

Current Evidence on Safety and Practical Considerations for Administration of Sublingual Allergen Immunotherapy (SLIT) in the United States



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Liquid sublingual allergen immunotherapy (SLIT) has been used off-label for decades, and Food and Drug Administration (FDA)-approved grass and ragweed SLIT tablets have been available in the United States since 2014. Potentially life-threatening events from SLIT do occur, although they appear to be very rare, especially for FDA-approved products. Practice guidelines that incorporate safety precautions regarding the use of SLIT in the United States are needed. This clinical commentary attempts to address unresolved issues including controversy regarding the FDA mandate for the prescription of epinephrine autoinjectors for patients on SLIT; how to approach polysensitized patients; optimal timing and duration of SLIT administration; how to address gaps in therapy; whether antihistamines can prevent local reactions, if certain patient populations (such as persistent asthmatics) should not receive SLIT; and when to instruct patients to self-administer epinephrine. Key points are that physicians should focus on educating patients regarding: (1) when not to administer SLIT; (2) how to recognize a potentially serious allergic reaction to SLIT; and (3) when to administer epinephrine and seek emergency care. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:34-40)

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Allergen-specific immunotherapy (AIT) is a widely used, effective therapy for allergic rhinitis and asthma. Two forms of AIT are commonly used in the United States and Europe: subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT). Although there has been much recent focus on the efficacy, safety, and practical use of Food and Drug Administration (FDA)-approved SLIT tablets, there are multiple evolving issues yet to be addressed.¹⁻⁷ Prescription of an epinephrine autoinjector for patients on SLIT is mandated by the FDA in the United States, despite controversy regarding whether this is warranted. Other unresolved questions include: how to approach polysensitized patients, optimal timing and duration of SLIT administration, how to address gaps in therapy, whether antihistamines can prevent local reactions, if certain patient populations (such as persistent asthmatics) should not receive SLIT, and when to instruct patients to self-administer epinephrine. There is also significant interest in non-FDA-approved forms of SLIT, which are commonly prescribed in the United States despite concerns about lack of standardization, efficacy, and possibly safety. This paper will explore these issues and present the existing literature that supports or potentially refutes current patient-care guidelines for SLIT.

OVERVIEW ON AVAILABLE FORMS OF SLIT

SLIT with extracts that are not standardized in terms of potency or concentration has been used for decades in the United States and abroad. Based on double-blind randomized, placebo-controlled trials in the United States and Europe, in 2014 the FDA approved SLIT tablets for treatment of allergic rhinoconjunctivitis caused by short ragweed (Ragwitek), timothy grass (Grastek), and a mixture of 5 northern pasture grasses (Oralair).⁸⁻¹² Ragwitek is currently approved in adults aged 18-50 years, Grastek is approved between ages 5 and 65 years, and Oralair is approved between ages 10 and 65 years.¹³⁻¹⁵

At this time, house-dust mite (HDM) SLIT tablets have been approved for HDM-related allergic rhinitis and asthma in Europe, but not in the United States. A multinational trial of HDM SLIT tablets for allergic rhinitis met statistical significance for the primary endpoint of average adjusted symptoms score, and benefits were maintained for a year after treatment.¹⁶ A recent study on HDM SLIT in asthmatic adults (mean forced expiratory volume in 1 second [FEV1] 91%-92%) who were not well controlled on inhaled corticosteroids (ICS; 400-1200 µg Budesonide equivalent) also reported a significantly reduced risk of moderate or severe asthma exacerbations.²

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Abbreviations used

AIT-Allergen specific immunotherapy
EoE-Eosinophilic esophagitis
FDA-Food and Drug Administration
FEV1-Forced expiratory volume in 1 second
HDM-House-dust mite
ICS-Inhaled corticosteroid
LAR-Local application site reaction
SAR-Systemic allergic reaction
SCIT-Subcutaneous allergen immunotherapy
SLIT-Sublingual allergen immunotherapy
WAO-World Allergy Organization

