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

MEMORANDUM

To:	Scott Proestel, MD Director, Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Craig Zinderman, MD, MPH Associate Director for Product Safety, DE, OBE, CBER Adamma Mba-Jonas, MD Acting Chief, Pharmacovigilance Branch (PVB), DE, OBE, CBER
From:	Patricia Rohan, MD Medical Officer, PVB, DE, OBE, CBER
Subject:	ORALAIR Safety and Utilization Review for the Pediatric Advisory Committee
Manufacturer:	Stallargenes S.A.
Product:	ORALAIR (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) Tablet for Sublingual Use
STN:	125471
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 any of the five grass species contained in this product. ORALAIR is approved for use in persons 10 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 ORALAIR in persons 10 through 65 years of age on April 1, 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 ORALAIR. The product does not have a requirement for a postmarketing safety study or Risk Evaluation and Mitigation Strategy (REMS). A safety related label change under Section 505(0)(4) of the Federal Food, Drug and Cosmetic Act (FDCA) was approved shortly after ORALAIR approval on April 1, 2014. CBER became aware of cases of eosinophilic esophagitis (E0E) following allergen extract sublingual tablet immunotherapy with another manufacturer's product and issued a Safety Labeling Change Notification Letter on August 18, 2014. The manufacturer's Supplemental Biologics License Application to update the ORALAIR USPI with respect to the risk of EoE was approved on October 28, 2014. The risk of EoE is considered applicable to all sublingual immunotherapy products (see Section 3) and labelled for this product class. There were no changes to the label in response to adverse events following ORALAIR use.

1.2. Product Description

ORALAIR is a freeze-dried tablet formulation of a mixed grass pollen extract for sublingual use.

1.3. Regulatory History

ORALAIR was first approved in the United States for use in individuals 10 – 65 years of age on April 1, 2014, and it was the first approved allergen extract in the U.S. for sublingual immunotherapy (SLIT). The product was first approved in Germany in June 2008 for adults and in January 2009 for children, and subsequently in 29 additional countries including the US.

2. MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
  - FAERS reports for ORALAIR for dates April 1, 2014 – December 31, 2016
- Manufacturer's Submissions
  - ORALAIR US package insert, updated December, 2016[1]
  - Letter regarding dose distribution data, received April 14, 2017

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

- Pharmacovigilance Plan (US), submitted January 14, 2013
- Periodic Adverse Experience Reports for ORALAIR for April 1, 2014 – March 31, 2017

- FDA Documents
  - ORALAIR Approval Letter, dated April 1, 2014
  - ORALAIR Safety Labeling Change Notification Letter, dated August 18, 2014
  - ORALAIR Supplement Approval letter, dated October 28, 2014
  - Status of Postmarketing Study Commitments and Requirements: Data through January 31, 2017

- Publications (see Literature Search in Section 7)

3. LABEL CHANGES IN REVIEW PERIOD

FDA required and approved a safety related label change under Section 505(o)(4) of the FDCA (ORALAIR Supplement Approval Letter, dated October 28, 2014) to include new safety information on the risk of eosinophilic esophagitis in the label and patient medication guide, consistent with all other approved sublingually-administered allergen extracts in this product class. No cases of eosinophilic esophagitis had been reported from the clinical development program or in foreign postmarketing experience for ORALAIR at the time of U.S. approval. However, FDA considered this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA based on FDA's review of a published case report for another manufacturer's SLIT product (Antico, J Allergy Clin Immunol May 2014) and three additional postmarketing reports of eosinophilic esophagitis associated with the use of another SLIT product approved shortly after ORALAIR. These findings, together with consideration of the biologic plausibility of eosinophilic esophagitis, resulted in the decision to include eosinophilic esophagitis in the label for all sublingual immunotherapy products. Eosinophilic esophagitis was added to the Contraindications, Warnings and Precautions, and Patient Counseling Information sections of the ORALAIR package insert.

