

Summary Basis for Regulatory Action

Date: November 9, 2018

From: Kelsy Hoffman, PhD, Chair of the Review Committee

BLA/ STN#: 125471/230

Applicant Name: Stallergenes, SAS

Date of Submission: January 11, 2018

Goal Date: November 11, 2018

Proprietary Name/ Established Name: ORALAIR®

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 included in this product. ORALAIR is currently approved for use in persons 10 to 65 years of age.

Recommended Action: The Review Committee recommends approval.

Review Office(s) Signatory Authorities: Doran Fink, MD, PhD, Deputy Division Director-Clinical, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA.

Document title	Reviewer name, Document date
Clinical Review(s) <ul style="list-style-type: none">• <i>Clinical</i>• <i>Postmarketing safety epidemiological review (OBE/DE)</i>	Joohee Lee, MD 11/9/2018 Patricia Rohan, MD 11/2/2018
Statistical Review(s) (OBE)	Jennifer Kirk, PhD 10/16/2018
Pharmacology/Toxicology Review(s) <ul style="list-style-type: none">• <i>Toxicology (product office)</i>• <i>Developmental toxicology (product office)</i>	Ching-long Sun, DVM 10/31/2018
CMC Review/Consult (OVR/DBPAP)	Jennifer Bridgewater 10/29/2018
Labeling Reviews <ul style="list-style-type: none">• <i>Labeling (OCBQ/APLB)</i>• <i>Labeling (OVR/DVRPA)</i>	Oluchi Elekwachi 9/27/2018 Daphne Stewart 11/9/2018

1. Introduction

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 included in this product (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass). ORALAIR is currently approved for use in persons 10 to 65 years of age.

ORALAIR is a round, biconvex, slightly speckled white to beige tablet for sublingual use. Tablets are engraved with '100' or '300' on each side, depending on dose strength. ORALAIR sublingual tablets are provided in aluminum/aluminum blister packs in two dose strengths, 100 IR and 300 IR. The 100 IR tablets are provided in a starter pack (for children and adolescents 10 through 17 years of age) containing 3 blister packaged tablets. The 300 IR tablets are also provided in a starter pack (for adults 18 through 65 years of age) containing 3 tablets and in a sample pack (for children, adolescents and adults) containing 30 blister packaged tablets.

On January 11, 2018, CBER received an efficacy supplement for ORALAIR under STN 125471/230, which included safety data from an open-label single arm postmarketing study of ORALAIR (Study 140224/ Protocol SL 74.14). With this Biologics License Application supplement (sBLA), Stallergenes, SAS proposed to expand the use of ORALAIR to include children 5 through 9 years of age. The sBLA included data from a study that enrolled 307 children 5 through 9 years of age with grass pollen-related allergic rhinitis with or without conjunctivitis confirmed by positive skin prick test or *in vitro* testing for grass pollen-specific IgE. The primary objective was to evaluate safety and tolerability during the first 30 days of treatment. This study was required under 505B(a) of the Food, Drug, and Cosmetic Act to be conducted as a post-marketing study as outlined in the approval letter for STN 125471, dated April 1, 2014. Additionally, a post-hoc analysis of the efficacy data from 5 through 9-year-olds enrolled in a double-blind placebo-controlled randomized pre-licensure Phase 3 study (V052.06) conducted in 278 children and adolescents 5 through 17 years of age were analyzed to verify that ORALAIR is effective in the 5 through 9-year-old age group.

2. Background

Symptoms of allergic rhinitis (AR) include rhinorrhea, nasal itching, sneezing and nasal congestion and can be accompanied by itchy ears, palate, ocular itching (allergic conjunctivitis), coughing, and wheezing. Often AR is accompanied by allergic conjunctivitis (AC) and may be accompanied by allergic asthma. About 10% of adults and children in the US have AR, AC, or both (ARC). Epidemiological studies have shown that about 20% to 40% of individuals with allergic rhinitis also have asthma. Conversely, about 30% to 80% of individuals with asthma have allergic rhinitis. According to the CDC, allergic rhinitis has been diagnosed in about 20 million adults (8.2%) and 6.1 million children and adolescents (8.4%).