OVERVIEW ON SAFETY OF SLIT

There is little question that SLIT is safer than SCIT in terms of systemic allergic reactions (SARs) and the potential for life-threatening events. Although fatality rates from SCIT have been declining, there have been 84 confirmed fatalities attributed to SCIT in the United States since 1973, including at least 2 fatalities since 2007.¹⁷⁻²¹ No fatalities from SLIT have ever been reported.^{22,23}

Based on data from the first 5 years of a national surveillance study with voluntary reporting from United States and Canadian physicians, SCIT-related SARs occur in 82%-85% of practices, and with 0.1% of injection visits.^{20,21,24-26} This includes on average 6.7 World Allergy Organization (WAO) grade 1 (mild) SARs, 2.9 WAO grade 2 (moderate), 0.4 WAO grade 3 (severe) SARs, and 0.1 WAO grade 4 (very severe) SARs per 10,000 injection visits annually.^{21,27} Preliminary estimates from the most recent year are that 1.9% of patients on SCIT experience SARs, including grade 1 SARs in 1.1%, grade 2 in 0.69%, grade 3 in 0.08%, and grade 4 SARs in 0.02% of patients, although these figures may be falsely low due to under-reporting.²¹ Comparable surveillance data for FDA-approved SLIT products are not yet available. Surveillance data for off-label liquid SLIT (nonstandardized and generally multiallergen) in the United States identified 45 SARs in 3343 patients (1.4% of patients) between 2012 and 2013, including 9 grade 2 SARs (0.3% of patients) and 1 grade 3 SAR (0.03% of patients).²¹

One of the difficulties in evaluating safety data for SLIT is that, as opposed to SCIT, there has not been a standard classification system for SLIT-related adverse events.^{5,28-30} Direct comparisons between SLIT and SCIT safety have been limited by this lack of standardization. Common adverse events from SLIT, which are classified under the heading of local application site reactions (LARs), include oral pruritus, throat irritation, ear pruritus, oral paresthesia, mouth edema, stomatitis, and pharyngeal edema.³¹ LARs occur with a fairly high frequency, although a wide range of values exist. Some studies report that up to 70% of patients with SLIT experience LARs.²⁸ Most LARs are mild, self-limited, resolve quickly, and have little impact on adherence.^{9,32} Nevertheless, local symptoms in the oral cavity may spread, on rare occasions, to the larynx, causing life-threatening laryngeal edema.

In a review of 66 SLIT studies conducted outside of the United States, including 4378 patients, 14 probable treatment-related serious adverse events were described, including 7 asthma exacerbations, abdominal pain and vomiting, severe uvular edema, and urticaria.²³ In those studies, SARs occurred with only 0.056% of doses. Most US SLIT studies have reported no SARs,

although at least 2 have reported SARs to SLIT.^{8-10,33-38} In a recent summary of 29 SLIT-tablet trials, epinephrine was administered in 35 subjects; 25 were receiving active treatment with SLIT, and 16 administrations were for SLIT treatment-related events.³⁹ The authors calculated that 0.2% of subjects (16/8152) received epinephrine for SLIT-related events, and that none of the events were considered serious or resulted in airway compromise.

There are case reports from outside the United States of at least 11 severe SARs and/or anaphylactic events from liquid SLIT and SLIT tablets.⁴⁰⁻⁴⁸ Risk factors identified in these reports included overdose, newly started SLIT (first dose), multiallergen SLIT, and previous SARs to SCIT or asthma exacerbations with SCIT. As mentioned above, 1.4% of patients in the United States on off-label liquid SLIT between 2012 and 2013 experienced SARs, including grade 2 SARs in 0.3% and grade 3 SARs in 0.03%.²¹ It is important to note that *uncontrolled* asthmatics are likely at higher risk for severe adverse reactions from SLIT, as this has been a risk factor for severe reactions to SCIT. Retrospective surveys found that uncontrolled asthma was implicated in 62% of fatal reactions and 10% of near-fatal reactions to SCIT.^{18,19,49} In a study involving 43 patients on HDM liquid SLIT, which included 63% asthmatics, 7 SARs occurred in 23,154 doses and 11.6% of patients, all of which were grade 2 or 3 SARs.⁴⁵ In contrast, a recent study of HDM SLIT tablets in 834 adults with asthma that was not well controlled by ICS or ICS-long-acting beta-agonist combination inhalers did not report any SARs, and only reported 1 possible treatment-related moderate asthmatic exacerbation.²

