be weakened.

Summary Statement 6: Prescribe epinephrine auto-injectors to patients receiving SLIT. Patients should be trained how to use the device, instructed on how to recognize and manage adverse reactions and missed doses, and when to contact their physician or other health care professional. Recommendations for when to withhold the SLIT dose to avoid potential situations when systemic reactions may be more likely should also be provided. [Strength of Recommendation: Strong; Evidence: D]

Following the first dose in the physician’s office, SLIT is administered at home without direct medical supervision. Patients should be given specific written instructions about how to manage adverse local/SR, missed doses, and the clinical situations that indicate they should withhold SLIT. They should also be instructed on when to contact their physician or other health care professional regarding SLIT adverse reactions, treatment gaps or other events that may impact treatment (e.g., new medication or illness). As indicated in the FDA-approved SLIT tablet PI, patients should not take SLIT treatments if their asthma is not well controlled. Treatment discontinuation should be considered if there are repeated asthma exacerbations. Treatment instructions should include information about oral lesions that require a temporary discontinuation of SLIT, e.g., oral lichen planus, mouth ulcers, thrush, or wounds following oral surgery or dental extraction.\textsuperscript{4,5,9} Although there have been no fatalities to SLIT recorded to date in the European Union, where it is not the usual practice to prescribe auto-injectable epinephrine for SLIT patients, the FDA has directed that auto-injectable epinephrine be prescribed for all patients receiving SLIT and that they be instructed in its use. Local reactions are common and physicians should describe local
reactions as well as systemic reactions. He/she should describe instances when patients should use epinephrine. Patients also should be instructed on the clinical signs and symptoms of a SAR and when to administer epinephrine if such an event occurs.

**Summary Statement 7: A reduction in SLIT dose is advised if the patient has missed more than 7 continuous days worth of doses. [Strength of Recommendation: weak; Evidence: D]**

There is little evidence to guide how long discontinuation of SLIT can be tolerated before the risk of a local or systemic reaction becomes elevated. No controlled trials have examined the safety of resuming SLIT treatment after missed doses. The FDA-approved patient labeling (Medication Guide) for all three SLIT tablet recommends contacting the healthcare provider if more than one dose is missed “take (Oralair® and 7 days for Grastek® and Ragwitek®) as prescribed by your doctor until the end of the treatment course. If you forget to..., do not take a double dose. Take the next dose at your normal scheduled time the next day. If you miss more than one dose..., contact your healthcare provider before restarting.” 4,5,10 The three products’ clinical trial protocols differed in the length of a treatment gap allowed patient was required to contact the clinic: one day for Oralair® and 7 days for Grastek® and Ragwitek®. However Oralair® and Grastek® demonstrated similar safety in trials with no up-dosing or discontinuous (pre-co-seasonal) protocols. This suggests that recommendations for treatment gaps should be the same. Data regarding the safety resuming Ragwitek® after treatment interruptions are limited as all of the pivotal clinical trials were conducted during a single season. In the clinical trials, treatment interruptions for up to seven days were allowed.

No controlled trials have examined the safety of resuming SLIT treatment after missed doses. The FDA-approved patient labeling (Medication Guide) for all for all three SLIT tablet recommends contacting the healthcare provider if more than one dose is missed “take (Oralair® and 7 days for Grastek® and Ragwitek®) as prescribed by your doctor until the end of the treatment course. If you forget to..., do not take a double dose. Take the next dose at your normal scheduled time the next day. If you miss more than one dose..., contact your healthcare provider before restarting.” 4,5,10 The three products’ clinical trial protocols differed in the length of a treatment gap allowed patient was required to contact the clinic: one day for Oralair® and 7 days for Grastek® and Ragwitek®. However Oralair® and Grastek® demonstrated similar safety in trials with no up-dosing or discontinuous (pre-co-seasonal) protocols. This suggests that recommendations for treatment gaps should be the same. Data regarding the safety resuming Ragwitek®, after treatment interruptions are limited as all of the pivotal clinical trials were conducted during a single season. In the clinical trials, treatment interruptions for up to seven days were allowed.

Although there have been no fatalities to SLIT recorded to date in the European Union, where prescribing auto-injectable epinephrine for SLIT patients is atypical, the FDA has directed that auto-injectable epinephrine be prescribed for all patients receiving SLIT and that they be instructed in its use. Local reactions are common and physicians should describe local reactions as well as systemic reactions. He/she should describe instances when patients should use epinephrine. Patients also should be instructed on the clinical signs and symptoms of a SAR and when to administer epinephrine if such an event occurs.
Summary Statement 8: Schedule patients on SLIT therapy for regular follow-up care with a specialist trained in the evaluation of patients with allergic conditions, in order to monitor efficacy and safety and as a strategy for optimizing adherence. [Strength of Recommendation: Moderate; Evidence: D]

Patients on SLIT will benefit from regularly scheduled care with a health care provider skilled in the assessment and management of patients with allergic conditions, as is the case with SCIT.\textsuperscript{11} This is to assess for issues with symptom control and overall efficacy with SLIT. There are no studies or provider experience to date describing follow-up care with FDA-approved SLIT formulations, but this recommendation follow common sense clinical practices that should be followed with prescribing any form of immune modulating therapy, in particular therapy where the FDA strongly recommends such patients be prescribed auto-injectable epinephrine. The experience outside the US regarding patient follow up for non-FDA approved SLIT forms is discussed in the parallel recommendation in section II.

II. Executive Summary of SLIT Studies on Non-FDA Approved Allergens or Formulations

Sublingual immunotherapy has been used worldwide for many years. In the US, the Food and Drug Administration has only recently approved three sublingual tablets for use, as was detailed in section I. However, the Joint Task Force on Practice Parameters is aware that many providers in the US have used off-label preparations of subcutaneous extract (or other preparations) as sublingual therapy based on data and experience from outside the US. Many such preparations have approval for the treatment of allergic rhinitis/rhinoconjunctivitis and asthma in Europe. However, at present, the FDA has not approved the use of any sublingual product or preparation beyond the aforementioned tablets. Though the JTFPP unequivocally does not endorse the use of off-label preparations of sublingual products given incomplete evaluation of their safety and efficacy for use in US populations, the SLIT workgroup and the JTFPP felt obligated to discuss the evidence supporting the use of such preparations that have been approved outside the US. In doing so, the workgroup and the JTFPP very clearly caution that the following review of the literature is for educational purposes only, and is not an endorsement of any particular product in any particular age group for specific indications or treatments of allergic disease. These statements in this section are therefore only recommendations on how the available evidence could be applied for those providers who do choose to use non-FDA approved SLIT formulations in an off-label application. The quality of the majority of the studies to be discussed in this section is variable. This assessment is based on review of these studies and concern that some demonstrate lack of scientific rigor, lack of power, substandard design, unclear dosing/potency, and small enrollment numbers compared to the FDA approved studies for the sublingual tables. The JTFPP will not reverse this sentiment until the FDA formally reviews such data and issues approval for these alternative preparations.
Summary Statement 1: The only FDA approved products for SLIT in the US are the Oralair®, Grastek®, and Ragwitek® tablets, indicated for the treatment of allergic rhinitis and asthma. Though alternative regimens and preparations for SLIT have been proposed and are used off-label in the US (e.g. use of SCIT extract for sublingual delivery, or use of specific sublingual “drops”), these products do not have FDA approval at present, nor have they been systematically studied in a rigorous manner in US populations. Their use at present is off-label, at a provider’s discretion, and not currently recommended for any particular indication. Therefore, off-label use of SLIT liquid extracts is not endorsed. [Strength of Recommendation: Strong; Evidence: D]

There are 84 randomized-DBPC studies in non-US patients evaluating SLIT for the treatment of allergic rhinitis/rhinoconjunctivitis and asthma, of which 60 have been conducted using grass, ragweed, and dust mite extracts (see eTable-1 summarizing the RCT published since the World Allergy Organization Position Paper). The reported effective dose ranges for SLIT are very broad, unlike in SCIT. Furthermore the effective dose may vary for a particular allergen depending how it formulated (e.g., tablet vs. extract solution). Many allergens have not been formally evaluated in a RCT or open SLIT clinical trial, and effective SLIT dose ranges for many allergens cannot be extrapolated from the collective literature. Each particular SLIT formulation must independently demonstrate a safe and effective dosing regimen.