Clinical management typically relies on combined regimens of medications such as intranasal corticosteroids and oral and nasal antihistamines. AIT involves the administration of gradually increasing doses of the allergen to desensitize the subject.

ORALAIR was licensed in the United States in 2014 for use in persons 10 to 65 years of age for 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 ORALAIR. At time of approval in 2014, ORALAIR was the first US licensed allergen extract administered through SLIT.

Prior to the licensure of ORALAIR, the Allergenic Products Advisory Committee (APAC) discussed the adequacy of the clinical data to support safety and effectiveness of ORALAIR in children 5 through 9 years of age. The clinical development program included a double-blind placebo-controlled Phase 3 study (VO52.06 EU). VO52.06 was a multi-national, multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of ORALAIR in 278 European children 5 to 17 years of age who were randomized 1:1 to receive either placebo (n=139) or ORALAIR (n=139) for four months prior to the start of and throughout the grass pollen season. The primary objective of VO52.06 was to assess the efficacy of SLIT for grass pollen allergens as measured by the average rhinoconjunctivitis total symptom score (ARTSS). For each subject, the ARTSS is the average over the pollen season of their daily sum of six rhinoconjunctivitis symptom scores: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes. The study met its pre-specified primary endpoint success criterion, a reduction of at least 20% in the mean ARTSS for ORALAIR compared to placebo. For the intent to treat population, the percent difference in the mean ARTSS between ORALAIR and placebo groups was -25.6% (95% CI: -40.4%, -10.3%). In a post-hoc analysis, ORALAIR demonstrated a -30.6% difference in the daily RTSS score between treatment and placebo arms (95% CI: -47.0%; -14.1%); a -29.5% difference in the daily rescue medication score (-50.9%; -8.0%); and a -30.1% difference in the daily combined score (95% CI: -46.9%; 13.2%). The efficacy data from VO52.06 were considered adequate to support the effectiveness of ORALAIR in children 5 through 17 years of age.

Since Study VO52.06 EU included only 57 children 5 through 9 years of age, this study was not considered adequate to support safety of ORALAIR in this age group. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), Stallergenes, SAS was required to conduct Study 140224 to evaluate the safety of ORALAIR in children 5 through 9 years of age.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

The sBLA did not contain CMC information for review, but a CMC reviewer was consulted regarding the updated label.

b) CBER Lot Release

A review of Product Release Branch records indicates that there are no pending lots or issues that would affect approval of the submission.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new pharmacology/toxicology data were submitted as part of this supplement. However, the toxicology reviewer assessed the language added to the label to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and determined it to be acceptable.

5. CLINICAL PHARMACOLOGY

No new clinical pharmacology data were submitted as part of this supplement.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The clinical data submitted to the supplement included descriptive safety data from Study 140244, an open-label study conducted in children 5 through 9 years of age. Additionally, a post-hoc analysis of the effectiveness data from a pre-licensure Phase 3 study (VO52.06) in children by age subgroups (5 through 9 years and 10 through 17 of age) was requested and reviewed.

Study 140224

Study 140224 was an open-label multi-center study of ORALAIR (Study 140224/ Protocol SL 74.14) conducted in Europe. The study included 307 children 5 through 9 years of age with grass pollen-related allergic rhinitis with or without conjunctivitis (ARC) confirmed by positive skin prick test or *in vitro* testing for grass pollen-specific IgE. The primary objective of the study was to evaluate safety and tolerability during the first 30 days of treatment. The frequencies of local application site reactions, particularly throat irritation and oral pruritus, among the 5- through 9-year-olds (see details in Section 7 below) were comparable to those in adults and older children and adolescents reported in pre-licensure studies.

Pre-licensure Phase 3 study (VO52.06)

VO52.06 was a multi-national, multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of ORALAIR in European children 5 to 17 years of age who were randomized 1:1 to receive either placebo (n=139) or ORALAIR (n=139) for four months prior to the onset of and throughout the grass pollen season. The primary objective of VO52.06 was to assess the efficacy of SLIT for grass pollen allergens as measured by the average rhinoconjunctivitis total symptom score (RTSS). The RTSS is defined as the sum of six rhinoconjunctivitis symptom scores: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes.