PATIENT GUIDANCE

Given the novelty of commercial SLIT in the United States, best practices governing its use are still evolving. As with any form of AIT, patients should be counseled about the benefits, risks, and logistics of SLIT, and informed consent should be obtained (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). For all FDA-approved SLIT tablets, the first dose is administered in the office with a 30-minute observation period. If the patient tolerates the first dose, subsequent doses can be given at home. Asthma should be well controlled before administration. Dosing is started at least 12 weeks before the season and continued through the season. The tablet is placed under tongue for at least 1 minute until completely dissolved. Important practical points include having the patient wash their hands after touching the tablet and to avoid eating or drinking for 5 minutes. Although administration practices for off-label liquid SLIT are not uniform, physicians prescribing off-label SLIT generally employ a build-up phase, and at least the first dose should be given in the practitioner's office. Of note, off-label SLIT drops do allow for a slow build-up in highly sensitive patients, whereas SLIT tablets, with the exception of Oralair in children, do not.

Contraindications

Contraindications for initiating SLIT listed in the package inserts for all commercially available SLIT products include severe or uncontrolled asthma, history of eosinophilic esophagitis (EoE), history of severe local reaction to SLIT, or history of any severe SAR.¹³⁻¹⁵ In addition, caution should be used when administering SLIT to individuals at risk of not surviving

anaphylaxis. Medications that may interfere with epinephrine, such as beta-blockers, should be changed.

SLIT safety in asthmatics

Asthmatic patients in the clinical trials for FDA-approved SLIT tablets were at most on a low-dose ICS, and the great majority were only using as needed beta-agonists.¹³⁻¹⁵ Caution should therefore be used when initiating SLIT in moderate-to-severe persistent and high-risk asthmatics, and SLIT should not be initiated in uncontrolled asthmatics. It is important that proper steps are taken for diagnosis and management of asthma, including spirometry with reversibility testing, adjustment of medications to achieve control, instruction on avoidance of triggers, and possibly reporting exposures to relevant allergens before SLIT dosing. On the day of the first dose, consideration should be given to performing standardized questionnaires to verify asthma control, such as the asthma control test and spirometry or peak flow measurement before and after dosing.

For the 9 Grastek studies cited in the package insert, 31% of children and 25% of adults had mild well-controlled asthma.¹⁵ The number of patients on ICS in these studies is not listed, and in some studies patients could not be on any controller medications. A clinical history of severe persistent asthma was an exclusion in all Grastek trials. For most studies, FEV1 had to be >70% of predicted or was otherwise not specified. In the North American pediatric study, children had a mean FEV1 of 95% of predicted.¹¹ In studies that included asthmatics, there were no increases in treatment-related adverse events compared with nonasthmatics.^{9,11,12,50-53} A post hoc analysis of 8 Timothy grass SLIT tablet trials concluded that subjects with allergic rhinoconjunctivitis who had well-controlled mild asthma had similar treatment-related adverse event frequency as subjects without asthma.⁵⁴

In 6 placebo-controlled trials for the 5-grass pollen tablet Oralair, approximately 17% of 1038 adult subjects and 21% of 154 subjects aged 5-17 years had mild intermittent asthma, and none were on controller medications.^{10,13,55-59} There were generally no mean FEV1 values given in the studies, although the inclusion criterion was FEV1 > 80%, if stated.¹⁰ Adverse events were mild and similar between asthmatics and nonasthmatics in the pivotal phase 3 US trial, with no worsening of asthma control.¹⁰ A pooled analysis on the safety of Oralair came to similar conclusions.⁶⁰