4. PRODUCT UTILIZATION DATA

Note: The unit of potency is designated "IR" which stands for the Index of Reactivity, the biological unit of measure of product potency based upon prick skin test performed in a group of 30 subjects sensitized to the allergen in question, which produced a wheal measuring 7 mm in diameter (geometric mean).ORALAIR daily dose in adults is 300 IR, while the dose in children 10-17 years of age is 100 IR on Day 1, 2 x 100 IR on Day 2, and 300 IR daily on Day 3 and thereafter.

Stallargenes S.A. provided distribution data for the US and worldwide for April 1, 2014 (marketing start) – December 31, 2016:

US:	100 IR tablets: 126,708	300 IR tablets: 2,377,173
Worldwide:	100 IR tablets: 687,858	300 IR tablets: 29,961,666

The distribution for use in different patient age ranges was not available and the manufacturer did not provide any estimate of the number of patients treated.

5. PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1. Pharmacovigilance Plan

The current Pharmacovigilance Plan for ORALAIR was submitted on January 14, 2013. Identified risks for ORALAIR are: allergic reactions (including severe laryngopharyngeal disorders), anaphylactic shock, severe anaphylactic reactions and eosinophilic esophagitis. An important potential risk for ORALAIR is autoimmune disorders. A summary of the identified and potential risks and areas of missing information is included in the following table.

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

Identified Risks	**Planned Pharmacovigilance Actions**
Allergic Reactions (including severe laryngopharyngeal disorders)	Enhanced surveillance via a specialized report intake form and a focused list of MedDRA preferred terms (PTs) to periodically screen and analyze reports of severe laryngopharyngeal disorders.
Anaphylactic Shock	An "anaphylactic reaction" standardized MedDRA Query (SMQ) is run periodically to identify and screen potential cases.
Eosinophilic Esophagitis	Routine pharmacovigilance Package Insert / Patient Package Insert Phase 4 study
Potential Risks	**Planned Pharmacovigilance Actions**
Autoimmune Disorders	Routine pharmacovigilance with a special focus on cases related to auto-immune disease or potential signs of an autoimmune disorder. It was not considered feasible to create a list of PTs or specific notification form to monitor this disparate group of symptoms and target organs.
Missing Information	**Planned Pharmacovigilance Actions**
Use during pregnancy and lactation	Routine pharmacovigilance Package Insert / Patient Package Insert
Use in children 5 to <10 years of age	Routine pharmacovigilance Package Insert / Patient Package Insert Postmarking study in children 5 to <10 years of age
Use in children <5 years of age	Routine pharmacovigilance Package Insert / Patient Package Insert
NOTE: Given that the ORALAIR is not approved for use in recipients less than 10 years of age, it is reasonable for the manufacturer to include this category as missing information in the PVP.	

The allergic reactions included in the PVP as identified risks, including allergic reactions, anaphylactic shock, severe anaphylactic reactions and eosinophilic esophagitis, are listed in the ORALAIR package insert, and the manufacturer's plans to further assess these risks in a clinical study of children and adolescents and an observational postmarketing study of adults (see Section 5.2. below). A boxed warning in the package insert states that ORALAIR can cause life-threatening allergic

reactions such as anaphylaxis and severe laryngopharyngeal edema, and is to be prescribed with auto-injectable epinephrine. The package insert includes instructions to observe patients for at least 30 minutes after administering the first dose of ORALAIR 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 ORALAIR 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 ORALAIR.

5.2. Postmarketing studies

5.2.1. Postmarketing Requirement (PMR)

During the reporting period, there was one ongoing safety and tolerability study conducted as a PMR under the Pediatric Research Equity Act (PREA), pediatric study 140224, to support use of ORALAIR in children 5 to 9 years of age. As per the study milestone dates in the ORALAIR Approval Letter, the Final Report Submission date was planned for December 31, 2016. A deferral extension was granted due to delays in recruitment and the Final Report Submission milestone date is now December 31, 2017.

5.2.2. Postmarketing surveillance studies

During the reporting period, there was one ongoing observational postmarketing study (Study 140225) to further describe the safety profile in approximately 6,000 patients 10 to 65 years of age receiving Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract approximately 4 months before the expected onset of the grass pollen season and throughout the grass pollen season. As per study milestone dates in Approval Letter, Final Report Submission date was planned to be June 30, 2018.