Since the first DBPC SLIT trial in 1986, there has been a progressive increase in SLIT prescriptions worldwide. In some parts of the world, it represents the majority of new allergen immunotherapy (AIT) prescriptions. Despite no FDA-approved SLIT formulations in the US until 2014, ACAAI surveys suggest US SLIT prescriptions among respondents increased from 5.9% to 11.4% between 2007 and 2011, 86% of whom reported prescribing commercially available SCIT extracts for ‘off-label’ use. Given this degree of off-label use, the JTFPP felt that some discussion of non-approved forms was necessary. Comprehensive study of liquid forms and the non-FDA approved tablet forms of SLIT is necessary to provided data regarding indications for therapy, effective dose ranges for liquid SLIT extracts, and the overall safety/efficacy of such preparations. Given some degree of off-label use, some discussion of non-approved forms is necessary.

Summary Statement 2: Outside the US, sublingual immunotherapy for multiple allergens has been shown to be effective treatment for seasonal and perennial allergic rhinitis and allergic asthma in both adults and children. [Strength of Recommendation: Strong; Evidence: A]

Meta-analyses and systematic reviews of RCT’s in non-US populations have demonstrated the efficacy of SLIT in both children and adults to improve outcomes related to both allergic rhinitis and allergic asthma (eTable-1). Such outcomes include improved symptoms, quality of life, and medication use compared to usual medical care for these conditions. The Agency for Healthcare Research and Quality (AHRQ) recently performed a comprehensive a systematic review on “Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review” (evidence tables provided in the online document at http://www.effectivehealthcare.ahrq.gov/ehc/products/270/1427/Allergy-Asthma-Immunotherapy-130319.pdf.) This review assessed 63 SLIT studies inclusive of 5131 participants that met the inclusion
criteria (RCT’s that compared SLIT with placebo, pharmacotherapy, or other SLIT regimens). 6 The review concluded that the strength of evidence was moderate to support the effectiveness of SLIT for the treatment of symptoms of allergic rhinitis/rhinoconjunctivitis, conjunctivitis, asthma plus allergic rhinitis/rhinoconjunctivitis as well as medication use, and quality of life related to treatment of these conditions. The strength of evidence for reduction in asthma symptoms was high. Evidence was insufficient to address optimal dosing questions for these indications. (See statement 2, section I).

**Summary Statement 3:** Sublingual immunotherapy has been studied in children as young as 3 years and adults 75 years old and was found to be effective and safe in these age ranges.

[Strength of Recommendation: Moderate; Evidence: A]

A 2006 meta-analysis of 9 non-US randomized placebo-controlled, double blind trials of SLIT in the treatment of allergic rhinitis in 441 pediatric patients 3-18 years of age found a significant reduction in both symptom and medication scores.29 The AHRQ systematic review included 18 randomized-controlled SLIT trials with 579 children less than 18 years of age, noting the strength of evidence was high for SLIT in reducing asthma symptoms (9 studies) and moderate for reducing rhinitis/rhinoconjunctivitis symptoms (12 studies).28 When all domains with pertinent clinical outcomes were considered, SLIT in children and adolescents demonstrated moderate evidence of improving symptom control. However, the AHRQ systematic review found the evidence was insufficient to comment on the effectiveness of SLIT versus placebo on improving disease-specific quality of life (2 studies).

Two subsequent European studies with timothy 30 and a 5-grass SLIT tablets31 (inclusive of children age 5 to 16 or 17 years of age) reported a significant reduction in rhinitis symptoms. However, observational studies suggest treatment adherence may be problematic in young children. An observational study of 150 Italian children age 3 to 6 years of age on SLIT found that 52% of the 3-year olds, compared to 18% of the 4-year olds and 13% of the 5-year olds, discontinued treatment in the first year.32 The most common causes for discontinuation in the 3-year olds were oral discomfort or the child’s refusal to take the treatment. For this reason, the authors recommended that SLIT be started at age 4 years or older.

There is limited data regarding SLIT safety and efficacy in the ≥ 65 years old population from non-US studies. A Polish DBRCT study of liquid SLIT HDM extract vs. placebo, in subjects 60 to 75 years of age with symptoms of perennial rhinitis and allergy only to house dust mites, noted significant reduction in total nasal symptoms and medication scores in those receiving active treatment versus placebo after 3 years of treatment.33 Similarly in a double-blind placebo-controlled study in patients 60-70 years old with allergic rhinitis to grass pollen, receiving a 5-grass SLIT tablet, showed nasal symptom scores were reduced 61% in the active compared to the placebo group after 3 years of treatment.34

There is no recommendation regarding an upper age limit for AIT in the 2011 Allergen Immunotherapy Practice Parameter, and outside the US, no upper-age limit has been recommended for SLIT.11 However, the AHRQ systematic review cautioned that there is insufficient evidence to comment on the effectiveness of SLIT in the elderly, and theoretical concern regarding handling of potential allergic reactions in this age group.28

**Summary Statement 4:** Studies have demonstrated that SLIT with various allergen types can result in disease modification manifesting as persistent clinical improvement after
discontinuation of treatment, reduction in new allergen sensitizations in monosensitized patients, and reduction in the development of asthma in patients with allergic rhinitis. [Strength of Recommendation: Moderate; Evidence: A]

Persistent clinical benefits were demonstrated in the year after discontinuation of a one year course of a HDM SLIT tablet\(^35\) and after 3 years of co-seasonal grass liquid SLIT.\(^36\) Sustained clinical improvement, including reduction in symptom-medication scores and development of neo-sensitization, was demonstrated for up to 8 years after a 4 to 5 year course of HDM SLIT in monosensitized adults with allergic rhinitis.\(^37\) A 3-year course provided 7 years of clinical benefits. This study also demonstrated a marked reduction in developing sensitization to new allergens on prick skin testing in all of the actively treated patients versus the untreated control population. Children with allergic rhinitis treated with SLIT (grass pollen, birch pollen, Parietaria, and HDM) have also been shown to less often develop asthma.\(^38,39\)

**Summary Statement 5:** There are insufficient studies directly evaluating subcutaneous and sublingual immunotherapy to make a definitive statement regarding comparative efficacy. However, available studies suggest that SCIT is more effective during the first year of treatment than SLIT. Comparative long-term efficacy studies have not been conducted. [Strength of Recommendation: Weak; Evidence: B]

There are no powered, well-designed studies comparing SCIT and SLIT, though expert reviews have included direct and indirect comparisons of available SLIT and SCIT studies.\(^28,40,41-43\) The AHRQ systematic review identified 8 studies where SCIT and SLIT were directly compared. Only 3 such studies had statistical comparison of outcomes, and the review concluded there was low evidence supporting superiority of SCIT versus SLIT for rhinitis or conjunctivitis control or medication use. However, there was insufficient evidence to evaluate if SCIT vs. SLIT was superior for asthma symptoms or medication use.

