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A practical guide to the sublingual immunotherapy tablet adverse event profile: implications for clinical practice

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ABSTRACT

Objectives: Treatment with allergy immunotherapy improves allergic rhinoconjunctivitis, but can also improve comorbidities associated with allergic rhinitis such as asthma. Sublingual immunotherapy (SLIT)-tablets are a convenient and efficacious method of allergy immunotherapy. They are self-administered after the first tablet has been provided under medical supervision. Therapy may elicit local reactions or, rarely, systemic allergic reactions. The objective of this report is to inform healthcare practitioners about the safety and tolerability profile of SLIT-tablets and use this information to provide practical guidance that may inform patients regarding potential adverse reactions and how to manage them.

Methods: Pooled analyses of safety data from completed randomized, multicenter, double-blind, placebo-controlled phase 2 and phase 3 US and EU trials of timothy grass, short ragweed, and SQ house dust mite SLIT-tablets were conducted to characterize safety and tolerability.

Results: SLIT-tablets are generally well tolerated. No life-threatening events, serious systemic allergic reactions, or events that compromised the airway have been reported. The most common treatment-related adverse events (AEs) are oral site reactions, most of which begin on day 1 of treatment, recur for less than 2 weeks, and resolve after approximately 30–60 minutes. Systemic allergic reactions have been managed with conventional pharmacotherapy. Reactions treated with epinephrine are uncommon, but have been reported. Treatment of AEs, treatment discontinuation considerations, and patient FAQs regarding SLIT-tablet safety/tolerability are discussed.

Conclusions: This report gives healthcare providers valuable information to educate patients regarding what to expect in terms of SLIT-tablet safety and tolerability. Practical guidance is also provided to ensure proper treatment of any adverse reactions.

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1. Introduction

Allergic rhinitis with or without conjunctivitis is not considered a serious health-care concern, but the burden of this disease is significant, and primary care physicians frequently care for allergic rhinoconjunctivitis patients [1,2]. In addition to interfering with sleep, work/school performance, and daily activities, allergic rhinitis is often associated with other comorbid disorders including asthma [3,4]. Asthma exacerbations in patients with allergic rhinitis may manifest as a spectrum of symptoms ranging from a chronic cough to severe episodes that require office or emergency department treatment [3,5]. Compared to patients with asthma alone, adults and children with concomitant allergic rhinitis are 1.5-fold and 2.3-fold, respectively, more likely to have an asthma-related hospitalization [6,7]. The close link between allergic rhinitis and asthma suggests that treatment of allergic rhinitis could have an impact on asthma. Indeed, treatment of allergic rhinitis with antihistamines and intranasal corticosteroids has been reported in some (but not all) studies to be associated with improved asthma symptoms, bronchial hyperresponsiveness,

and lung function [8–13]. Thus, treatment of allergic rhinitis can have more beneficial effects than merely reducing nasal symptoms.

Allergic rhinoconjunctivitis is typically treated with pharmacotherapies such as antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists. However, pharmacotherapies are not effective in all patients, and some patients are intolerant to medication due to adverse effects (e.g. epis-taxis associated with intranasal corticosteroid). Another treatment option is allergy immunotherapy (AIT). Compared with pharmacotherapy, subcutaneous or sublingual AIT can reduce rhinoconjunctivitis symptoms triggered by aeroallergens and the need for rescue medications. Benefit may continue for 2 years (or even longer) after AIT is discontinued, presumably due to its ability to modify the underlying immunologic mechanisms of the allergic response [14–16]. Primary care physicians are most familiar with subcutaneous allergy immunotherapy (SCIT), which requires administration in a health-care setting every 2–4 weeks with a physician present, due to its known risk of rare but serious systemic allergic reactions which can very rarely be fatal [17]. Most allergists agree that

SCIT is effective, but may be underutilized because only 2–9% of patients in the US diagnosed with allergic rhinoconjunctivitis receive SCIT and a large proportion of patients prematurely discontinue therapy. The requirement for regular office visits to receive SCIT has been cited by patients as a major reason for discontinuing immunotherapy [18–21]. Therefore, an at-home self-administered AIT that is well tolerated and safe, such as a sublingual tablet, may benefit an additional group of patients for whom immunotherapy is indicated.