In 4 placebo-controlled trials on Ragwitek, 25% of 1057 subjects 18 years and older had mild asthma with an FEV1 > 70%.^{14,61} Low-dose ICS were allowed, although the percentage of patients receiving ICS is not listed. In one of the pivotal trials, safety events were similar between asthmatics and nonasthmatics, with the most common events being LARs and not asthma related.⁶²

The HDM SLIT tablet has been studied in more patients with mild-to-moderate persistent asthma compared with grass and ragweed.^{2,63} In a phase 1 safety trial of 12- to 17-year-old North American adolescents with allergic rhinoconjunctivitis, 34% had asthma and 9%-21% had ICS use; no problems with asthma exacerbations were observed.³⁸ A study of 834 adults on HDM SLIT tablets reported only one possible treatment-related moderate asthmatic exacerbation.² In another HDM SLIT tablet study involving 604 asthmatics 14 years and older, there were asthma-related adverse events during adjustment of asthma medications, but no life-threatening events.⁶³

In summary, physicians should use caution when prescribing the currently approved SLIT products (grass and ragweed) for moderate-to-severe persistent asthmatics, although HDM SLIT may find greater use among asthmatics of at least moderate severity. SLIT should not be prescribed in uncontrolled asthmatics of any severity grade.

SLIT and eosinophilic esophagitis

New-onset EoE has been reported after initiation of grass, mixed tree pollen, and HDM SLIT.⁶⁴⁻⁶⁶ EoE resolved with discontinuation of SLIT in these case reports. There is a wider body of literature regarding the risk of EoE with food SLIT, with a meta-analysis reporting an overall prevalence of EoE in 2.7% (95% confidence interval 1.7%-4.0%) of patients on food SLIT.⁶⁷ Physicians should be aware of this potential SLIT complication and educate patients to report worsening dysphagia and/or heartburn.

When to hold a dose?

Patients on SLIT should hold their dose for any increased asthma symptoms in the previous 24 hours, any worsening heartburn or dysphagia, any recent dental or oral procedures/surgery or lesions, increased viral upper respiratory tract infection symptoms, urticaria or angioedema (regardless of etiology), or fever. They should also hold their dose and notify their allergist for any new blood pressure medications, if newly pregnant, or if diagnosed with a new medical condition. A form developed by the American Academy of Allergy, Asthma, and Immunology (AAAAI) to assist patients in determining when to hold a dose of SLIT can be found in Figure E2, available in this article's Online Repository at www.jaci-inpractice.org.

What about missed doses?

In clinical trials, treatment interruptions for up to 7 days were allowed.^{14,15} Data regarding the safety of missed doses are limited. One would expect that missed doses would not be a major safety issue for most patients, as there is no build-up regimen needed for commercially available tablets other than for Oralair in patients ages 10-17 years. It is important to remind patients that they should not take extra doses if they miss any doses, and they should take the next dose at their normal scheduled time on the following day. Patients are advised to contact their health care provider before restarting SLIT if they miss more than 1 dose.¹³⁻¹⁵ In the opinion of the authors, patients who had minimal problems with previous doses should tolerate a missed dosing interval without significant difficulties. Patients who had severe LARs or SARs with initial dosing should return to the office for their first dose after a prolonged period of missed doses (>1 week), and when restarting SLIT in subsequent seasons. Information regarding the safety of the first dose of subsequent seasons (2nd, 3rd years) is not published in package inserts. It may not be advisable to restart SLIT during peak pollen season if a patient has missed >1 week.

Epinephrine autoinjector prescription

The FDA mandates that patients receiving SLIT tablets in the United States be prescribed an epinephrine autoinjector, and be instructed on use.¹³⁻¹⁵ This is based on the premise that although adverse events from SLIT that are severe enough to require the use of epinephrine are rare, they do occur, as described above.⁹ As with SCIT, early treatment with epinephrine of SARs from SLIT should lead to improved outcomes.⁶⁸ In addition, patients

SLIT Local Reaction and Systemic Allergic Reaction Emergency Plan

Patient name: _____ Age: _____
Allergies: _____
Additional health problems: _____
Concurrent medications: _____