A 2013 review of AIT for allergic rhinitis compared the efficacy of SCIT and SLIT in separate meta-analyses.\(^43\) The review found a standardized mean difference (SMD) reduction in symptom scores and medication use in 17 trials significantly in favor of SCIT. In an 11 study comparison of SCIT and SLIT (4 were DBPC and 7 were open but randomized), SCIT provided significantly favorable clinical and immunologic responses compared to placebo more often than SLIT, though some of this may be attributable to sub-optimal SLIT dosing and frequency. These drawbacks appear to have been overcome in a study that directly compared optimal dosing with a timothy extract (SCIT, Alutard SQ and SLIT, Grazax) produced by the same company, ALK-Abello, Hørsholm, Denmark.\(^44\) Only SCIT-treated subjects had a significant change in nasal challenge threshold compared to the controls in this 15-month study. Other outcomes, including IgG4, IgE-blocking factor, facilitated allergen presentation and basophil activation were significantly different from controls in both active treatment groups, favoring the response in SCIT twice as much as SLIT. However, well-designed head-to-head trials of SCIT vs. SLIT, specifically powered to show superiority of outcomes, are needed to truly resolve this issue.

**Summary Statement 6:** Non-FDA approved SLIT formulations should not be used in routine clinical practice for treatment of non-rhinitis/asthma conditions such as oral allergy syndrome, food allergy, latex allergy, atopic dermatitis and venom allergy since there is limited evidence demonstrating SLIT is either safe or efficacious for management of these conditions. Furthermore, these formulations have not undergone rigorous FDA evaluation of
There are no FDA approved indications of SLIT for the treatment of oral allergy syndrome, food allergy, latex allergy, atopic dermatitis or venom allergy. Due to a lack of large scale, well-designed studies showing clear safety and clinical effectiveness in US populations, SLIT should not be used routinely to treat OAS, food allergy, atopic dermatitis or venom allergy. There have, however, been selected Investigational New Drug status approvals issued to investigators for past or ongoing research of the following potential applications using liquid SLIT preparations:

**Oral allergy syndrome:** Pollen sensitization is considered to be a primary event with food allergic reactions to foods of plant origin. In a small study comparing SCIT and SLIT for OAS, complete tolerance to raw apple was achieved in two of eight and one of seven patients receiving injection and oral IT, respectively. An additional three in the SCIT group and two in the SLIT group tolerated increased doses of raw apple. In contrast, a trial of SLIT for birch pollen allergy did not show efficacy for alleviating OAS symptoms, however this study used a relatively low maintenance dose of Bet v 1 (4.5 µg daily). SLIT for OAS has also been studied with recombinant major apple allergen Mal d 1 and with a cross-reactive Bet v 1. Two sublingual administrations of 50 µg of Mal d 1 were well tolerated and induced transient immune responses with decrease in Bet v 1 and Mal d 1 specific IgE and an increase in IL-10 and IFN gamma production from T cells. These results suggest that recombinant Mal d 1 might be suitable allergen for sublingual treatment of birch pollen-related apple allergy.

**Food allergy:** There are multiple case reports of successful SLIT reported for milk, peanut, hazelnut, kiwi, and peach. These reports have been followed by initiation of clinical trials of SLIT involving milk, peanut, hazelnut, kiwi, and peach extract in multiple subjects. However, the quality of this evidence is heterogeneous, as are the conduct of the individual trials relative to one another. Some trials evaluated SLIT efficacy in patients with symptoms of pollen food syndrome rather than systemic food allergy. In both controlled and uncontrolled food allergy trials, SLIT has been generally better tolerated with lower rates of SR as compared to oral immunotherapy (OIT). This may be due to significantly lower starting doses in SLIT (100-1000 fold lower than those in OIT) related to formulation potency, and a lower density of pro-inflammatory cells, such as mast cells, in the oral mucosa. However, the degree of desensitization produced from SLIT appears to be significantly less effective compared to OIT in limited available data. A retrospective comparison of SLIT versus OIT for peanut allergy shows that peanut OIT resulted in greater changes in peanut-specific IgE, IgG4, and basophil activation as compared to peanut SLIT, and eliciting dose thresholds were lower during DBPCFC at 12 months in patients who underwent SLIT. A single-centered, randomized study compared milk SLIT vs. OIT. Thirty milk-allergic children (ages 6 to 17 years) were randomized to SLIT or SLIT followed by low or high dose of milk OIT. Following therapy, 1 of 10 subjects in the SLIT-group, 6 of 10 subjects in the SLIT/low dose OIT group, and 8 of 10 subjects in the SLIT/high dose OIT group passed the 8g desensitization challenge (P = 0.002, SLIT vs. oral immunotherapy). Systemic reactions were more common during OIT escalation and maintenance (0.43% with high doses, 0.08% with low doses) than during SLIT maintenance (0.02%). Milk OIT was more efficacious for desensitization than SLIT alone but was associated with more systemic side effects. However, this study was underpowered to find any effect, a common problem with most of the early phase food SLIT trials.
**Latex allergy:** A number of clinical trials explored the safety and efficacy of SLIT for latex allergy in adults and children with inconsistent results. 57-61 SCIT and SLIT native latex immunotherapy appears to be effective in reducing symptoms upon latex exposure in a subset of latex-allergic health care workers and children. Native latex SLIT has a better safety profile compared with native latex SCIT. Mutated recombinant latex allergens are being evaluated as a potential approach for latex immunotherapy. 64,65 Although standardized latex allergen extracts are commercially available in Europe, latex SLIT is limited to the research at this time.

**Atopic dermatitis** (AD): Only one randomized controlled trial of SLIT in AD met the rigorous inclusion criteria as outlined in a recent systematic review using the GRADE system. Fifty-six children 5-16 years old with AD and mono-sensitization to dust mites and without food allergy or chronic asthma were randomized 1:1 to SLIT with dust mites or placebo for 18 months. 66 Forty-eight completed the study, with 2 dropouts in the active and 6 in the placebo groups. The difference from baseline in the SCORAD was significant (P = .025) between the 2 groups starting from month 9. Similarly, there was a significant reduction in the use of medications only in the active group. A significant difference was found only in patients with mild-moderate disease, whereas patients with severe disease had only a marginal benefit. SLIT was discontinued in 2 patients because of exacerbation of dermatitis. In another study, adult subjects (mean age 27.3 years ± 8.2 years) were randomized to active dust mite SLIT and pharmacotherapy (n=58) or to control pharmacotherapy only (n=49) for 12 months. Twenty-three cases withdrew from the study. The treatment group had a significant reduction in daily drug scores and visual analog scores compared with the control group at 12 months follow-up. At the end of therapy, a significant difference was found in the change in average daily drug scores (difference from 1 month) between the two groups (P < 0.01); The treatment versus the control group had a higher level of serum-specific IgG4 at 6 and 12 months of treatment (P < 0.05). While these results are encouraging, additional high-quality evidence from rigorous randomized, controlled clinical trials is necessary to support the use of SLIT in AD.

