Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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From: Patricia Rohan, MD
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Subject: GRASTEK Safety and Utilization Review for the Pediatric Advisory Committee

Manufacturer: ALK-Abelló A/S

Product: GRASTEK® (Timothy Grass Pollen Allergen Extract) Tablet for Sublingual Use

STN: 125473

Indication: An allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age.

Meeting Date: Pediatric Advisory Committee Meeting, September 2017

Contents

1. INTRODUCTION

1.1. Objective

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the initial approval, which included use in children, in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the initial approval for use of GRASTEK in persons 5 through 65-years-old on April 11, 2014.

This memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature. During the surveillance period, no new safety signals were identified and there were no reports of deaths following GRASTEK. The product does not have a requirement for a postmarketing safety study or Risk Evaluation and Mitigation Strategy (REMS), and there were no label changes regarding safety during the PAC review period (April 11, 2014- December 31, 2016).

1.2. Product Description

GRASTEK is a partially purified and standardized extract of Timothy grass (*Phleum pratense*) pollen which was referred to as MK-7243 during development. GRASTEK is formulated as a freeze-dried tablet and is intended for sublingual administration.

1.3. Regulatory History

GRASTEK was approved in the United States for use in individuals 5 – 65 years of age on April 11, 2014. GRASTEK is indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. The product was first approved under the trade name GRAZAX in Sweden in 2006 and has subsequently received marketing authorizations in 31 countries.

2. MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for GRASTEK for dates April 11, 2014 – December 31, 2016

- Manufacturer's Submissions
    - GRASTEK US package insert (USPI), dated September 2016[1]
    - Letter regarding dose distribution data, received April 14, 2017
    - Pharmacovigilance Plan (US), submitted January 25, 2013
    - Periodic Adverse Experience Reports for GRASTEK for April 11, 2014 – April 10, 2017

[1] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1d7f3e56-c233-47a4-9bcd-80098ffff47d

• FDA Documents
    - GRASTEK Approval Letter, dated April 11, 2014
    - GRASTEK Supplement Approval Letter, dated February 13, 2015, amending the patient medication guide
    - Status of Postmarketing Study Commitments and Requirements: Data through January 31, 2017
    - Previous Approval Supplement to add "stridor" to USPI Section 6.2 Postmarketing Experience approved April 28, 2017

• Publications (see Literature Search in Section 8)

3. LABEL CHANGES IN REVIEW PERIOD

FDA approved a label change (as per GRASTEK Supplement Approval Letter, dated February 13, 2015) to amend the patient medication guide to make it consistent with the package insert regarding concomitant dosing with other allergen immunotherapy under the section entitled "What Should I Tell My Doctor Before Taking GRASTEK?" The revision states that GRASTEK has not been studied in subjects receiving concomitant allergen immunotherapy, and that concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual immunotherapy.

A Prior Approval Supplement was approved April 28, 2017, to add the postmarketing adverse event term "stridor" to Section 6.2, Postmarketing Experience, of the USPI. The term "stridor" reflects a symptom seen in certain allergic/hypersensitivity reactions, which are included in the label for GRASTEK.

4. PRODUCT UTILIZATION DATA

Merck Sharp & Dohme Corp. provided distribution data for the US and Canada for April 11, 2014 (marketing start) – December 31, 2016, and for countries outside the US and Canada, for April 1, 2014 – December 31, 2016:

US:	2,426,873 tablets
Worldwide:	46,294,430 tablets

The distribution for use in different patient age ranges was not available and no estimate of number of patients treated was provided by the manufacturer.

5. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1. Pharmacovigilance Plan

The current Pharmacovigilance Plan (PVP) for GRASTEK was submitted January 25, 2013. Identified risks for GRASTEK are: serious systemic allergic reactions, including anaphylactic reactions, local allergic reactions with potential to compromise airway, acute worsening of asthma symptoms (exacerbations) and eosinophilic esophagitis. Important potential risks for GRASTEK are: anaphylactic shock, severe laryngopharyngeal disorders including the potential for respiratory compromise in children due to their relatively smaller airway and autoimmune disorders. The following table summarizes the identified potential risks and areas of missing information.