Numerous studies have demonstrated the efficacy of sublingual immunotherapy (SLIT) tablets for allergic rhinoconjunctivitis [22–31]. In North America, three SLIT-tablets are approved for the treatment of grass and ragweed allergic rhinitis [32–34]. SQ house dust mite (HDM) SLIT-tablets are approved in the United States, Europe, Japan, and Australia in the treatment of perennial allergic rhinitis due to HDM. Furthermore, treatment of allergic asthma with HDM SLIT-tablet significantly reduced the risk of a moderate or severe asthma exacerbation [35] and significantly improved asthma symptoms [29]. Thus, HDM SLIT-tablet is approved in Europe and Australia for the treatment of HDM allergic asthma. The HDM SLIT-tablet is also under review for approval in Canada. SLIT-tablets provide a convenient alternative treatment option to SCIT since they are administered at home after the first dose has been administered under medical supervision and are well tolerated. Although rare near-fatal and fatal systemic allergic reactions have been reported with SCIT [36–38], no fatal systemic allergic reactions have been attributed to SLIT-tablets. Reactions treated with epinephrine in response to SLIT-tablet treatment have been reported.

Primary care physicians should be aware of the well-documented efficacy and comparative safety of SLIT-tablets in order to provide appropriate information for their patients about different AIT options and to begin to identify which patients are best suited for SLIT-tablets [39]. An objective of this report is to provide health-care practitioners with the safety and tolerability profile of SLIT-tablets and use this information to provide practical guidance that may allay patient concerns regarding potential adverse events (AEs). The information provided here may also guide patients' decisions when considering treatment options for respiratory allergic diseases.

2. Methods

2.1. Data sources

Pooled analyses of safety data from completed, randomized, multicenter, double-blind, placebo-controlled phase 2 and phase 3 trials of timothy grass, short ragweed, and SQ HDM SLIT-tablets were conducted.

For the timothy grass SLIT-tablet (GRASTEK®/GRAZAX® MK-7243, Merck & Co., Inc., Kenilworth, NJ, USA/ALK, Hørsholm, Denmark), the pooled safety data from the US Food and Drug Administration (FDA)-approved dose of 2800 bioequivalent allergen units/75,000 SQ-T evaluated in eight clinical trials was used. The trials were GT-02, GT-07, GT-08, GT-12, GT-14, P05238, P05239, and P08067, all of which have been previously described [25,27,28,40–44]. Separate pools were generated for adult (aged ≥18 years) and pediatric (aged

5–17 years) safety data in the grass SLIT-tablet trials; no pediatric data (<12 years of age) from phase 2 or phase 3 trials are currently available for ragweed and SQ HDM SLIT-tablets.

For the ragweed SLIT-tablet (RAGWITEK® MK-3641, Merck & Co., Inc./ALK), the 28-day pooled safety data from the FDA-approved dose of 12 Amb a 1-U evaluated in four clinical trials was used. The trials were P06081, P05751, P05233, and P05234, all of which have been previously described [24,30,45].

For the SQ HDM SLIT-tablet (ACARIZAX®/MITICURE®/ODACTRA® MK-8237, Merck & Co., Inc./ALK/Torii Pharmaceuticals Co., Ltd., Tokyo, Japan), the pooled safety data from the approved European dose of 12 SQ-HDM evaluated in four clinical trials conducted in the US and European Union (EU) was used. The trials were MT-04, MT-06, P001, and P003, all of which have been previously described [29,31,35,46]. The epinephrine use analysis also included data from three clinical trials of SQ HDM SLIT-tablets conducted in Japan [47,48].

Data evaluated in the pooled analyses were overall incidence of AEs, incidence of treatment-related AEs, onset of AEs, recurrence of AEs, intensity of AEs, incidence of serious and systemic AEs, and epinephrine use. The duration in minutes for the most common treatment-related AEs were evaluated in phase 1 studies of the timothy grass (GT-04) and ragweed (RT-01) SLIT-tablets, which have been previously described [49,50], and the pooled phase 2 and 3 SQ HDM SLIT-tablet trial data described above.