**Venom immunotherapy** SLIT with venom has been evaluated in 2 proof-of-concept studies that reported preliminary encouraging results with honeybee SLIT and vespula SLIT.67 68 SLIT with venom was safe and well tolerated. Considering limited evidence and the well-established efficacy of SCIT with venom, at this time, SLIT with venom is not recommended for treatment of venom allergy. 69

**Summary Statement 7:** Localized symptoms (e.g. oromucosal itching and swelling) are very common during the first week of SLIT treatment, similar to the experience with the FDA-approved formulations. These usually disappear within a few days to weeks without treatment or dose modification. However, some local reactions can be severe enough to cause discontinuation of treatment. SLIT systemic allergic reactions are very uncommon. [Strength of Recommendation: Strong; Evidence: A]

SLIT produces both localized oropharyngeal side effects as well as systemic allergic reactions (SR). The majority of SLIT adverse events reported in non-US clinical trials and other studies are local reactions (oral, pharyngeal, or abdominal).

The AHRQ systematic review analyzed 63 studies in 5,131 subjects undergoing SLIT and found local reactions were predominant and systemic events rare. 6 SLIT local reactions generally occurred in the first few days or weeks of treatment and resolve with medication and dosing adjustments. A comprehensive review of SLIT adverse reactions indicates that isolated oral and/or abdominal manifestations can be considered local reactions unless they are associated with other organ system
involvement (e.g., skin, upper and lower respiratory tract, and cardiovascular manifestations), which would then classify them as a SR.70

A proposed grading system for classifying SLIT LR based on information obtained from pre-marketing pivotal trials, randomized control trials, and post-marketing surveys and case reports was developed by the World Allergy Organization (WAO).70 A list of local reaction symptoms is also included in the WAO SLIT local reaction classification document. (Tables 4 and 5) These criteria were not accepted for LR rating by the FDA during the US SLIT tablet approval process. SLIT SRs should be graded 1-5 using the World Allergy Organization classification for SRs to subcutaneous immunotherapy (SCIT).71 These recommendations for classifying SLIT LR and SAR are adopted for section I of this Practice Parameter.

SLIT SRs are rare and are believed to occur with significantly lesser frequency than with SCIT. In available data regarding documented SLIT reactions, most of these have not required the administration of epinephrine and no fatalities attributable to SLIT, to date, have been reported.72 Across 66 SLIT studies, inclusive of 4,378 subjects and approximately 1,181,654 SLIT doses, serious SAR has been shown to occur at a rate of one serious SAR per 384 treatment years.21 A Cochrane review of SLIT for allergic rhinitis examined 2,333 SLIT-treated and 2,256 placebo controls.7 In these subjects there were no SRs and only one subject required treatment with epinephrine. Thirteen SRs of a severity to be classified as anaphylaxis have been described in case reports.73-75

In review of available SLIT data, most SLIT adverse reactions have been noted to occur outside of the medical-supervised setting and therefore these reports are dependent on patient's recall and appropriate recognition of symptoms associated with a SR. In contrast, in SCIT, where the current 2011 practice parameter recommends a 30 minute observation post-administration, most SCIT SR are directly observed. Thus, there is potential that SARs to SLIT may be under-reported and mischaracterized.

**Summary Statement 8:** SLIT is contraindicated in patients with medical conditions that may reduce the patient’s ability to survive a SR, may actively inhibit the resulting treatment, or may be potentiated by ongoing mucosal exposure to allergen potentially triggering the condition. [Strength of recommendation: Strong; Evidence: D]

The same guidance issued in summary statement 2 for FDA approved SLIT preparations are recommended to be applicable to non-FDA approved forms until firm data regarding the safety of administering the non-FDA approved SLIT formulations is established. Providers may also wish to evaluate use of SLIT in patients with medical conditions that may reduce their ability to survive a serious SR or increase the risk of adverse reactions after epinephrine administration, such as markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.

**Summary Statement 9:** Patients should be instructed to temporarily discontinue SLIT in the presence of oral pharyngeal inflammation or wounds (e.g., dental surgery, tooth loss or extraction) until complete healing occurs. [Strength of Recommendation: Moderate; Evidence: D]

A unique possible risk factor for SLIT not applicable to SCIT is oral inflammation, since damaged oral mucosa may allow for increased systemic absorption of the allergen. It is recommended in European
guidelines and ‘mandated’ in the FDA-approved SLIT tablet PIs that, in cases of oral inflammation, such as mouth ulcers, lichen planus or dental extractions, administration of SLIT be temporarily discontinued until there is “…complete healing of the oral cavity.” 3-5 (See recommendations in appendix table)

Summary Statement 10: There is limited data regarding the safety of any SLIT product (FDA-approved or non-approved) in pregnancy and no safety data for any SLIT product during lactation. [Strength of Recommendation: Weak; Evidence: C]

There is little data on the safety or efficacy of allergen immunotherapy (SLIT or SCIT) in pregnancy, and the AHRQ systematic review specifically commented that there are insufficient data to rate the safety and efficacy of SLIT in pregnant women.3 There is similar limited data in SCIT, as a parallel. Current AIT practice parameters discourage initiation of SCIT during pregnancy, but do not actively recommend discontinuing SCIT in established patients who become pregnant. Observational, retrospective SCIT studies and case reports provide reassuring safety data that SCIT is likely safe to continue in pregnancy.

Preliminary controlled data regarding SLIT safety in pregnancy was demonstrated in a prospective study of 155 patients who were treated with SLIT during 185 pregnancies.76 In 24 patients the SLIT was initiated during pregnancy. Controls included pregnant women on either budesonide or rescue beta-agonist but not on any form of AIT. There were no SRs reported. The incidence of abortion was significantly higher in the control group compared with the SLIT group. Prematurity, toxemia, and perinatal deaths were higher in both control groups as compared to the SLIT group. It is not known if any of the FDA approved SLIT products are secreted in breast milk and no specific recommendations can be made about the safety of SLIT during breastfeeding.

Summary Statement 11: There are no head-to-head studies directly comparing the same allergen extract administered as a SLIT tablet versus a liquid. Therefore, it is unknown if SLIT tablet vs. liquid has efficacy and safety at similar doses of the two preparations. Each formulation should be evaluated to establish its own safety regulation. [Strength of Recommendation: Moderate; Evidence: C]

Liquid SLIT doses, some varying over 500-fold, have been reported to be effective. Dose response studies with liquid extract are lacking, or have shown a strong degree of heterogeneity.77,78,79,80,23,19,81,15 Furthermore, the issue of relative potency among different liquid SLIT extracts and between selected liquid SLIT extracts and approved tablets remains unresolved and in need of further studies of comparative efficacy. It is not recommended to try to compare different SLIT formulations. As noted in statement 2, each allergen must be studied for optimal dosing including the SLIT form (liquid vs. tablet).