Table 1: GRASTEK Safety Concerns and Planned Pharmacovigilance Actions[1]

Identified Risks	**Planned Pharmacovigilance Actions**
Serious systemic allergic reactions, including anaphylactic reactions	Routine pharmacovigilance Follow-up questionnaire Package Insert / Patient Package Insert Phase 4 studies
Local allergic reactions with potential to compromise airway	Routine pharmacovigilance Follow-up questionnaire Package Insert / Patient Package Insert Phase 4 studies
Acute worsening of asthma symptoms exacerbations	Routine pharmacovigilance Follow-up questionnaire Package Insert / Patient Package Insert Phase 4 studies
Eosinophilic esophagitis	Routine pharmacovigilance Follow-up questionnaire Package Insert / Patient Package Insert Phase 4 studies
Potential Risks	**Planned Pharmacovigilance Actions**
Anaphylactic shock	Routine pharmacovigilance Follow-up questionnaire Package Insert / Patient Package Insert Phase 4 studies
Respiratory compromise in children due to their relatively smaller airway	Routine pharmacovigilance
Autoimmune disorders	Routine pharmacovigilance
Missing Information	**Planned Pharmacovigilance Actions**
Use during pregnancy and lactation	Routine pharmacovigilance Package Insert / Patient Package Insert
Use in children < 5 years of age	Routine pharmacovigilance Package Insert / Patient Package Insert
NOTE: Given that the GRASTEK clinical studies did not include recipients less than 5 years of age and that this product could be used post-approval in this group, it is reasonable for the sponsor to include this category as missing information in the PVP.	

The allergic reactions included in the PVP as identified and potential risks, including anaphylactic reactions and eosinophilic esophagitis, are listed in the GRASTEK package insert, and the sponsor plans to further assess these risks in two post-marketing studies (see Section 5.2.1 below). A boxed warning in the package insert states that GRASTEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. The package insert includes instructions to observe patients for at least 30 minutes after administering the first dose of GRASTEK to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home.

Contraindications to GRASTEK include severe, unstable or uncontrolled asthma, a history of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy, a history of eosinophilic esophagitis and hypersensitivity to any of the inactive ingredients contained in GRASTEK.

5.2. Postmarketing studies

5.2.1. Postmarketing surveillance studies

During the reporting period, there were two ongoing US epidemiologic safety studies conducted as post-marketing commitments (PMCs): a post-market claims-based study enrolling all new users of GRASTEK identified through claims data from a large US health insurance database, and a post-market electronic medical record study enrolling all new users of GRASTEK identified through electronic medical records in a large US integrated health system.

The studies have a combined observation period of at least 3 years and until at least 10,000 patients are accrued between them. The final study report is planned to be submitted by June 30, 2018 (or one year after completion, whichever is later).

The purpose of these uncontrolled observational cohort studies is to assess the incidence of serious allergic reactions and eosinophilic esophagitis among patients exposed to GRASTEK using real-world, health insurance claims and electronic healthcare record data.

6. ADVERSE EVENT REVIEW

6.1. Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following use of GRASTEK received between April 11, 2014 and December 31, 2016. FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports

originate from a variety of sources, including healthcare providers, consumers, and manufacturers.

Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2. Results

The results of the FAERS search of adverse event reports for GRASTEK during the review period are listed in Table 2 below.

Table 2: FAERS Reports for GRASTEK (April 11, 2014 through December 31, 2016)

Age	Serious* US	Serious* Non-US	Deaths US	Deaths Non-US	Non-Serious US	Non-Serious Non-US	Total US	Total Non-US
< 5 years	0	0	0	0	0	0	0	0
5-17 years	12	5	0	0	38	0	50	5
≥ 18 years	33	1	0	0	72	1	105	2
Unknown	18	2	0	0	132	0	150	2
Total	63	8	0	0	242	1	305	9

*Serious adverse events (including Otherwise Medically Important Conditions (OMIC)) are defined in 21CFR600.80

6.2.1. Deaths

There were no deaths following use of GRASTEK reported to FAERS during this surveillance period.