FOR MILD TO MODERATE LOCAL REACTION

MOUTH: bothersome itching, and/or mild swelling of lips and/or tongue
THROAT: bothersome itching, irritation, and/or mild tightness
EAR: bothersome itching
GASTROINTESTINAL: mild abdominal pain, nausea, and/or cramps

ACTION → Use antihistamine: _____ mg or mL

FOR SEVERE LOCAL REACTION*

MOUTH/THROAT: swelling that causes hoarseness and/or throat closing

OR FOR SYSTEMIC REACTION*

SKIN: hives all over body and/or redness all over body
LUNG: shortness of breath, cough, and/or wheezing
HEART: weak pulse, dizziness, and/or passing out
GASTROINTESTINAL: severe abdominal pain, vomiting, diarrhea, and/or cramping

*You may only have a few symptoms. Symptoms can be life-threatening.

ACTION → Inject epinephrine in thigh using (circle one):

Adrenaclick (0.3 mg) Adrenaclick (0.15 mg)
EpiPen (0.3 mg) EpiPen Jr. (0.15 mg)

- Call 911 (before calling contact)

Emergency contact #1: home _____ work _____ cell _____
Emergency contact #2: home _____ work _____ cell _____
Emergency contact #3: home _____ work _____ cell _____

Comments _____
Doctor's Signature/Date/Phone Number _____

FIGURE 1. Action plan for management of local and systemic allergic reaction to SLIT.

on SLIT may not be able to receive medical care in a timely manner because they are outside of the clinical setting. The question of whether this recommendation translates into improved clinical outcomes is, in reality, more complicated. The recommendation depends on patients correctly identifying scenarios that require the use of epinephrine and then following through on administration. In the AAAAI/American College of Allergy, Asthma & Immunology (ACAAI) national surveillance study on SCIT, only half of patients who were prescribed an

epinephrine autoinjector self-administered the drug for severe delayed SARs.²⁵ In addition, compliance with purchasing an epinephrine autoinjector has become more difficult in recent years, because of rising autoinjector prices and rising insurance deductibles that translate to greater out-of-pocket costs for patients.⁶⁹ The average cost of an EpiPen dual-pack (the only form generally available) in the United States has reached \$300-\$400, with average prices closer to \$600-\$800 in some areas of the country. This is more than the monthly cost of SLIT for most

patients, and for some patients may be greater than the cost of SLIT for an entire season. Moreover, even when patients can afford autoinjectors, compliance with carrying them is historically poor.⁷⁰ That said, it is difficult to argue against prescribing a potentially life-saving device, even for very rare outcomes. In the opinion of the authors, perhaps even more important than prescribing an autoinjector is the discussion and reminders by the physician regarding how to recognize a severe allergic reaction to SLIT, as described below.⁷¹

Local application site reactions

The most common side effects from SLIT include oral pruritus, ear pruritus, throat irritation, tongue pruritus, and mouth edema. These most often occur in the first 10 days, and usually occur less often with subsequent administration. In a study involving 834 patients receiving HDM SLIT tablets, the median onset of LARs was within 1-2 days, and within 1-2 minutes of SLIT tablet administration.² Resolution of LARs, such that they no longer occurred with repeated administration, was a median of 4.5 days for oral pruritus, 7 days for throat irritation, and 23 days for mouth edema.² Another HDM SLIT tablet trial found that the median duration of individual LARs ranged from 1 to 43 minutes on day 1.³⁸

For mild-to-moderate oral symptoms, and for mild abdominal pain and nausea, antihistamine H1 and H2 blockers may be helpful. Antihistamines have been used in SCIT with benefit to help with large local reactions, mainly during accelerated inhalant and hymenoptera immunotherapy.⁷²⁻⁷⁶ A single trial for conventional SCIT showed that pretreatment with antihistamines reduced the occurrence of severe SARs using a conventional build-up schedule.⁷⁷ Patients who experience severe or recurrent LARs should be instructed to contact the prescribing physician and consider stopping SLIT if necessary. A grading system for SLIT LARs recommends using grade 1 for mild LAR (troublesome and no treatment required), grade 2 for moderate LAR (troublesome or symptomatic treatment required), and grade 3 for severe LARs (grade 2 and SLIT discontinued due to the LARs).^{30,78} It is important to remember that even with LARs patients should be counseled to monitor for signs of rapidly progressing reactions, such as worsening laryngeal edema, urticaria, or shortness of breath, which could necessitate treatment with epinephrine.