Summary Statement 12: Most SLIT studies involved single-allergen administration, and data are limited regarding multi-allergen SLIT safety and efficacy. [Strength of Recommendation: Strong; Evidence: A]

There are limited data on the safety and efficacy of multi-allergen SLIT. One study, which examined administration of an extract mixture containing more than two allergens, suggested that there was reduced efficacy in the mixture compared to the same dose administered as monotherapy. Two
studies have been performed comparing the safety of multi-allergen SLIT with up to 3 unrelated allergens to that with monoallergen SLIT in adults and children, and found no significant differences in rates of adverse events. Two studies have examined the efficacy of administering two unrelated allergen extracts, administered separately but in tandem, showing no improvement in symptom/medication scores over the four years in the drug treatment group, but all SLIT treated subjects improved in both the grass and the birch seasons, making it difficult to interpret outcomes based on regimen. In another study of timothy grass and HDM extracts were administered sublingually at the same time from separate vials demonstrated a significant reduction in HDM and timothy-pollen skin test reactivity and other favorable immunologic changes, e.g., increase in timothy grass and HDM sIgG4 and memory Treg cells. The only study to assess response to a SLIT multiple allergen mixture was one that evaluated timothy extract only vs. timothy plus 9 unrelated pollen extracts, or placebo. The authors noted significant differences vs. placebo for titrated nasal challenge, titrated prick skin tests and serum IgG4 levels to timothy, while those receiving the same dose of timothy in the mixture only differed from placebo in titrated prick skin tests and then to a lesser degree than those receiving timothy monotherapy. There are no published studies to determine the best timing for administering SLIT as separate allergens in tandem combination on the same day. There is a need for further investigations to determine efficacy and optimal formulations and regimens for multi-allergen SLIT.

Summary Statement 13: The first dose of SLIT should be administered in a medical facility under the supervision of a physician or other health care professional with experience in the diagnosis and treatment of anaphylaxis. [Strength of Recommendation: Strong; Evidence: D]

Summary Statement 14: The patient should be observed in the clinic or medical facility for 30 minutes after the administration of the SLIT dose because the majority of systemic reactions requiring epinephrine have occurred with the first dose. [Strength of Recommendation: Strong; Evidence: D]

It is the general practice in Europe that the first SLIT dose be administered in a medically-supervised setting, and this statement is identical to summary statement 5 in Section I. This recommendation furthermore parallels the recommendation made in the 2011 Allergen Immunotherapy Practice Parameter regarding the initial dose of SCIT. Though SLIT in any formulation in general is associated with lesser rates of local and systemic reactions, these may be more likely to occur on the initial dose and thus precaution is warranted, pending additional data and provider experience showing a clear best-practices strategy.

Summary Statement 15: Prescribe auto-injectable epinephrine to any patient receiving SLIT, and train the patient in the indications and use of this device. Given SLIT patients a written anaphylaxis management plan with detailed instructions on how to recognize and manage adverse reactions, how to manage missed doses, and when to contact their physician or other health care professional. [Strength of Recommendation: Strong; Evidence: D]

The recommendations for epinephrine auto-injector prescription, written anaphylaxis/event management plans, and clinical situations indicative of when they should withhold SLIT or contact their prescribing healthcare provider regarding adverse reactions or treatment gaps should apply to non FDA-
approved SLIT formulations as discussed in summary statements 6 and 7 in section I. Although there have been no fatalities to SLIT recorded to date in the European Union, where it is not the usual practice to prescribe auto-injectable epinephrine for SLIT patients, the FDA has directed that auto-injectable epinephrine be prescribed for all patients receiving SLIT and that they be instructed in its use and indications for treatment.

**Summary Statement 16**: Establish routine follow-up care with patients receiving SLIT for monitoring efficacy and safety and as a strategy for optimizing adherence. [Strength of Recommendation: Moderate; Evidence: D]

Patients on SLIT will benefit from regularly scheduled care with a health care provider skilled in the assessment and management of patients with allergic conditions, as is the case with SCIT. This is to assess for issues with symptom control and overall efficacy with SLIT. Controlled trials and short-term studies with SLIT suggest adherence rates are 80-90%. This recommendation is identical to summary statement 8 in section 1.

Claims analysis and prescription renewals outside the US suggest SLIT adherence is poor and similar to other long-term therapies. In retrospective and prospective, observational and randomized-controlled trials evaluating SLIT adherence, premature discontinuation rates ranging from 21% to 93% of patients have been reported. Lack of efficacy, side effects, and costs are some of the reasons reported for premature SLIT discontinuation. Strategies that have been shown to improve SLIT adherence include a comprehensive patient educational program prior to treatment initiation, which includes information on the patient’s allergic disease; e.g. allergic rhinitis: ‘natural history’, SLIT’s benefits and adverse effects, optimal length of SLIT treatment. An educational program, in conjunction with scheduled telephone or email follow-up, use of electronic devices to remind patients to take their medication and more frequent follow-up visits with the prescribing physician have all been demonstrated to improve SLIT adherence.