6.2.2. Serious Non-fatal Reports

During the reporting period, there were 71 serious non-fatal reports, including one report of eosinophilic esophagitis diagnosed by esophageal biopsy in an adult.

Serious non-fatal reports were received about seventeen individuals <18 years of age as summarized below, including 2 reports of ulcerative keratitis and 15 reports related to hypersensitivity/allergic reactions.

Serious Adverse Events of Note

Five patients received epinephrine for treatment of adverse events following administration of GRASTEK:

A 5-year-old male experienced anaphylactic shock with symptoms including throat swelling and severe pruritus several minutes after his third or fourth dose of GRASTEK. He was treated in the emergency room with epinephrine and antihistamines and his symptoms resolved after several hours. Of note, this patient's concomitant medications included ciclesonide, montelukast and fluticasone, medications typically used to treat asthma.

A 9-year-old female with a history of intermittent asthma began to repeatedly clear her throat, felt her throat closing up, experienced post-nasal drainage and persistent cough 15 minutes after the first dose of GRASTEK. She was treated with epinephrine, diphenhydramine and prednisone.

A 14-year-old female with a history of asthma, vocal cord dysfunction, gastroesophageal reflux disease and chronic sinusitis developed dysphagia, throat pruritus and throat tightness 2 hours following the third dose of GRASTEK. She was treated with diphenhydramine hydrochloride, epinephrine, corticosteroids and a bronchodilator, hospitalized overnight and subsequently discharged. GRASTEK was discontinued.

14-year-old male was treated w/ epinephrine and diphenhydramine after developing dysphagia in a physician's office following the first administration of GRASTEK.

A 16-year-old male experienced throat tightening, shortness of breath, chest tightness, and nausea while under physician supervision at the clinic after having taken his first dose of GRASTEK. The throat tightening lasted 10 to 15 minutes, and the shortness of breath, chest tightness, and nausea each lasted between 30 and 50 minutes. The patient was treated with albuterol, cetirizine hydrochloride, diphenhydramine hydrochloride and epinephrine. GRASTEK was discontinued.

Serious systemic allergic reactions, including anaphylactic reactions and local allergic reactions with potential to compromise airway are known risks of GRASTEK.

One pediatric report of asthma exacerbation was received during the review period. A 9-year-old female experienced an asthma attack and tongue itching on the third day after starting GRASTEK, as well as several similar subsequent episodes, which were treated at home with her asthma rescue medication (albuterol). GRASTEK was discontinued after one and one-half months of treatment. Asthma exacerbation is a labelled risk of GRASTEK.

Two pediatric patients reported ulcerative keratitis:

A 12-year-old male with a history of vernal keratoconjunctivitis developed a corneal ulcer 8 days after GRASTEK was begun. He was treated with ophthalmic steroids and antihistamines and recovered. GRASTEK was discontinued.

A 14-year-old male with a history of acne, eczema and severe vernal keratoconjunctivitis, developed ulcerative keratitis following administration of GRASTEK. Concomitant medications included omalizumab, ORALAIR, fluticasone, salmeterol, salbuterol and levocetirazine. During this same time period the patient developed a facial rash attributed to misuse of a topical acne product. It is unknown whether GRASTEK was continued.

Given that the two above reports involved individuals with a history of vernal keratoconjunctivitis, a chronic swelling of the outer lining of the eye due to an allergic reaction which can result in ulceration or scarring of the cornea, these reports do not represent a new safety concern for GRASTEK.

All the remaining serious, non-fatal reports in patients < 18 years of age involved hypersensitivity / allergic events and are summarized in the following table.