2.2 AE reporting and definitions

AEs were captured by daily reporting in symptom diaries and at study visits in all trials except P001 (an HDM SLIT-tablet trial). In P001, AEs were solicited daily by a list of closed-ended questions for the first 28 days of treatment. In all trials, AEs were assessed by the investigators as mild, moderate, or severe in intensity. The relationship of the AE to treatment was also assessed by the investigators. A serious AE was any AE that resulted in death or was life-threatening, that required prolonged hospitalization, that resulted in persistent or significant disability or incapacity, that was a congenital anomaly or birth defect in offspring of a study subject, or that consisted of any other medically important event as determined by the investigator.

3. Results and discussion

3.1 Overall safety of SLIT-tablets

A high proportion of patients report mild-to-moderate AEs at initiation of treatment with the SLIT-tablets, but few patients discontinued treatment due to treatment-related AEs (Table 1). Overall, the incidence of treatment-related AEs ranged from 46% to 69% (Table 1). Of the 4556 patients treated with marketed doses of SLIT-tablets during the clinical trials, only one serious treatment-related AE (seriousness was due to hospitalization of subject) was reported. It was an event of asthma exacerbation (assessed as moderate in intensity) associated with SQ HDM SLIT-tablet that was determined to have been likely caused and triggered by a recent viral infection.

Table 1. Adverse event summary for SLIT-tablets.

% of patients reporting	Placebo adult grass pool (N = 1645)	Grass SLIT-tablet adult pool (N = 1669)	Placebo pediatric grass pool (N = 434)	Grass SLIT-tablet pediatric pool (N = 447)	Placebo ragweed pool (N = 757)	Ragweed SLIT-tablet pool (N = 1057)	Placebo HDM pool (N = 1540)	HDM SLIT-tablet pool (N = 1383)
Any TEAE	68	83	79	82	38	57	64	83
Any TRAE	24	67	24	58	21	46	23	69
Any serious TRAE	0.10	0.00	0.00	0.00	0.10	0.00	0.10	0.07
Any TRAE leading to discontinuation from study	1	5	1	6	1	4	1	7

AE: adverse event; HDM: house dust mite; SLIT: sublingual immunotherapy; TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event.

3.2 Commonly reported AEs with SLIT-tablets

Local adverse reactions similar to cutaneous allergy skin test reactions are expected in oral tissues with SLIT therapy because the allergen extract presumably elicits an IgE-mediated response [51]. Consequently, nearly all (>80%) of the most common treatment-related AEs among the SLIT-tablets were oral reactions (Table 2). The AE profile was consistent among the SLIT-tablets, with the most reported treatment-related AEs overall being throat irritation, oral pruritus, ear pruritus (reaction presumably funneled through the Eustachian tube), and mouth edema (typically under the tongue where the tablet is placed). These oral reactions are more of a tolerability issue as they may be annoying to the patient rather than a safety concern; very few patients (approximately 5%) discontinued the trials due to treatment-related AEs which indicates that the oral reactions are tolerable, although if patients did discontinue it was generally due to persistent oral reactions. The vast majority (approximately 95%) of the treatment-related AEs were assessed as mild to moderate, meaning that the events were typically not severe enough to considerably inhibit daily activities and require medical treatment. It is imperative that patients be educated regarding what these oral reactions may feel like, how long they will last, and whether they will continue to experience these reactions with each treatment. If unprepared the patient may become nervous and discontinue treatment prematurely.