Sublingual Immunotherapy Practice Parameters


3. RAGWITEK™ (Short Ragweed Pollen Allergen Extract) Tablet for Sublingual Use

4. GRASTEK® (Timothy Grass Pollen Allergen Extract)


10. Medication Guide - RAGWITEK RAGWITEKTM (RAG-wi-tek)


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<table>
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<th>Dose and Administration</th>
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<td>3/4</td>
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<td>20 mcg Phl p 5/day Tablets</td>
<td>RC</td>
<td>STA</td>
<td>Significant reduction in RC score in Vienna challenge chamber at 4 mo in SLIT vs baseline and vs placebo. Reduction 29% vs placebo. Increased IgE and IgG4</td>
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<td>18-50</td>
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<td>Ragweed</td>
<td>6 mo</td>
<td>4.8 or 48 mcg Amb a 1/day Metered pump</td>
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<td>GRE</td>
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<td>RC</td>
<td>ALK</td>
<td>Increase in IgE, IgG4, and IgE blocking activity only in active</td>
<td></td>
</tr>
<tr>
<td>Yonekura, 2010</td>
<td>7-15</td>
<td>20/11</td>
<td>1/2</td>
<td>Mite</td>
<td>1 y</td>
<td>0.5 mcg Der f 1 once a week</td>
<td>RC</td>
<td>TOR</td>
<td>Significant decrease in symptoms and combined score in wk 0–3 and 37–40 only in SLIT</td>
<td>Medication score</td>
</tr>
<tr>
<td>Blaiss, 2011</td>
<td>5-17</td>
<td>349/358</td>
<td>33/30</td>
<td>Grass</td>
<td>6 mo</td>
<td>450 g Phl p 5/mo</td>
<td>RC</td>
<td>STA</td>
<td>Significant reduction in combined score (~26%) VS placebo. Quality of Life 38% improvement vs placebo</td>
<td>Asthma symptoms</td>
</tr>
<tr>
<td>Nelson, 2011</td>
<td>18-63</td>
<td>213/225</td>
<td>33/33</td>
<td>Grass</td>
<td>10 mo</td>
<td>450 mcg Phl p 5/mo Tablets</td>
<td>RCA</td>
<td>STA</td>
<td>Significant reduction in combined score (~20%) and medication score (~20%) vs placebo</td>
<td>Daily medication score</td>
</tr>
<tr>
<td>Bush, 2011</td>
<td>18-50</td>
<td>High 10 Low 10 Pla 11</td>
<td>2 3 5</td>
<td>Mite (Der f)</td>
<td>18 mo</td>
<td>70 or 1 mcg Der f 1 per dose. Drops</td>
<td>RA</td>
<td>GRE</td>
<td>Significant reduction in specific bronchial reactivity Increase in IgG4</td>
<td>Symptoms and medication scores</td>
</tr>
<tr>
<td>Stelmach, 2012</td>
<td>6-18</td>
<td>Cont 20 Prec 20 Pla 20</td>
<td>3 1 2</td>
<td>Grass</td>
<td>2 y</td>
<td>Cumulative 7.3 and 3.6 mcg Phl p 5. Drops</td>
<td>RCA</td>
<td>ALK</td>
<td>Significant improvement in drugs +symptoms with both continuous and preseasonal regimen. Reduction in FeNO</td>
<td>Symptom score Medication score Pulmonary function</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Age</td>
<td>Gender</td>
<td>Allergen</td>
<td>Duration</td>
<td>Treatment</td>
<td>Double-blind</td>
<td>Randomization</td>
<td>Outcome Measures</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
<td>--------</td>
<td>----------</td>
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<td>--------------</td>
<td>--------------</td>
<td>------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>de Bot, 2012</td>
<td>6-18</td>
<td>126/125</td>
<td>Mite</td>
<td>2 y</td>
<td>4.06 mcg Der p 1/week Drops</td>
<td>RC</td>
<td>ART</td>
<td>Symptom score, QoL</td>
<td>Significant improvement in symptom and medication scores; reduction of skin wheal diameter</td>
<td></td>
</tr>
<tr>
<td>Ahmadiasfshar, 2012</td>
<td>5-18</td>
<td>12/12</td>
<td>Grass</td>
<td>6 mo</td>
<td>Cumulative: about 6,000 IR Spray</td>
<td>RC</td>
<td>STA</td>
<td>Symptom score, Medication score, Well days</td>
<td>Significant improvement in symptom and medication scores; reduction of skin wheal diameter</td>
<td></td>
</tr>
<tr>
<td>Wahn, 2012</td>
<td>4-12</td>
<td>158/49</td>
<td>Grass</td>
<td>8 mo</td>
<td>Cumulative: 7.2 – 8.4 mg group 5 Drops</td>
<td>RC</td>
<td>ALL</td>
<td>Significant reduction VS placebo in combined symptom/medication and individual scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox, 2012</td>
<td>18-65</td>
<td>233/240</td>
<td>Grass</td>
<td>6 mo</td>
<td>Cumulative: approx 3.6 mg group 5 allergen Tablets</td>
<td>RC</td>
<td>STA</td>
<td>Significant reduction of combined symptom + medication score (28% VS placebo) and overall quality of life</td>
<td>Itchy nose symptom score VS placebo</td>
<td></td>
</tr>
<tr>
<td>Bozek, 2013</td>
<td>60-75</td>
<td>51/57</td>
<td>Mite</td>
<td>3 y</td>
<td>NS</td>
<td>RC</td>
<td>STA</td>
<td>Total nasal scores decreased by 44% VS baseline in SLIT and by 6% in placebo. Medication score decreased vs baseline 35% in SLIT group.</td>
<td>Symptoms after specific nasal provocation VS placebo</td>
<td></td>
</tr>
<tr>
<td>Wang, 2013</td>
<td>4-65</td>
<td>60/60</td>
<td>Mite</td>
<td>6 mo</td>
<td>NS</td>
<td>RC</td>
<td>ZHE</td>
<td>Significant decrease in each individual rhinitis symptom VS placebo starting from week 14.</td>
<td>No change VS placebo in medication intake</td>
<td></td>
</tr>
<tr>
<td>Nolte 2013</td>
<td>19-50</td>
<td>High 187 Low 188 Pla 190</td>
<td>Ragweed</td>
<td>1 y</td>
<td>6 or 12 mcg Amb A 1 Daily tablet</td>
<td>RCA</td>
<td>MSD</td>
<td>Significant decrease in combined symptom + medication score for both active groups vs placebo (27% and 21%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creticos, 2013</td>
<td>18-50</td>
<td>Low 197 Med 195 High 194 Pla 198</td>
<td>Ragweed</td>
<td>1 y</td>
<td>Cumulative dose 4.38 mg Amb a 1 Tablets</td>
<td>RCA</td>
<td>MSD</td>
<td>Only the high dose decreased daily symptom-medication- and combined-score during peak pollen season and whole season VS placebo.</td>
<td>Low dose overall less effective than the 2 other doses on symptoms/medications VS placebo</td>
<td></td>
</tr>
<tr>
<td>Aydogan 2013</td>
<td>5-10</td>
<td>10/18</td>
<td>Mite</td>
<td>1 y</td>
<td>Cumulative dose 11.7 mcg Der p 1, 28 mcg Der f</td>
<td>RC</td>
<td>STA</td>
<td>Significant decrease in wheal skin test to mite only in the active group VS placebo</td>
<td>No change in symptoms, medications and</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Placebo Dose</td>
<td>Treatment</td>
<td>Follow-Up</td>
<td>Meds</td>
<td>Effect</td>
<td>Remarks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td>--------------</td>
<td>-----------</td>
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<td>------</td>
<td>--------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergmann 2014</td>
<td>18-50</td>
<td>Low 153</td>
<td>Low 31</td>
<td>1 y + 1</td>
<td>Cumulative: High Der p 1 11 mg; Low Der p 1 5.8 mg. Tablet</td>
<td>RC, STA</td>
<td>Adjusted symptom-medication score decreased in both active groups vs placebo (17 and 20%). Decrease in wheal diameter No significant change in IgE, but significant increase in IgG4 in active.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creticos 2014</td>
<td>18-55</td>
<td>Act 218</td>
<td>Act 27</td>
<td>3 m</td>
<td>18-50 mcg Amb a 1/day Drops</td>
<td>RCA, GRE</td>
<td>Significant reduction in combined score versus placebo (43%). Significant increase in IgG4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maloney 2014</td>
<td>5-65</td>
<td>ACT 752</td>
<td>Act 149</td>
<td>5 m</td>
<td>15 mcg Phl p 5/day. Tablet</td>
<td>RCA, ALK</td>
<td>Reduction in total combined score: 29% peak season, 21% entire season VS placebo No change vs placebo in QoL, FEV1, PEF in the active groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosbeck 2014</td>
<td>14-65</td>
<td>LOW 146</td>
<td>Pla 17</td>
<td>1 y</td>
<td>1 or 3 or 6 SQ-HDM daily Tablet</td>
<td>RCA, ALK</td>
<td>Significant reduction in ICS daily dose in the 6 SQ group vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nolte 2015</td>
<td>LOW HIGH PLA</td>
<td>Mite</td>
<td>24 wks</td>
<td>6 or 12 DU daily Tablet</td>
<td>RC, MK</td>
<td>Reduction in symptom score in challenge chamber at 6 mo: -46% (12 DU) and -21% (6 DU) vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang 2014</td>
<td>ACT 308</td>
<td>Mite</td>
<td>1 y</td>
<td>RCA, STA</td>
<td>Only in moderate asthma more well controlled (80%) and totally controlled (54%) subjects vs placebo (66% and 39%) No change in % of well and totally controlled asthma in overall population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A/P= active/placebo; QoL= quality of life; RC=rhinoconjunctivitis; RCA= rhinoconjuntivitis/asthma:  STA= Stallergenes;  GRE= Greer, ANA= Anallergo, ALL= Allergopharma; ALK=ALK-Abellô; MSD= Merck Sharp and Dome; TOR=Torii Pharmaceuticals ; ZHE= Zheng Wolwo Bio Pharm;.
<table>
<thead>
<tr>
<th>Recommendation strength</th>
<th>Definition</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B)*. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.</td>
<td>Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
</tr>
<tr>
<td>Moderate</td>
<td>A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C)*. In some clearly identified circumstances, moderate recommendations may be made based on lower-quality evidence when high-quality evidence is impossible to obtain and the anticipated benefits moderately outweigh the harms.</td>
<td>Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.</td>
</tr>
<tr>
<td>Category of Evidence</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Strong</td>
<td>Identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.</td>
<td></td>
</tr>
<tr>
<td>Weak</td>
<td>A weak recommendation means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach versus another. Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.</td>
<td></td>
</tr>
<tr>
<td>No recommendation (NR)</td>
<td>No recommendation means there is both a lack of pertinent evidence (Grade D)* and an unclear balance between benefits and harms. Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.</td>
<td></td>
</tr>
</tbody>
</table>

