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

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy Office of Biostatistics and Pharmacovigilance (OBPV) Center for Biologics Evaluation and Research (CBER)
From:	Jonathan Reich, MD Medical Officer, Pharmacovigilance Branch 2 (PB2) Division of Pharmacovigilance (DPV), OBPV, CBER Christopher Jason, MD Branch Chief, PB2, DPV, OBPV, CBER Meghna Alimchandani, MD Deputy Director, DPV, OBPV, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Stallergenes S.A.
Product:	Oralair (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract)
STN:	BL 125471/302
Indication:	Oralair is 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 5 through 65 years of age. Oralair is not indicated for the immediate relief of allergy symptoms.
Meeting Date:	Pediatric Advisory Committee Meeting, September 2023

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval 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 approval of the supplemental Biologics License Application (sBLA) 125471/230, on November 9, 2018, to extend the indication for use in persons 5 through 9 years of age.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Indication and Product Description

Oralair is 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 5 through 65 years of age. Oralair is not indicated for the immediate relief of allergy symptoms.

This product is available as a freeze-dried tablet formulation of a mixed grass pollen extract for sublingual use.

1.3 Regulatory History

- April 1, 2014: Initial FDA approval of BLA 125471/0 for use in individuals 10 – 65 years of age. Oralair 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.
    - This was a trigger for a previous PAC review conducted in 2017 (please see PAC review memorandum under STN 125471/189)
- November 9, 2018: FDA approval of sBLA 125471/230 to extend the indication for use in persons 5 through 9 years of age. (Trigger for the current review memorandum.)

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS) reports for Oralair during November 9, 2018 to May 31, 2023 (safety review period)
- Manufacturer's submissions

    - Oralair U.S. package insert; updated December 9, 2022
    - Applicant response to information request regarding dose distribution data, received July 14, 2023
    - U.S. Pharmacovigilance Plan, Updated June 2023
    - Periodic safety reports
- FDA Documents
    - Oralair BL 125471/230 approval letter
    - Oralair BL 125471/230 Pharmacovigilance Plan Review Memorandum
    - Oralair BL 125471/251 Postmarketing Commitment (PMC) Final Study Report Review Memorandum
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There were no safety related labeling changes during November 9, 2018 to May 31, 2023 (safety review period).

Of note, as described in the previous 2017 PAC review memorandum, a safety labeling change under Section 505(o)(4) of the Federal Food, Drug and Cosmetic Act (FDCA) was required shortly after initial approval of Oralair in 2014. CBER became aware of cases of eosinophilic esophagitis (EoE) following allergen extract sublingual tablet immunotherapy with another manufacturer's product and issued a Safety Labeling Change Notification Letter on August 18, 2014. The updated label was approved on October 28, 2014. The label was updated to include EoE under *Contraindications, Warnings and Precautions,* and *Patient Counseling Information* sections of the USPI. The risk of EoE is considered applicable to all sublingual immunotherapy products and labelled for this product class.

4 PRODUCT UTILIZATION DATA

Stallargenes S.A. provided estimates of U.S. and worldwide Oralair distribution data and estimated patient exposure data for the safety review period of November 9, 2018 to May 31, 2023:

Age	U.S. Distribution (Number of Tablets Sold)	Estimated Patient Exposure (Patient-Years)
< 18 years	61,260	340
18 years and older	307,170	1,707
Unknown	11,190	62
Grand Total	**379,620**	**2,109**

Age	Worldwide Distribution (Number of Tablets Sold)	Estimated Patient Exposure (Patient-Years)
< 18 years	28,672,560	159,292
18 years and older	50,180,760	278,782
Grand Total	**78,853,320**	**438,074**

As per the sponsor, based on the available sales data, the following assumptions were used for the patient exposure estimate: treatment is initiated about 4 months before the expected onset of pollen season and maintained throughout the pollen season, estimated to be in average 2-months long. It is assumed that a patient is treated over 6 months per year, corresponding to 180 tablets (or treatment-days) yearly. Considering that this "180-tablet treatment" corresponds to a patient-year, patient exposure expressed in Patient-Years (PY) is obtained by dividing the total number of tablets sold by 180.