- Throat irritation was reported by 17–43% of patients who were treated with SLIT-tablets and 3–12% of placebo-treated patients. Patients describe this AE as the sensation of a scratchy feeling at the back of the throat. Throat irritation generally first occurred on day 1 and recurred for a range of 4–12 days. Events of throat irritation lasted a range of 10–55 min after tablet intake.
- Oral pruritus was reported by 11–43% of patients who were treated with SLIT-tablets and 2–8% of placebo-treated patients. Patients describe this AE as the sensation of itching in the mouth. Oral pruritus generally first occurred on day 1 and recurred for a range of 5–12 days. Events of oral pruritus lasted a range of 4–30 min.
- Ear pruritus was reported by 7–29% of patients who were treated with SLIT-tablets and 0.5–6% of placebo-treated patients. Patients describe this AE as the sensation of itching inside the ear and a need to scratch the tongue near the orifice around the Eustachian tube. Ear pruritus generally first occurred on day 1 and recurred for a range of 4–10 days. Events of ear pruritus lasted a median range of 20–30 min.
- Mouth edema was reported by 4–11% of patients who were treated with SLIT-tablets and 0.1–1% of placebo-treated patients. Patients describe this AE as the sensation of swelling at the site of tablet placement similar to feeling a small bump under the tongue. Mouth edema generally first occurred from day 7 to day 11 and

Table 2. Treatment-related adverse events in ≥5% of patients in one or more SLIT-tablet groups.

Adverse event, % of patients	Placebo adult grass pool (N = 1645)	Grass SLIT-tablet adult pool (N = 1669)	Placebo pediatric grass pool (N = 434)	Grass SLIT-tablet pediatric pool (N = 447)	Placebo ragweed pool (N = 757)	Ragweed SLIT-tablet pool (N = 1057)	Placebo HDM pool (N = 1540)	HDM SLIT-tablet pool (N = 1383) ^a
Throat irritation	3	23	3	21	3	17	12	43
Oral pruritus	4	27	2	24	2	11	8	43
Ear pruritus	1	13	1	7	1	10	6	29
Mouth edema	1	11	0.2	10	1	6	0.1	4
Oral paresthesia	2	10	1	5	4	10	2	7
Tongue pruritus	1	6	1	9	1	5	1	5
Lip swelling	0.2	4	1	7	0.4	3	1	11
Swollen tongue	0.1	3	0.0	3	1	3	1	10
Glossodynia	0.3	1	0.2	1	0.1	1	2	9
Nausea	1	2	1	2	0.3	1	2	8
Tongue ulceration	0.2	0.1	0.0	0.2	0.3	0.1	1	7
Upper abdominal pain	0.1	1	1	1	0.4	0.2	2	6
Mouth swelling	ND	ND	ND	ND	ND	ND	1	6
Mouth ulceration	0.2	0.1	0.0	0.0	0.3	0.2	1	6
Palatal swelling	ND	ND	ND	ND	ND	ND	1	6
Dysgeusia	0.4	0.4	0.0	0.2	0.3	0.3	2	5

HDM: house dust mite; ND: not determined; SLIT: sublingual immunotherapy.

^aAEs in one of the HDM SLIT-tablet trials (n = 741 HDM SLIT-tablet-treated patients) were actively solicited in a daily questionnaire.

recurred for a range of 6–27 days. Events of mouth edema lasted a median of 30 min.

This list of AEs is the ordinary manifestations of the symptoms. In some cases, the intensity of symptoms is more pronounced or extended to oral tissues beyond the tablet application site and may worsen over time. In such cases, the patient should be advised to stop treatment and contact the health-care provider. In summary, the most common treatment-related AEs are oral reactions experienced the first day of treatment, recur for less than 2 weeks, and generally resolve within 30–60 min. Notably, approximately half of patients who discontinued due to AEs did so within 14 days of the first SLIT-tablet dose. The onset of mouth edema tends to be delayed compared with the other AEs and recur over more days compared with non-swelling AEs. Other oral reactions that may be physically visible, beyond just a sensation, such as uvular swelling and tongue and lip swelling, are uncommon but may appear more dramatic. The oral reactions typically do not require medical treatment; however, if these reactions are bothersome or severe, they may be treated with an oral antihistamine (i.e. diphenhydramine and desloratadine) and rarely with an oral or intravenous corticosteroid (i.e. prednisone). In general, pre-treatment with antihistamines is not encouraged without medical advice as it may mask severe symptoms or progression to worsening of AEs.