**Category of Evidence**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence from meta-analysis of randomized controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence from at least one randomized controlled trial</td>
</tr>
<tr>
<td>Ila</td>
<td>Evidence from at least one controlled study without randomization</td>
</tr>
<tr>
<td></td>
<td>Strength of Recommendation*</td>
</tr>
<tr>
<td>---</td>
<td>------------------------------</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence from at least one other type of quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from non-experimental descriptive studies, such as comparative studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from expert committee reports or opinions or clinical experience of respected authorities or both</td>
</tr>
<tr>
<td>A</td>
<td>Directly based on category I evidence</td>
</tr>
<tr>
<td>B</td>
<td>Directly based on category II evidence or extrapolated recommendation from category I evidence</td>
</tr>
<tr>
<td>C</td>
<td>Directly based on category III evidence or extrapolated recommendation from category I or II evidence</td>
</tr>
<tr>
<td>D</td>
<td>Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence</td>
</tr>
<tr>
<td>LB</td>
<td>Laboratory Based</td>
</tr>
<tr>
<td>NR</td>
<td>Not rated</td>
</tr>
<tr>
<td><strong>Based on Shekelle method</strong></td>
<td>¹</td>
</tr>
</tbody>
</table>
Table 2: Comparison of US Licensed Sublingual Immunotherapy Tablet per FDA approved Product Information Insert

<table>
<thead>
<tr>
<th>Product name</th>
<th>ORALAIR®</th>
<th>RAGWITEK®</th>
<th>GRASTEK®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Stallergenes</td>
<td>Merck &amp; Co</td>
<td>Merck &amp; Co</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Grass pollen-induced allergic rhinitis and allergic rhinoconjunctivitis confirmed by skin prick test or in vitro pollen-specific IgE testing for any of the 5 grass species contained in the product</td>
<td>Short ragweed pollen-induced allergic allergic rhinitis and allergic rhinoconjunctivitis confirmed by skin prick test or in vitro pollen-specific IgE testing for short ragweed pollen</td>
<td>Timothy grass pollen-induced allergic allergic rhinitis and allergic rhinoconjunctivitis confirmed by skin prick test or in vitro pollen-specific IgE testing for timothy grass pollen</td>
</tr>
<tr>
<td><strong>Ages</strong></td>
<td>10-65 years</td>
<td>18-65 years</td>
<td>5-65 years</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>100 IR, 300 IRA Age 10-17 years: Day 1: 100 IR Day2: 2 x 100 IR Day3 and following: 300 IR Age 18-65 years Day 1 and following: 300 IR</td>
<td>1 tablet daily, 12 Amb a 1-unit</td>
<td>1 tablet daily, 2800 Bioequivalent Allergy Units (BAUs)</td>
</tr>
<tr>
<td><strong>First dose administration</strong></td>
<td>Observe patients in the office for at least 30 minutes following the initial dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Instructions for dose administration</strong></td>
<td>Place the tablet under the tongue for at least 1 minute, until completely dissolved, the swallow</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Active ingredients</strong></td>
<td>Grass pollen mix: Sweet Vernal, Orchard, Perennial</td>
<td>Short Ragweed Pollen</td>
<td>Timothy Grass Pollen</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Rye, Timothy, Kentucky Blue Grass</td>
<td>Gelatin NF (fish source)*, mannitol USP, and sodium hydroxide NF</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Initiation of therapy in relation to pollen season</td>
<td>Four months before the expected onset of each grass pollen season and continue throughout the season</td>
<td>At least 12 weeks before the expected onset of ragweed pollen season and continue throughout the season</td>
<td></td>
</tr>
</tbody>
</table>
| Contraindications | -Severe, unstable or uncontrolled asthma  
-History of any severe systemic allergic reaction or any severe local reaction to SLIT  
-Hypersensitivity to any of the inactive ingredients contained in this product | -Severe, unstable or uncontrolled asthma  
- History of any severe systemic allergic reaction or any severe local reaction to SLIT  
- Hypersensitivity to any of the inactive ingredients contained in this product  
-A history of eosinophilic esophagitis |
<table>
<thead>
<tr>
<th>Precautions</th>
<th>esophagitis</th>
<th>*Gelatin is derived from skin of cold water fish</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. ORALAIR® / RAGWITEK™ / GRASTEK® may not be suitable for patients being treated with beta-blockers or with underlying medical condition that may reduce the ability to survive a serious allergic reaction. In case of oral inflammation or wounds, stop treatment to allow complete healing of the oral cavity.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source such as cod, pollock, or haddock. Gelatin constitutes a fraction of the 28 mg tablet weight. In one study, commercial, food-grade fish gelatin derived from the skins of codfish was evaluated in a double-blind, placebo-controlled food challenge. None of the 30 fish-allergic patients reacted adversely to the ingestion of cumulative dose of 2.6 g fish gelatin. Investigators concluded with a 95% certainty that 90% of fish-allergic consumers will not react to ingestion of a 3.61 g cumulative dose of fish gelatin. 

Table 3: WAO Grading System for SLIT Local Reactions

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>Grade 1: Mild</th>
<th>Grade 2: Moderate</th>
<th>Grade 3: Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus/swelling of mouth, tongue,</td>
<td>● Not troublesome AND ● No symptomatic treatment required AND ● No discontinuation</td>
<td>● Troublesome OR ● Requires symptomatic treatment AND ● No discontinuation</td>
<td>● Grade 2 AND ● SLIT discontinued because of local side effects</td>
</tr>
<tr>
<td>or lip; throat irritation, nausea,</td>
<td>of SLIT because of local side effects</td>
<td>of SLIT because of local side effects</td>
<td></td>
</tr>
<tr>
<td>abdominal pain; vomiting; diarrhea;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heartburn; or uvular edema</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each local AE can be early (<30 minutes) or delayed.

*See Table 1 for the MedDRA code that applies to exactly report and describe the AE.