Table 3: Additional Serious Adverse Events in Patients < 18 years of age

Age (years)	Gender	Location	MedDRA Preferred Terms
10	Male	USA	Lip swelling
			Urticaria
16	Male	USA	Chest discomfort
			Dyspnoea
			Nausea
			Throat tightness
16	Male	CAN	Dizziness
			Erythema
			Eye swelling
			Feeling abnormal
			Musculoskeletal stiffness
			Neck pain
			Pain in extremity
			Urticaria
			Vision blurred
15	Female	USA	Hypersensitivity
16	Male	USA	Lacrimation increased
			Sneezing
			Swelling face
10	Male	CAN	Eye swelling
			Lip swelling
10	Male	USA	Ear pruritus
			Mouth swelling
			Swelling face
			Throat irritation
			Tinnitus
11	Male	USA	Drug hypersensitivity
11	Male	CAN	Abdominal pain upper
			Dyspnoea
			Pharyngeal paraesthesia

6.2.3. Non-serious Reports

During the reporting period, there were 243 non-serious reports, thirty-eight of those involving patients < 18-years-old. Most reports described labeled events including allergic/hypersensitivity reactions and/or local reactions, and there was no clustering around individual adverse event preferred terms (PTs) or clinical syndromes that would suggest a pattern of concern for ORALAIR.

All of the non-serious AE reports in patients < 18-years-old were from the US, and included one anaphylactic reaction. Many of the 38 reports included one or more hypersensitivity or local allergic events (e.g., edema, erythema, hypoesthesia, irritation, pruritus, swelling) involving the mouth, throat, eyes, ears, or nose.

Gastrointestinal events included five cases of abdominal pain or discomfort, and two cases each of eosinophilic esophagitis, gastro-esophageal reflux disease, diarrhea and vomiting.

Other preferred terms that appeared more than once included: Chest discomfort, Chest pain and Rash, and these PTs were not clustered around any particular type of event or other pattern of concern.

Several additional PTs, including Anxiety, Discomfort, Dizziness, Drug ineffective, Gingival bleeding, Hallucination, Headache, Influenza and Nodule were each reported once.

6.3. Data mining

Data mining was performed to evaluate whether any events following the use of GRASTEK were disproportionally reported compared to other products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point of April 6, 2017. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean.

A query of Empirica Signal using the Trade (S) run identified the following PTs with a disproportional reporting alert for GRASTEK:

- Anaphylactic reaction
- Asthma

- Chest discomfort
- Chest pain
- Ear pruritus
- Eosinophilic oesophagitis
- Eye pruritus
- Flushing
- Hypersensitivity
- Incorrect route of drug administration*
- Lip pruritus
- Lip swelling
- Mouth swelling
- Oral discomfort
- Oral pruritus
- Oropharyngeal discomfort
- Paraesthesia oral
- Pharyngeal oedema
- Pruritus generalised
- Swelling face
- Swollen tongue
- Throat irritation
- Throat tightness
- Tongue blistering*
- Tongue pruritus
- Urticaria

*The above events are described in the USPI, except for the following two PTs:

- *Tongue blistering* (4 reports, EB05=3.34):

All reports were characterized as non-serious.

GRASTEK is administered sublingually to individuals with known allergy to grass pollen. Acute mucocutaneous allergic reactions can manifest as vesicles and bullae. Of the four reports coded as Tongue blistering none actually described tongue blistering: two reports described blisters under the tongue, one report described a blister on the lip and swelling of the tongue, and one report described swelling of the tongue but no blisters at any site.

Other adverse events in these reports included: Ear pruritus, Erythema, Flushing, Lip blister, Lip pruritus, Lip swelling, Paresthesia oral, Swollen tongue, Tachycardia, Throat irritation and Tongue pruritus.

- *Incorrect route of drug administration* (7 reports, EB05=2.20):

Six reports were characterized as non-serious and one report was characterized as serious: an overnight hospitalization in a 14-year-old female asthmatic, further described in Section 6.2.2.

In all seven cases, the route was reported as "oral", or the reports did not indicate the route of administration.

One of these cases described incorrect route of drug administration in the case narrative: a 20-year-old female developed Dizziness, Headaches, Throat irritation and Throat tightness which resolved after the first three days of treatment; on an unspecified date her physician found that she had been placing the GRASTEK tablet between her teeth and lower lip. No further details were provided except that the patient continued using GRATEK.