Systemic allergic reactions to SLIT

SARs to SLIT are defined as systemic side effects such as rhinitis, asthma, urticaria, angioedema, and/or hypotension that do not consist of oropharyngeal or gastrointestinal LARs alone.³⁰ It is very important that patients are instructed regarding how to identify an SAR to SLIT. They should also be specifically instructed regarding when and how to use epinephrine. Patients should have their epinephrine autoinjector available at all times. Figure 1 contains an action plan for LARs and SARs that should be discussed with patients. Epinephrine should be given for severe local throat swelling (even if it is a result of a LAR) causing difficulty speaking, breathing, or swallowing and for severe gastrointestinal symptoms such as severe abdominal pain, vomiting, diarrhea, and cramping. Epinephrine should also be given for the systemic symptoms of hives, flushing, angioedema, cough, dyspnea, wheezing, severe lightheadedness, and dizziness. Severe nasal symptoms in isolation may be treated with antihistamines plus nasal decongestant alone, but in the opinion of

the authors, treatment with epinephrine is reasonable if there is concern for a rapidly progressing SAR.

What about patients sensitized to multiple allergens?

One of the most challenging obstacles for use of SLIT is that most patients are sensitized to multiple allergens. Almost all studies on SLIT have involved single allergens, and most studies on multiple allergen SLIT have involved off-label liquid SLIT preparations that are derived from extracts for SCIT. Questions remain regarding whether adequate doses can be achieved for more than 2 extracts delivered sublingually at the same time.^{35,79,80} Safety data for multiallergen liquid SLIT (off-label) are not well established, and cases of anaphylaxis have been reported.^{21,41,42} A recent study involving Timothy grass and ragweed SLIT tablets administered to 102 adults found that 4-week sequential dosing of tablets followed by simultaneous administration was well tolerated, with no severe LARs, SARs, asthma exacerbations, or use of epinephrine.⁸¹ This finding is helpful for practitioners treating cosensitized patients, particularly given that overlapping treatment may be necessary to initiate SLIT tablets at least 3 months before the start of grass and ragweed pollen seasons. Studies regarding the safety of coadministration of SLIT and SCIT simultaneously are lacking, and this practice has not been recommended.

CONCLUSIONS

Since FDA approval of grass and ragweed SLIT tablets in 2014, practice recommendations regarding administration of SLIT in the United States have been developing. The experience and training of allergists/immunologists in SCIT administration makes them ideally suited to guide and supervise administration of these new forms of AIT. Potentially life-threatening events from SLIT do occur, although they appear to be very rare, especially for FDA-approved products. Perhaps more important than the FDA-mandated prescription of an epinephrine autoinjector for these events is the process of educating patients regarding: (1) when not to administer SLIT; (2) how to recognize a potentially serious allergic reaction to SLIT; and (3) when to administer epinephrine and seek emergency care. Administration of SLIT in uncontrolled or severe asthmatics is contraindicated, and it remains to be seen if reassuring safety data for HDM SLIT in persistent asthmatics will prompt FDA approval in this population. Strategies for administering multiallergen SLIT, in the form of multiple SLIT tablets, are in the early phases of development.