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Table 4: Description of local side effects related to SLIT (MedDRA 14.1)

<table>
<thead>
<tr>
<th>Local side effect</th>
<th>MedDRA preferred term</th>
<th>MedDRA code</th>
<th>MedDRA low-level term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth/ear</td>
<td>Altered taste perception</td>
<td>Dysgeusia</td>
<td>10013911</td>
</tr>
<tr>
<td>Itching of lips</td>
<td>Oral pruritus</td>
<td>10052894</td>
<td>Itching of mouth</td>
</tr>
<tr>
<td>Swelling of lips</td>
<td>Swelling of lips</td>
<td>10024570</td>
<td>Swelling of lips</td>
</tr>
<tr>
<td>Itching of oral mucosa</td>
<td>Oral pruritus</td>
<td>10052894</td>
<td>Itching of mouth</td>
</tr>
<tr>
<td>Swelling of oral mucosa</td>
<td>Mucosal edema</td>
<td>10030111</td>
<td>Mucosal swelling</td>
</tr>
<tr>
<td>Itching of ears</td>
<td>Ear pruritus</td>
<td>10052138</td>
<td>Ear pruritus</td>
</tr>
<tr>
<td>Swelling of tongue</td>
<td>Swollen tongue</td>
<td>10042727</td>
<td>Swelling of tongue, nonspecific</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>Glossodynia</td>
<td>10018388</td>
<td>Glossodynia</td>
</tr>
<tr>
<td>Mouth ulcer</td>
<td>Mouth ulceration</td>
<td>10028034</td>
<td>Mouth ulcer</td>
</tr>
<tr>
<td>Tongue ulcer</td>
<td>Tongue ulceration</td>
<td>10043991</td>
<td>Tongue ulceration</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>Throat irritation</td>
<td>10043521</td>
<td>Throat irritation</td>
</tr>
<tr>
<td>Uvular edema</td>
<td>Pharyngeal edema</td>
<td>10034829</td>
<td>Pharyngeal edema</td>
</tr>
<tr>
<td>Upper</td>
<td>Nausea</td>
<td>10028813</td>
<td>Nausea</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>Nausea</td>
<td>10028813</td>
<td>Nausea</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>Abdominal pain, upper</td>
<td>10000087</td>
<td>Stomach ache</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Vomiting</td>
<td>10047700</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Lower</td>
<td>Abdominal pain</td>
<td>10000081</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>Diarrhea</td>
<td>10012735</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

The current knowledge of adverse reactions caused by SLIT is based on randomized controlled trials (RCTs), postmarketing surveys, and case reports.

Table 5: Suggested guidelines for the practicing allergist regarding the use of FDA approved SLIT products

The JTF of PP recognizes that there are many questions regarding the use of SLIT in clinical practice for which there are insufficient evidence-based answers. In an effort to provide some guidance in these areas, the JTF has developed a table of suggestions on answering some of the most frequently asked questions. Using a Delphi method of reaching consensus, the following table has been developed. Unless otherwise stated, this is based solely on expert opinion.

<table>
<thead>
<tr>
<th>Item of concern and/or increased risk factors</th>
<th>Expert Suggestion and Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Late administration: Missed days 1-7</td>
<td>Based upon the experience obtained with the SLIT trials, the lack of dose escalation, in general, and the experience with SCIT, no dose reduction is recommended.</td>
</tr>
<tr>
<td>2 Late administration: Missed days 8-14</td>
<td>Follow the above guidelines except for those SLIT products that do have a dose escalation. For products with a dose escalation, it is recommended to restart from dose 1 and escalate as indicated in the package insert.</td>
</tr>
<tr>
<td>3 Late administration: Missed days &gt;14</td>
<td>It is suggested that the patient return to the physician's office for the next dose to be administered under supervision.</td>
</tr>
<tr>
<td>4 Delay in the administration of epinephrine by the patient</td>
<td>While local and GI symptoms are very common side effects, the patient should be educated to have a low threshold for use of their epinephrine auto-injector and for calling 911 when experiencing a systemic reaction. Consider the use of epinephrine for the rapid onset (&lt; 15 minutes) of any of the following: 1) symptoms beyond the local oral &amp; mild GI symptoms 2) moderate to severe tongue or throat swelling 3) wheezing or respiratory distress 4) generalized urticaria and/or angioedema and 5) any serious, potentially life threatening symptom. (1) (2)</td>
</tr>
<tr>
<td>5 Following the administration of epinephrine for SLIT induced anaphylaxis, it is strongly suggested</td>
<td>The patient should discontinue SLIT and schedule an office visit with the prescribing allergist. Once the allergist has confirmed that the patient experienced anaphylaxis, most patients should be advised to permanently discontinue SLIT when administered in a medically non-supervised setting, e.g., at home. The</td>
</tr>
<tr>
<td>Step</td>
<td>Description</td>
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<tr>
<td>------</td>
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</tr>
<tr>
<td>6</td>
<td>Following professional dental cleaning</td>
</tr>
<tr>
<td>7</td>
<td>Following brushing and flossing of teeth</td>
</tr>
<tr>
<td>8</td>
<td>Following dental extraction/gum surgery</td>
</tr>
<tr>
<td>9</td>
<td>Aphthous stomatitis/Herpes/oral lichen planus</td>
</tr>
<tr>
<td>10</td>
<td>High degree of sIgE allergen sensitivity</td>
</tr>
<tr>
<td>11</td>
<td>Administration of SLIT during active allergen season</td>
</tr>
<tr>
<td>12</td>
<td>Use of SLIT in a patient who has been diagnosed to have asthma</td>
</tr>
<tr>
<td>13</td>
<td>Symptomatic asthma or an asthma exacerbation</td>
</tr>
<tr>
<td>14</td>
<td>Increased symptoms of AR, AC, atopic dermatitis</td>
</tr>
<tr>
<td></td>
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<td>---</td>
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</tr>
<tr>
<td>15</td>
<td>Overdosing errors with SLIT</td>
</tr>
<tr>
<td>16</td>
<td>Administration in conjunction with SCIT (using different allergens, e.g., perennial allergens)</td>
</tr>
<tr>
<td>17</td>
<td>Increased risks of SLIT when using multiple allergen, multiple tablet treatment</td>
</tr>
<tr>
<td>18</td>
<td>Use of concurrent thyroid medication, 1st generation antihistamines, tricyclic antidepressants, alpha-adrenergic blockers, and/or cardiac glycosides/diuretics</td>
</tr>
<tr>
<td>19</td>
<td>Must Monoamine oxidase inhibitors be stopped?</td>
</tr>
<tr>
<td>20</td>
<td>Must beta-blockers be stopped?</td>
</tr>
<tr>
<td>21</td>
<td>Must Angiotensin converting enzyme inhibitors be stopped?</td>
</tr>
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</tr>
<tr>
<td>22</td>
<td>Do NSAIDS need to be stopped?</td>
</tr>
<tr>
<td>23</td>
<td>Do AH help with GI symptoms due to SLIT?</td>
</tr>
<tr>
<td>24</td>
<td>Can AH be taken prior to SLIT administration? Will this help with oral symptoms of SLIT?</td>
</tr>
<tr>
<td>25</td>
<td>Concurrent GI infection and the administration of SLIT</td>
</tr>
<tr>
<td>26</td>
<td>Risk with a history of food induced anaphylaxis.</td>
</tr>
<tr>
<td>27</td>
<td>Risk with a history of oral allergy syndrome (OAS)</td>
</tr>
<tr>
<td>28</td>
<td>Following a recent moderate to severe allergic reaction to a food or medication</td>
</tr>
</tbody>
</table>

* This is based solely upon expert opinion as there is no published evidence to offer guidance.

**Abbreviations:** SLIT- sublingual immunotherapy; SCIT- subcutaneous immunotherapy; GI- gastrointestinal; AIT- allergen immunotherapy; AR- allergic rhinitis; AC-allergic conjunctivitis; NSAIDS: nonsteroidal anti-inflammatory drugs;