The manufacturer coded the remaining six reports with the PT: Incorrect route of administration, presumably because the reports did not explicitly indicate the route of administration as sublingual. Other adverse events in these six reports included Anaphylactic reaction, Hypersensitivity, Increased appetite, Nausea, Off label use, Paraesthesia oral, Throat irritation, Weight increased.

6.4. Periodic Adverse Event Reports (PAERs)

The manufacturer's postmarketing periodic safety reports for GRASTEK covering the surveillance period were reviewed. There were between 4 and 84 initial reports received by the sponsor in each quarter, with a not surprising seasonal variation in the number of reports. The adverse events reported were consistent with those seen in FAERS. Other than the addition of the term "stridor" to Section 6.2, Postmarketing Experience, of the USPI, as described in Section 3, above, no additional safety issues were identified and no actions were taken by the sponsor for safety reasons.

7. LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on March 15, 2017, for peer-reviewed literature published between April 11, 2014 and December 31, 2016, with the search term "GRASTEK" and "safety", "GRAZAX" and "safety" and "MK-7243" and "safety" retrieved 8 articles on human safety. The articles were reviewed, and the safety conclusions are listed in the table below. No new safety issues for GRASTEK were identified in these articles.

Table 4: Literature Review

Article	Safety Conclusion
Antico A, Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. The Journal of Allergy and Clinical Immunology. 2014 May; 133(5):1482-1484.	A patient developed the sensation of retrosternal constriction, pain and dysphagia related to tablet and food ingestion 1 month after initiating GRAZAX. He was treated for gastroesophageal reflux with without improvement. Grass SLIT was discontinued and proton pump inhibitor therapy was withdrawn. The patient was reported as recovered within a couple of weeks. Skin prick tests (SPTs) confirmed previously diagnosed sensitization to mites and grass, and also to profilin (palm pollen profilin) and non-specific lipid transfer protein (peach lipid transfer protein) confirmed by ImmunoCAP testing. SPTs were negative to a large array of other food allergens. The patient resumed GRAZAX with recurrence of symptoms within 1 week. He underwent an upper endoscopy and biopsy specimens from the upper, middle and lower esophagus revealed significant esophinophila, while gastric antrum and duodenum specimens were normal. *Helicobacter pylori* testing was negative. GRAZAX was discontinued and no relapse of clinical symptoms was seen. Repeat biopsy of the upper, middle and lower esophagus soon after the end of grass pollen season showed complete healing of mucosa without signs of inflammation or eosinophils.
Canadian Agency for Drugs and Technologies in Health; Common Drug Review. Standardized Allergenic Extract, Timothy grass (Phleum pratense) (GRASTEK) (sublingual tablet 2,800 BAU). 2014 December.	The Canadian Agency for Drugs and Technologies in Health reviewed eight multicenter, randomized, double-blind, placebo-controlled studies of GRASTEK and found AEs were higher in the GRASTEK group compared with the placebo group and were reported as being mild or moderate in severity. The most frequent AEs were those associated with the mouth or throat. Treatment durations were approximately 24 weeks in most studies; however, longer-term data (seasonal treatment over three years) available from an extension to study did not reveal additional safety issues. Serious AEs and withdrawals due to AEs were few and similar in both groups across the trials. Three studies reported one death each in the GRASTEK groups, but these were not considered to be related to GRASTEK.