3.3 Risk of asthma

Asthma is a common concomitant condition of allergic rhinoconjunctivitis; up to 40% of patients with allergic rhinoconjunctivitis also have asthma [52]. In the phase 2 and 3 trials of the SLIT-tablets, 20–50% of the patients had a history of asthma. Patients were required to have a forced expiratory volume in 1 second percent predicted of at least 70% for enrollment into all trials (and at least 80% for some trials). Due to the fact that approximately one-quarter to one-half of allergic rhinitis patients had a history of asthma, the effect of SLIT-tablets on asthma outcomes in patients with asthma (with or without allergic rhinoconjunctivitis) was evaluated in clinical trials. The SQ HDM SLIT-tablet protected against asthma worsening when inhaled corticosteroids were tapered [35].

Overall, there was no difference in the proportion of patients with treatment-related AEs among patients with asthma compared to patients without asthma. There was also no difference in the incidence of asthma-related AEs between SLIT-tablet-treated and placebo groups. The most frequently reported asthma-related AEs were asthma, cough, and dyspnea, and the majority of the events were reported by the investigator to be mild or moderate in intensity. The reported number of patients with AEs of asthma assessed as severe in intensity by the investigator was similar across the treatment groups. SLIT-tablets are contraindicated in patients with severe, unstable, or uncontrolled asthma and should not be initiated in asthmatic patients with ongoing respiratory tract infections.

3.4 Potential for systemic reactions with SLIT-tablets

Systemic allergic reactions to SLIT-tablets may occur. The signs and symptoms associated with a systemic allergic reaction may include, but are not limited to, syncope, hypotension, tachycardia, rhinorrhea, sneezing, dyspnea, cough, wheezing, bronchospasm, chest discomfort, rash, pruritus, flushing, and urticaria. Abdominal symptoms such as abdominal pain and diarrhea may also occur, but for SLIT-tablet, these abdominal symptoms, as well as oral reactions, are not considered part of a systemic reaction unless they occur with other systemic manifestations [53,54]. Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly in response to contact with an allergen. There is no universal definition for anaphylaxis, but the US National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network Report have proposed a definition (Table 3) [55].

Across the clinical development programs of the timothy grass, ragweed, and SQ HDM SLIT-tablets, there have been no life-threatening or serious systemic allergic reactions or events that resulted in a compromised airway. There have been 11 systemic allergic reactions reported with SLIT-tablets, 10 of which were mild to moderate. One severe SLIT-tablet-related systemic allergic reaction was reported (symptoms of throat swelling, dyspnea, nausea, light-headedness, and oral reactions), which occurred on day 6 of treatment with ragweed SLIT-tablet. The subject self-administered epinephrine, sought medical help, and was treated successfully with prednisone and antihistamine. The majority (6 out of 11 events) of the reported systemic allergic reactions have occurred on day 1 of treatment, and as such, the first dose of a SLIT-tablet should be administered under medical supervision and the patient observed for at least 30 min.

Table 3. Definition of anaphylaxis.

Anaphylaxis is highly likely when one of the following three criteria is fulfilled:
(1) The event is an acute onset (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus, flushing, or swollen lips–tongue–uvula) AND at least one of the following: a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b) Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence)
(2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours) a) Involvement of the skin-mucosal tissue b) Respiratory compromise c) Reduced BP or associated symptoms d) Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
(3) Reduced BP after exposure to known allergen for that patient (minutes to several hours) a) Infant and children: low systolic BP ^a (age specific) or greater than 30% decrease in systolic BP b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Adapted from Sampson et al. [55] with permission from Elsevier.

BP: blood pressure.

^aLow systolic BP for children is defined as <70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg for 11 to 17 years of age.

3.5 Safety of SLIT formulations

Aside from the timothy grass, ragweed, and SQ HDM SLIT-tablets, a 5-grass SLIT-tablet (ORALAIR®, Stallergenes S.A., Antony, France) is approved in North America and the EU, and an HDM SLIT-tablet (ACTAIR® Stallergenes S.A./Shionogi & Co. Ltd., Osaka, Japan) has been approved in Japan and Australia. Various SLIT drop products are also available in the EU.