The purpose of this study is to assess the incidence of serious allergic reactions and eosinophilic esophagitis among patients exposed to ORALAIR by actively enlisting prescribing physicians to provide comprehensive information on any of their patients who experience adverse reactions resulting in medical attention while receiving treatment with ORALAIR. With the objective of identifying potential risk factors for such adverse reactions, analyses will compare differences in outcomes between this observational study and those identified from a retrospective claims database of approximately 7.5 million Florida Medicaid enrollees, among whom nearly 5,000 have received subcutaneous immunotherapy (SCIT).

6. ADVERSE EVENT REVIEW

6.1. Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following use of ORALAIR between April 1, 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 ORALAIR during the review period are listed in Table 2 below.

Table 2: FAERS Reports for ORALAIR (April 1, 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
6 - < 10 years†	0	3	0	0	1	0	1	3
10 - 17 years	2	5	0	0	10	0	12	5
≥ 18 years	6	4	0	0	33	1	39	5
Unknown	2	0	0	0	6	1	8	1
Total	10	12	0	0	50	2	60	14

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

† ORALAIR is approved outside the US for use in children ≥6 years old.

6.2.1. Deaths

There were no deaths following ORALAIR reported to FAERS during this surveillance period.

6.2.2. Serious Non-fatal Reports

During the reporting period, there were 22 serious non-fatal reports including one report of eosinophilic esophagitis diagnosed by biopsy in an adult.

Serious non-fatal reports from ten individuals <18 years of age were reviewed and are summarized below. The clinical symptoms/conditions in these serous pediatric reports are isolated events, and there is no pattern or clustering among types of events. Several of the cases have concomitant treatments or co-morbid conditions that could represent alternative causes for the observed events.

A 14-year-old male with a history of severe vernal keratoconjunctivitis developed corneal ulceration, eye infection, acne, contact dermatitis, episcleritis and rash while being treated with ORALAIR, GRAZAX, omalizumab, fluticasone, salmeterol, levocetirizine and salbutamol. The rash and contact dermatitis were attributed to misuse of a topical acne treatment. The patient was reported as recovered from episcleritis, but no information is provided as to the status of the other reported conditions. The patient continued on ORALAIR.

A 9-year-old male experienced two episodes of chest pain, pallor, paresthesias of the arm and rolling eyes; recurrent episodes of respiratory distress and anxiety; and belly ache and diarrhea beginning 10 days after initiation of ORALAIR. In the first episode, the patient's mother called an emergency doctor who evaluated the patient at home and the patient remained at home. A few hours later that patient experienced similar symptoms and was hospitalized. His oxygen saturation was reportedly normal, no heart problem was detected and he was evaluated with an ECG and Doppler ultrasound, but did not receive any corrective treatment and was discharged 3 days later. ORALAIR was discontinued and the patient was reported as recovering. Since discharge the patient has experienced daily episodes of respiratory distress associated with anxiety that resolve after taking half a tablet of cetirizine.

A 13-year-old female reported pelvic muscle inflammation, rheumatic discomfort and inflammatory bowel disease while taking ORALAIR, although date of initiation and timing with respect to onset of adverse events was not provided. No information was provided on any treatments, outcomes or whether ORALAIR was continued.

An 8-year-old male developed yellow tooth discoloration described as a dental plaque after a week and a half of initiating ORALAIR. ORALAIR was discontinued, the yellow discoloration was reported as decreased and the patient was considered recovered.

A 6-year-old male experienced onset of an unspecified number of tonic-clonic seizures 5 days after initiating ORALAIR treatment. MRI and EEG were reported as normal. No long-term anti-seizure treatment was initiated. ORALAIR was discontinued on an unspecified date. The patient was seen seven months later and no further seizures were reported.