Note that the number of doses distributed is an estimate of the number of patients exposed to this product because doses may have been distributed without being administered to patients.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The Pharmacovigilance Plan (PVP) for Oralair, updated June 2023, lists the following important identified and potential risks, and missing information (see Table 1).

Table 1: Oralair Safety Concerns

Important Identified Risks
Severe laryngopharyngeal disorders
Anaphylactic Reaction
Eosinophilic Esophagitis (EoE)
Important Potential Risks
Anaphylactic Shock
Autoimmune Disorders
Missing Information
Pregnant and lactating women
Elderly patients (older than 65 years)

The allergic reactions included in the PVP as identified risks, including anaphylactic reaction and EoE, are labeled events. The Oralair USPI includes a boxed warning that states that Oralair can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction, and Oralair 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 an allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home. Severe Allergic Reactions and EoE are also included under Warnings. 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.

The important identified and potential risks listed in Table 1 are monitored with routine pharmacovigilance, including review of adverse event reports submitted to FDA, manufacturer submitted periodic safety reports, published literature, and data mining. There are no postmarketing requirement (PMR) safety studies or Risk Evaluation and Mitigation Strategy (REMS) for Oralair. The sponsor had a postmarketing commitment for a general safety surveillance study (see Section 5.2 below).

5.2 Postmarketing Studies

The following postmarketing studies were described in BL 125471/0 approval letter dated April 1, 2014.

Postmarketing requirement under Pediatric Research Equity Act (PREA)

- Deferred pediatric study (Study 140224) for ages 5 to <10 years, for 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 the product.

Study status: Fulfilled
(Note that this pediatric study provided data that was the basis for the approval to extend the indication for use in persons 5 through 9 years of age, which serves as the regulatory trigger for the current PAC review.)

The applicant has fulfilled the pediatric study requirement for all relevant pediatric age groups for this application. Note that FDA waived the pediatric study requirement for children less than 5 years because necessary studies are impossible or highly impracticable. This is because the number of children younger than 5 years of age with allergic rhinitis who have been diagnostically confirmed with sensitivity to one or more of the allergens in Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract is too small.

Postmarketing commitment (PMC)

- *To conduct an 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.*

Study status: Fulfilled

Study 140225 was completed, and the Final Study Report (FSR) was reviewed under BL 125471/251. This general safety surveillance study (which included eosinophilic esophagitis as a study outcome) did not identify any new safety concerns for Oralair.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of Oralair received by FDA between November 9, 2018, to May 31, 2023 (data lock point). 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 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 AE reports for Oralair during the safety review period are listed in Table 2 below. There were 183 reports including 89 US and 94 foreign reports for the review period November 9, 2018 to May 31, 2023.

Table 2: Oralair FAERS reports during November 9, 2018 to May 31, 2023

Age	Serious Non-Fatal*		Deaths		Non-Serious		Total Reported	
	US	Foreign	US	Foreign	US	Foreign	US	Foreign
<17 years	3	25	0	0	27	1	30	26
≥ 17 years	5	51	0	0	51	4	56	55
Unknown	1	11	0	0	2	2	3	13
All Ages	9	87	0	0	80	7	89	94

*Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, or significant disability or otherwise medically important conditions (OMIC).

6.2.1 Deaths

There were no deaths reported during the safety review period.

6.2.2 Serious Non-fatal Reports

During the safety review period, there were 96 serious non-fatal reports, including 28 pediatric reports and 56 adult reports. Age was unknown for the remaining 12 reports.