Article	Safety Conclusion
Larenas-Linnemann D. How does the efficacy and safety of Oralair® compare to other products on the market? Therapeutics and Clinical Risk Management 2016:12, 831–850.	A systematic review of published GRASTEK clinical trials found local, mild–moderate adverse reactions are common during the first 1–2 weeks of sublingual immunotherapy. In clinical trials with GRAZAX/GRASTEK, an epinephrine auto-injector was used in two patients because of adverse reactions, judged probably tablet-related. Discontinuation due to tablet-related adverse reactions, mostly moderate–severe local reactions, in double-blind, placebo-controlled trials occurred in approximately 5% of subjects.
Maloney J, Durham S, Skoner D, Dahl R, Bufe A, Bernstein D, Murphy K, Waserman S, Berman G, Shite M, Kaur A, Nolte H. Safety of sublingual immunotherapy Timothy grass tablet in subjects with allergic rhinitis with or without conjunctivitis and history of asthma. Allergy. 2015 Mar;70(3):302-9.	In a post hoc analysis of pooled data from randomized, double-blind, placebo-controlled trials of GRASTEK, in allergic rhinitis with or without allergic conjunctivitis subjects with reported well-controlled mild asthma, grass SLIT-tablet did not increase treatment-emergent adverse event frequency, severe local allergic swelling, or systemic allergic reactions versus subjects without asthma. There was no indication that treatment led to acute asthma worsening.
Maloney J, Bernstein DI, Nelson H, Creticos P, Hébert J, Noonan M, Skoner D, Zhou Y, Kaur A, Nolte H. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Ann Allergy Asthma Immunol. 2014 Feb;112(2):146-153.e2.	This article describing one of the pre-approval clinical trials concluded that most AEs were transient local application-site reactions, with no serious treatment-related AEs or anaphylactic shock. Three subjects (1 placebo, 2 MK-7243) had moderate systemic allergic reactions.
Nelson HS. Oral/sublingual Phleum pretense grass tablet (Grazax/Grastek) to treat allergic rhinitis in the USA 2014. Expert Rev. Clin. Immunol. 10(11), 1437–1451 (2014)	As compared to subcutaneous immunotherapy, sublingual immunotherapy is much less likely to result in a systemic reaction. Caution is indicated in administering Timothy sublingual immunotherapy tablets (SLIT) to patients who have had systemic reactions to grass subcutaneous immunotherapy. Two patients in the Netherlands who had systemic reactions to grass subcutaneous immunotherapy (SCIT) experienced anaphylactic reactions immediately following the first administration of the Timothy SLIT tablet.

Article	Safety Conclusion
Nolte H, Casale TB, Lockey RF, Fogh BS, Kaur A, Lu S, Nelson HS. Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets. The Journal of Allergy and Clinical Immunology: In Practice. 2017 Jan - Feb;5(1):84-89.e3.	Epinephrine administrations in response to SLIT-tablet-related reactions in clinical trials are uncommon, typically occur within the first week of treatment, and are rarely self-administered.
Scaparrotta A, Attanasi M, Petrosino M et al. Critical appraisal of Timothy grass pollen extract GRAZAX® in the management of allergic rhinitis. Drug Design, Development and Therapy 2015:9 5897–5909	In a review of published clinical studies, including placebo controlled and dose-ranging studies, most adverse events were localized to the mouth, throat, eyes or ears, and involved itching, swelling and irritation.

8. CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for GRASTEK does not indicate any new safety concerns. This PAC review was initiated due to the initial US approval of GRASTEK, in individuals 5-65 years of age. In general, very few adverse events were reported in the pediatric age group (<18 years) during the review period. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern. There were no reports of death. The adverse events in children are similar to those seen in adults and are consistent with the known safety profile for GRASTEK.

9. RECOMMENDATIONS

FDA recommends continued routine safety monitoring of GRASTEK. The results of the postmarketing studies assessing allergic reactions and eosinophilic esophagitis will be reviewed when complete.

10. APPENDIX

FAERS cases reviewed for pediatric serious non-fatal reports:

10102635	10967094	11986273
10168423	11102158	12170253
10190446	11173664	12173963
10389165	11399584	12740934
10614967	11432619	12180243
10722772	11983476	

FAERS cases reviewed for reports of “Eosinophilic esophagitis”:

11294954	12188626

FAERS cases reviewed for data mining finding of “Tongue blistering”:

10921043	11042386
10953165	12272377

FAERS cases reviewed for data mining finding of “Incorrect route of administration”:

10573201	11147568	12350169
10731550	11700130	
10947660	11986273	