A 15-year-old male experienced one episode of blurred vision, difficulties of concentration at school, anxiety and sleeping for 18 hours, one and a half weeks after initiating ORALAIR. The patient complained about difficulty differentiating dream from reality. A week later the patient was started on acetylcysteine 600 mg per day for an unspecified infection. Several days later ORALAIR was temporarily interrupted during 2-3 days due to oral infection and resumed. Subsequently, upon returning from 4 days

of travel, the patient experienced the same symptoms. It was not stated whether the patient received any corrective treatment and at time of the report, symptoms were fully resolved. ORALAIR was discontinued.

A 14-year-old male reported sublingual swelling, blocked ears, headache, abdominal pain and tiredness 30 minutes following the first dose of ORALAIR. The events resolved spontaneously within two hours. ORALAIR was decreased to half a tablet (150 IR) daily.

A 16-year-old female reported an anaphylactic reaction with a decrease in blood pressure (value not reported), itchy mouth and throat, throat swelling and difficulty breathing twenty minutes after the first dose of ORALAIR in a physician's office. She was treated with cetirizine, prednisone and epinephrine injections and observed for one and a half hours and discharged after resolution of symptoms with normal vital signs. One and a half hours after leaving the physician's office (3 hours after taking ORALAIR) she experienced throat swelling and her father treated her with an Epipen. She was taken to an ER and treated with steroids, diphenhydramine and famotidine, observed for several hours and discharged with a prescription for prednisone for 4 days at home. The patient was reported as recovered and ORALAIR was discontinued.

A 14-year-old male reported a urinary tract infection 2 months after initiating daily ORALAIR. No information was provided regarding treatment. ORALAIR was continued.

A 12-year-old male reported abdominal pain and nausea one week after initiating ORALAIR. He was hospitalized and found to be constipated. He recovered and ORALAIR was continued.

6.2.3. Non-serious Reports

During the reporting period, there were 52 non-serious reports, including one report of eosinophilic esophagitis in an adult male. Most reports described labeled events including allergic or hypersensitivity reactions and/or local reactions, and there was no clustering around individual PTs or clinical syndromes that would suggest a pattern of concern for ORALAIR. Eleven non-serious reports involved patients < 18-years-old and in this population the PTs, Throat Irritation and Lip Oedema, each appeared in two reports, and the following PTs each appeared in one report: Abdominal Pain Upper, Adverse Reaction, Bronchospasm, Chest Pain, Drug Ineffective, Dyspnoea, Generalised Erythema, Gingival Oedema Hypersensitivity Mouth Ulceration, Off Label Use, Oral Disorder, Oral Mucosal Blistering, Oral Pain, Pruritus Generalised, Rash Pruritic, Tongue Disorder, and Urticaria.

6.3. Data mining

Data mining was performed to evaluate whether any events following the use of ORALAIR 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 disproportional reporting alerts for ORALAIR for the following preferred terms:

- Eosinophilic oesophagitis
- Lip Oedema
- Oedema Mouth
- Oral Pruritus
- Pharyngeal Oedema
- Throat Irritation
- Throat tightness
- Tongue oedema

The above PTs are all symptoms related to local or systemic allergic reactions; they are all included in the ORALAIR label.

6.4 Periodic Adverse Event Reports (PAERs)

The manufacturer's postmarketing periodic safety reports for ORALAIR during the surveillance period were reviewed. There were between 1 and 28 initial reports received by the manufacturer in each quarter. The adverse events reported were consistent with those seen in FAERS. No additional safety issues were identified and no actions were taken by the manufacturer for safety reasons.

7. LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on March 21, 2017, for peer-reviewed literature published between April 1, 2014 and December 31, 2016, with the search term "ORALAIR" and "safety" retrieved 7 articles on human safety. The articles were reviewed, and the safety conclusions are listed in the table below. No new safety issues for ORALAIR were identified in these articles.