The most common Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for pediatric reports are displayed in Table 3. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 3: Most frequently reported PTs for pediatric (< 17 years) serious non-fatal reports

Preferred Term (PT)	# Serious Pediatric Reports	Label Status *USPI updated December 9, 2022*
Oral Pruritis	6	Labeled
Angioedema	4	Labeled
Cough	4	Labeled
Dyspnea	4	Labeled
Oedema mouth	4	Labeled
Sensation of Foreign Body	4	Not Labeled
Abdominal Pain	3	Black Box Warning
Anaphylactic Reaction	3	Labeled
Erythema	3	Labeled as “flushing or irritation of the skin”
Face Oedema	3	Labeled
Hypersensitivity	3	Labeled
Nausea	3	Labeled

Note: PTs occurring with a frequency >2 reports are shown in above table.

Reviewer comments: All PTs are labeled events or consistent with a labeled event. The PT, *Sensation of Foreign Body*, may be related to labeled event for “trouble swallowing or speaking.”

The most common PTs for adult reports are displayed in Table 4. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 4: Most frequently reported PTs for adult (≥ 18 years) serious non-fatal reports

Preferred Tern (PT)	# Serious Adult Reports	Label Status *UPSI updated December 9, 2022*
Chest Discomfort	5	Labeled
Dyspnea	5	Labeled
Eosinophilic Esophagitis	5	Labeled
Pruritis	5	Labeled
Angioedema	4	Black Box Warning
Dysphagia	4	Labeled
Nausea	4	Labeled
Oedema Mouth	4	Labeled
Urticaria	4	Labeled

Note: PTs occurring with a frequency >3 reports are shown in above table.

Reviewer comments: All PTs are labeled events or consistent with a labeled event.

6.2.3 Non-serious Reports

During the reporting period, there were 87 non-serious reports; of which 28 involved pediatric individuals. Table 5 below lists the 10 most frequently reported PTs in non-serious reports. Of note, these PTs are not mutually exclusive; a single report can include multiple PTs.

Table 5: Ten most frequently reported PTs in non-serious reports

Preferred Term (PT)	# Non-serious Reports	Label Status *UPSI updated December 9, 2022*
Throat Irritation	13	Labeled
Product Dose Omission Issue	11	Not labeled
Off label Use	10	Not labeled
Oral Pruritis	9	Labeled
Cough	7	Labeled
Dyspepsia	6	Labeled
Hypersensitivity	6	Black Box Warning
Oedema Mouth	6	Labeled
Drug Ineffective	5	Not labeled
Eosinophilic Oesophagitis	5	Labeled
Tongue Edema	5	Labeled
Urticaria	5	Labeled

Reviewer comments: Most PTs are labeled events. Unlabeled PTs, *Product Dose Omission Issue; Off label Use*, do not represent clinical adverse events. *Product Dose Omission Issue* reports involved adult patients who had missed doses. *Drug Ineffective* represents lack of efficacy; please see USPI for clinical trial data on efficacy. There are no new safety concerns from review of most frequently reported PTs in non-serious reports.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Oralair were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis of June 20, 2023. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product Name (S) run identified the preferred terms (PTs) summarized in Table 5, with a disproportional reporting alert. Note that a report may have one or more PTs. (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).

Table 6: Data mining findings

Preferred Term (PT)	**# Reports**	**Label Status** *UPSI updated December 9, 2022 (Label Section)*
Anaphylactic Reaction	13	Black Box Warning
Angioedema	10	Labeled
Asthma	13	Labeled
Chest Discomfort	11	Labeled
Cough	17	Labeled
Dyspnea	16	Labeled
Dyspepsia	16	Labeled
Dysphagia	8	Labeled
Dysphonia	8	Labeled
Ear Pruritis	6	Not Labeled[1]
Eosinophilic Esophagitis	19	Labeled
Facial Edema	6	Labeled
Hypersensitivity	19	Black Box Warning
Laryngeal Edema	4	Black Box Warning
Lip Edema	12	Labeled
Mouth Edema	23	Labeled
Oral Discomfort	8	Labeled
Oral Mucosal Blistering	5	Labeled
Oral Pruritis	37	Labeled
Oral Paresthesia	7	Not labeled
Pharyngeal Edema	14	Not labeled[2]