All of the SLIT-tablets have a similar safety profile, with the most common treatment-emergent AEs being mild-to-moderate local oral reactions [22,56–58]. The oral reactions with the 5-grass SLIT-tablet were most common during the first 2 weeks of treatment [57]. No fatalities, cases of anaphylactic shock, or reactions treated with epinephrine were reported in the 5-grass SLIT-tablet trials, although two serious treatment-related AEs were reported (one event of severe local allergic reaction and one event of angioedema) [57]. Similarly, no fatalities, cases of anaphylactic shock, or reactions treated with epinephrine (epinephrine auto-injectors were not provided) were reported in the HDM SLIT-tablet trials [22,58]. Four serious treatment-related AEs were reported (respiratory distress, pharyngeal edema, eczema, and urticaria) [22].

Gidaro et al. [59] systematically reviewed the safety of SLIT-drops (various doses and allergens) from 25 trials. Consistent with SLIT-tablets, the majority of the AEs were local oral reactions. No fatalities, cases of anaphylactic shock, or serious AEs were reported. The review did not report any events associated with epinephrine use.

3.6 When should epinephrine be used?

Essentially, when anaphylaxis (a severe allergic reaction) occurs, epinephrine should be administered. In the total

clinical development program (including all clinical trial phases) of the timothy grass, ragweed, and SQ HDM SLIT-tablets, representing 8152 subjects who received up to and including approved doses, there have been 16 epinephrine administrations for treatment-related AEs (event rate of 0.2% administrations/subject), although only 6 of the administrations were for systemic allergic reactions and none of the AEs were serious (Figure 1) [60]. Of the 16 administrations, 7 were administered by a health-care professional during the day 1 observation period. It may be difficult for health-care providers to decide if epinephrine should be administered. A couple of scenarios are described below:

Scenario 1: Five minutes after the first dose of a SLIT-tablet, the patient reports oral swelling, throat itching, diffuse itching, and flushing of the skin with abdominal cramps.

Epinephrine use? The symptoms and timing of the symptoms indicate a diagnosis of anaphylaxis (based on criteria 2a and 2d in Table 3), and epinephrine should be administered.

Scenario 2: Five minutes after the first dose of a SLIT-tablet, the patient reports oral swelling and throat tightness. The patient is not in respiratory distress and the physical exam is normal, although some oral or pharyngeal edema is noted.

Epinephrine use? Although some physicians may consider administering epinephrine, others may observe for resolutions and withhold epinephrine unless symptoms persist or progress. Treatment with antihistamine may be considered.

Patients should be educated as to the possibility, and the signs and symptoms, of a systemic allergic reaction. Only the US FDA requires that all patients prescribed SLIT-tablets also be prescribed auto-injectable epinephrine. In the clinical development program of the SLIT-tablets, there were five self-administration events related to SLIT-tablets; only one of these administrations was for a systemic allergic reaction (the