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SUBLINGUAL ALLERGEN IMMUNOTHERAPY PATIENT CONSENT FORM

Sublingual immunotherapy (SLIT) is an allergy tablet given under the tongue. SLIT should be taken under the care of a physician who is trained to prescribe the medication and to treat any possible reactions. The first dose is given at the medical office and, as long as this initial dosing is well tolerated, subsequent daily doses are taken at home. For the first week or so, it is not uncommon for you to experience some local reactions in your mouth consisting of minor itchiness or discomfort. These symptoms, should they occur, are typically brief and go away without any special treatment. Some individuals experience mild abdominal discomfort in the first days of treatment. Occasional serious reactions have been reported that may require immediate treatment. These reactions may consist of any or all of the following symptoms: itchy eyes, nose, ears or throat; stuffy nose; sneezing; runny nose; mouth, nose or abdominal discomfort; coughing; swelling of the lips, tongue or throat; difficulty breathing; nausea and vomiting; hives; itching all over your body; and very rarely, a life-threatening systemic reaction known as anaphylaxis. Severe reactions, even though very unusual, may rarely occur at any time during the course of SLIT therapy. Because of the risk of a severe reaction, **you must agree to have self-injectable epinephrine on hand with each dose of SLIT therapy.**

For the initial dosing, you are required to wait in the prescribing doctor's office for at least 30 minutes after using the tablet. If you are 17 years of age or younger, a parent or legal guardian must be present during the waiting period.

I have read (if new patient) or re-read (if established patient) the patient information sheet on sublingual immunotherapy and understand it. The opportunity has been provided for me to ask questions regarding the potential side effects of sublingual immunotherapy and these questions have been answered to my satisfaction. I understand that every precaution consistent with the best medical practice will be carried out to protect me against possible reactions associated with this treatment. I also agree that if I have an allergic reaction to the sublingual medication, I will follow the action plan I was given.

I acknowledge that I am aware of the risks/benefits/alternatives to sublingual immunotherapy and consent/agree to starting this treatment.

PATIENT _____ **DATE** _____

PARENT or LEGAL GUARDIAN _____ **DATE** _____

As parent or legal guardian, I understand that I must accompany my child throughout the entire 30-minute wait.

WITNESS _____ **DATE** _____

FIGURE E1. Example consent form for sublingual allergen immunotherapy (SLIT).

Sublingual Immunotherapy Pre-Dose Checklist

Patient
Name: _____ Date: _____

This checklist is to help you safely administer your sublingual (under the tongue) immunotherapy (SLIT) at home. If there are **ANY YES** responses, please contact the doctor who prescribed your SLIT **BEFORE** you take your dose. **If you are newly pregnant, have started any new prescription medications for blood pressure or headache, or have been diagnosed with a new medical condition, please notify your doctor immediately.**

Answer these questions: IF YOU ANSWER **YES** TO ANY QUESTION, DO NOT TAKE YOUR SLIT TABLET AND CONTACT YOUR DOCTOR IMMEDIATELY.

After your last SLIT dose, did you have:

YES NO

- ☐ ☐ Any increased allergy or asthma symptoms, hives (welts), or itching all over?
- ☐ ☐ Any new heartburn, severe abdominal discomfort, nausea, cramping, diarrhea, trouble swallowing or chest pain?
- ☐ ☐ Any new mouth symptoms (such as itching, tingling, swelling, or burning) not previously discussed with your doctor?

Since your last SLIT dose, have you:

- ☐ ☐ Had any dental procedures?
- ☐ ☐ Had any new mouth sores, cuts, lesions or breaks in the skin inside your mouth?
- ☐ ☐ Started taking any new blood pressure or headache medications (for example, beta-blocker or alpha-blocker)?

In the last 24 hours, have you had:

- ☐ ☐ Any asthma symptoms (chest tightness, cough, wheezing, or shortness of breath)?
- ☐ ☐ Worsened allergy symptoms (itchy eyes or nose, sneezing, runny nose, post-nasal drip, or throat-clearing)?
- ☐ ☐ A cold, respiratory tract infection, flu-like symptoms, or fever?

YOU MUST HAVE EPINEPHRINE AVAILABLE. IF YOU DO NOT HAVE AN EPINEPHRINE AUTOINJECTOR IMMEDIATELY AVAILABLE, **STOP** AND WAIT TO TAKE YOUR SLIT TABLET UNTIL YOU HAVE EPINEPHRINE AVAILABLE.

ENTER PRACTICE CONTACT INFORMATION HERE

FIGURE E2. Pre-dose checklist for patients receiving sublingual allergen immunotherapy (SLIT).

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