Table 3: Literature Review

Article	Safety Conclusion
Dranitsaris G, Ellis AK. Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost. J Eval Clin Pract. 2014 Jun;20(3):225-38.	The relative risks of stopping treatment due to adverse events were estimated across several studies and immunotherapy products using a univariate analysis, and not adjusting for differences in study characteristics. Safety outcomes for ORALAIR were not reviewed in this publication.
Di Bona D, Plaia A, Leto-Barone MS, et al. Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis: A Systematic Review and Meta-analysis. JAMA Intern Med. 2015 Aug;175(8): 1301-9.	Literature review of published, randomized, placebo-controlled clinical trials of grass pollen SLIT tablets approved by regulatory authorities in the European Union and the US for seasonal allergic rhinitis with or without conjunctivitis. Adverse events (AEs) were reported in 1384 of 2259 patients (61.3%) receiving SLIT and in 477 of 2279 patients (20.9%) receiving placebo. The SLIT group reported 3 times as many AE and a higher study withdrawal rate (6.0% vs. 2.2%) as compared to the placebo group. Nine events requiring epinephrine were reported in the SLIT group, seven considered treatment-related and three events requiring epinephrine were reported in the placebo group, none considered treatment-related.
Didier A, Bons B. Safety and tolerability of 5-grass pollen tablet sublingual immunotherapy: pooled analysis and clinical review. Expert Opin Drug Saf. 2015 May;14(5):777-88.	A review of safety data from the ORALAIR clinical development program and postmarketing experience found most adverse events mild to moderate in severity, the most frequent being local oropharyngeal reactions consistent with sublingual administration.
Didier A, Wahn U, Horak F et al. Five-grass-pollen sublingual immunotherapy tablet for the treatment of grass-pollen-induced allergic rhinoconjunctivitis: 5 years of experience. Expert Rev Clin Immunol. 2014 Oct;10(10):1309-24.	A review of the ORALAIR clinical development program found most adverse events (AEs) were mild or moderate in severity, with the most common (reported in ≥5% of patients) being oral pruritus, throat irritation, ear pruritus, mouth edema, tongue pruritus, cough and oropharyngeal pain. The majority of AEs showing an increased incidence in ORALAIR recipients as compared to placebo recipients were local reactions related to the route of administration, particularly oral pruritus and throat irritation. No death or intensive care unit admission was reported in any patient receiving ORALAIR, and no reports of anaphylactic shock or anaphylaxis were observed.
Iemoli E, Borgonovo L, Fusi A, et al. Sublingual allergen immunotherapy in HIV-positive patients. Allergy 71 (2016) 412–415.	A prospective, open-label study of ORALAIR in a group of grass pollen-allergic, highly active antiretroviral therapy-treated HIV-positive adults. All thirteen patients who received Oralair and symptomatic therapy and nine of thirteen patients who received symptomatic therapy alone completed the study. No significant alterations in TCD4 cell counts and viral load (VL) were observed. The ORALAIR group reported two cases of sublingual edema, one case of oral aphthosis and one case of epigastric distress.

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 review of published studies reports local, mild–moderate adverse reactions are very common the first 1–2 weeks of the sublingual immunotherapy, but generally disappear when treatment is continued. Also, they are less common and less severe when treatment is restarted before the next pollen season. In the double-blind, placebo-controlled trials, discontinuation due to tablet-related adverse reactions, mostly moderate–severe local reactions in the oral cavity, occurred in approximately 5% of subjects.
Shah-Hosseini K, Mioc K, Hadler M, et al. Optimum treatment strategies for polyallergic patients - analysis of a large observational trial. Curr Med Res Opin. 2015 Dec;31(12):2249-59.	In a review of a 2-year, open-label, multicenter observational study of 1408 patients including 434 children/adolescents receiving ORALAIR in Germany, adverse drug reactions (ADRs) were reported in 15.3% of study participants and were mostly local in nature and mild or moderate in intensity. The most common ADRs were throat irritation (2.9%) and mouth edema (2.3%). A total of 36 serious AEs (SAEs) occurred in nine patients, but none were considered life-threatening and there was no use of epinephrine.

8. CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the manufacturer's periodic safety reports, and the published literature for ORALAIR does not indicate any new safety concerns. This PAC review was initiated due to the initial US approval of ORALAIR in individuals 10-65 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 ORALAIR.

9. RECOMMENDATIONS

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

10. APPENDIX

FAERS serious, non-fatal cases reviewed:

10168423	11432308	12527876
11179672	11532633	12950601
11248451	11914420	
11306882	12219529	