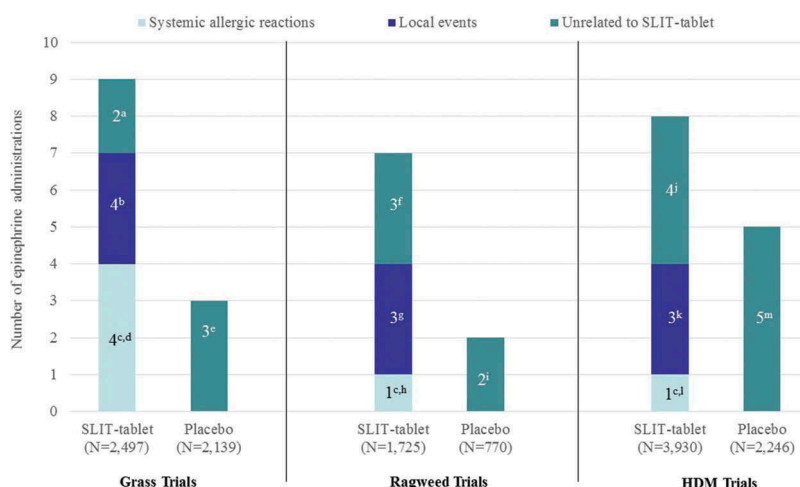


Figure 1. Epinephrine administrations in SLIT-tablet trials for all doses up to the marketed dose. ^aIn response to bed bug reaction, viral infection. ^bIn response to swelling in the mouth and/or throat (n = 2, moderate; n = 2, severe). ^cDefined as investigator-reported ‘anaphylactic reaction’, ‘hypersensitivity’, ‘systemic allergic reaction’, ‘anaphylaxis’, and ‘allergic reaction’. ^d(n = 2, mild; n = 2 moderate). ^eIn response to anxiety, wheezing, vasculitis. ^fIn response to food allergy (n = 2), vomiting/diarrhea (acute gastroenteritis, n = 1). ^gIn response to swelling in the mouth and/or pharynx/throat (n = 1, moderate; n = 2, severe). ^h(n = 1, severe). ⁱIn response to serious life-threatening anaphylaxis with protracted symptoms, 2 administrations in the same subject. ^jIn response to dust exposure (n = 1), cancer (n = 2), and melanocytic nevus (n = 1). ^kIn response to severe swelling in throat (n = 1), mild mouth/throat pruritus and dysphonia (n = 1), and moderate discomfort of throat and chest (n = 1). ^l(n = 1, moderate). ^mIn response to a complex constellation of symptoms (n = 1), dermal cyst (n = 1), cervical dysplasia (n = 1), and food allergies (n = 2). HDM, house dust mite; SLIT, sublingual immunotherapy. Reproduced from Nolte et al. [60] with permission from Elsevier.

severe systemic allergic reaction on day 6 with ragweed SLIT-tablet described above), whereas the other four administrations were for local site reactions [60]. It is important that the prescribing physician educate the patient about the signs and symptoms of anaphylaxis to ensure appropriate use of the auto-injector and avoid unnecessary epinephrine exposure.

3.7 When should SLIT-tablets be discontinued?

Prescribing information for SLIT-tablets in the US recommend that treatment be discontinued if a patient experiences persistent and escalating local site reactions or any swelling/throat tightness that causes difficulty speaking, breathing, or swallowing. Treatment should also be stopped if a patient experiences a severe systemic allergic reaction or has severe or persistent symptoms of esophagitis such as chest pain and difficulty swallowing (history of eosinophilic esophagitis is a contraindication in the United States). Patients experiencing inflammation or wounds in the mouth (including tooth extraction) should temporarily stop treatment until the wound is healed. In addition, patients with asthma should discontinue treatment with SLIT-tablets if they have difficulty breathing or their asthma becomes difficult to control. It is possible for a patient who experiences a systemic reaction or severe local site reaction to continue treatment, but treatment should be discontinued after a serious allergic reaction. Patients in the clinical trials were to contact the investigator before restarting treatment if SLIT-tablet use had been suspended for more than 7 days. This recommendation seems prudent outside clinical trials as well.

3.8 Patient FAQs regarding SLIT-tablet safety/tolerability

The local site reactions to SLIT-tablet may at first be startling to some patients. Table 4 provides a list of some of the patient FAQs regarding safety and tolerability of SLIT-tablets.

4. Conclusions

Reactions to SLIT-tablet are mainly local site reactions of mild-to-moderate intensity. In general, the local site reactions are

transient in nature, recur for less than 2 weeks, resolve within 30–60 min, and do not require medical treatment. Serious and severe AEs can occur, but events treated with epinephrine are uncommon. Patients need to be educated as to what to expect in terms of local site reactions, be made aware of the potential of systemic allergic reactions, and be educated regarding the proper use of auto-injectable epinephrine when SLIT-tablets are prescribed in the United States. Patients may also need practical information such as when to discontinue treatment.

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Declaration of interest

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Table 4. Patient FAQs regarding SLIT-tablet safety/tolerability.

Patient FAQ	Response
What should I do if I have an oral ulcer or a tooth extraction?	Temporarily discontinue treatment until the wound is healed
How long do the local side effects last?	Local side effects generally resolve in less than an hour and recur for less than 2 weeks
What do I do if I have a cold?	Patient without asthma should continue treatment as usual; patients with asthma experiencing an exacerbation of their asthma symptoms should temporarily discontinue treatment
Do I need an epinephrine auto-injector?	Patients in the United States prescribed SLIT-tablets are required to have a prescription for self-injectable epinephrine, but this is not a requirement in other countries

SLIT: sublingual immunotherapy.

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