Preferred Term (PT)	# Reports	Label Status *UPSI updated December 9, 2022 (Label Section)*
Pruritis	24	Labeled
Sensation of a Foreign Body	8	Not Labeled (may be related to labeled event "trouble swallowing or speaking")
Throat: Clearing/Irritation/Tightness	60	Throat irritation and tightness are labeled, throat clearing is not a labeled adverse event
Tongue: Edema/Pruritis	23	Labeled
Urticaria	18	Labeled

[1]Itching of the mouth, lips, tongue, skin, and throat is in the label, but not itching of the ear.
[2]Edema of every other part of the oral airway is labeled as is non-specific "edema", but the pharyngeal edema is not specifically mentioned.

Reviewer comments: Most PTs are labeled events or consistent with a labeled event, and are also represented among the most common PTs for serious and non-serious reports (please see discussion in sections 6.2.2 and 6.2.3). Most PTs with alerts for disproportional reporting represent allergic symptoms or reactions, including systemic allergic reactions, which are known risks for the sublingual immunotherapy product class and labeled events (please see discussion in section 5.1). These PTs can also be symptoms present in individuals receiving these products associated with their underlying grass pollen allergies. Disproportional alerts, in this case alerts of allergic symptoms and reactions, indicate that these PTs represent a higher proportion of all the AEs submitted for a specific product, when compared to the proportion of AEs submitted for all products. Disproportional reporting alerts for these types of AEs are expected for Oralair and other SLIT products, given the labeled allergic reactions and presence of underlying allergic symptoms in patients receiving these products. Ear pruritis and pharyngeal edema are unlabeled PTs but the general terms "pruritis" and "edema" are labeled in the USPI. Paresthesia and throat clearing are non-specific events and may occur in association with multiple conditions.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for Oralair were reviewed. The AEs reported were consistent with those seen in FAERS. 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 June 20, 2023 for peer-reviewed literature, with the search term "Oralair" and "safety" limited by human species, and dates from PAC trigger (November 9, 2018) to date of search June 20, 2023, retrieved 0 publications pertaining to safety.

A review of publications related to the search terms, "pollen induced allergic rhinitis therapy" and "safety", limited by human species, and the above dates produced two

studies. Both were reassuring, as they both supported the safety profile of this class of product. (SLIT-sublingual immunotherapy)

No new safety concerns for Oralair were identified in the review of these publications, summarized in the table below:

Publication	Authors' Safety Conclusion
Gonzalez-Bravo, L., Curr Drug Safety, Off-label Use of Oral Immunotherapy for Rhinoconjunctivitis and Asthma due to Grass Pollen: A Safe and Effective Alternative in Patients over 65 Years Old: A Series of Case Reports, 2023;18(4):599-602.	SLITs are generally not labeled for use in patients over 65 years of age. This series of case reports demonstrated they can be safely used in this population.
Sessions, J, Front Allergy, Pediatric eosinophilic esophagitis outcomes vary with co-morbid eczema and pollen food syndrome,2022 Sept., 981961.	Study reviewed prognosis of Eosinophilic Esophagitis (EoE) in children based on risk factors. The results demonstrated EoE caused by exposure to pollen or pollen therapy had a higher remission rate than other causes of EoE.

8 CONCLUSION

This postmarketing pediatric safety review for Oralair was triggered by the approval of sBLA 125471/230 on November 9, 2018, to extend the indication for use in persons 5 through 9 years of age.

Review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Oralair and this product class does not indicate any new safety concerns. Adverse events in pediatric patients were generally small in number and consistent with the safety data in pre-licensure studies and listed in the label. There were no deaths reported during the safety review period. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Oralair.