CBER evaluated post-hoc, age-stratified analyses of efficacy from this study based on the endpoints Combined Score (CS), RTSS, and Rescue Medication Score (RMS). These analyses, while not adequately powered to demonstrate uniformly statistically significant treatment effects in the younger age subgroup, showed that treatment effects were numerically similar in children 5 through 9 years of age when compared to children and adolescents 10 through 17 years of age.

These data were reviewed in aggregate with the study data from VO52.06 submitted to the original BLA, and CBER agreed that the data supported effectiveness down to 5 years of age.

b) Pediatrics

With this supplement, Stallergenes, SAS fulfilled the pediatric study requirement to evaluate safety of ORALAIR in children 5 through 9 years of age. The pediatric study requirement in children under 5 years of age is waived 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.

7. SAFETY

Study 140244 was a descriptive study evaluating the safety of ORALAIR during the first 30 days of use in children 5 through 9 years of age.

AEs

Adverse reactions reported at an incidence of $\geq 2\%$ were: throat irritation (22.1%), oral pruritus (11.7%), oral paresthesia (11.1%), tongue pruritus (8.1%), mouth edema (6.2%), cough (6.2%), oropharyngeal pain (4.2%), ear pruritus (5.2%), eye pruritus (4.6%), lip edema (3.3%), vomiting (2.6%), tongue edema (2.3%), abdominal pain (2.3%), oral discomfort (2.3%), and ocular hyperemia (2.0%).

Asthma associated with ORALAIR use was reported in three subjects, one of each for mild, moderate, and severe (this case of severe asthma was captured as one of 2 SAEs). AEs of cough in all 20 subjects whose caregivers reported this AE were graded as mild to moderate. Of the 4 subjects with mild-to-moderate dyspnea reported on their diary cards, none of the cases were considered related to ORALAIR. Sixteen subjects (5.2%) prematurely withdrew from the study due to an adverse event.

Overall, 138 (45.0%) patients reported at least one AR of mild intensity, 66 (21.5%) of moderate intensity and 10 (3.3%) of severe intensity. The severe ADRs were: oral pruritus, mouth edema, oral discomfort, oropharyngeal pain, asthma, eye pruritus, allergic conjunctivitis, ear pain, angioedema, non-cardiac chest pain, headache and anaphylactic reaction. No substantial differences in the AE profile (with respect to SOC, severity, recurrence) were observed between the subpopulations of patients by age classes, sensitization and asthma status.

Nonfatal Serious Adverse Events

Among the 307 children enrolled, 2 serious adverse events occurred. Both were considered related to ORALAIR. The first SAE occurred in an 8-year-old male with a history of asthma and suspected birch pollen allergy who developed oral pruritus within 15 minutes of ORALAIR on Day 5 and 50 minutes later developed conjunctivitis, urticaria, and lower airway symptoms (Grade 2 anaphylaxis). Symptoms resolved within 30 minutes of treatment with oral antihistamine and inhaled short-acting beta agonist (salbutamol 200 mcg) and did not require epinephrine. The subject continued taking ORALAIR and completed the study. The second SAE occurred in a 6-year-old female with concomitant peanut and hazelnut sensitization who developed severe lip, eyelid, periorbital swelling (angioedema) within 30 minutes of dosing on Day 26. No lower airway symptoms were noted. The subject recovered within 6 hours of receiving intravenous antihistamine and corticosteroid and remained stable during overnight hospitalization. ORALAIR was discontinued.

Adverse Events of Special Interest (AESI)

Systemic allergic reactions (inclusive of anaphylaxis), such as laryngeal edema and eosinophilic esophagitis, are adverse events of special interest for SLIT products. There were two cases of systemic allergic reaction including one case of anaphylaxis and one case of angioedema, both described in the Nonfatal Serious Adverse event section, but no cases of laryngeal edema or eosinophilic esophagitis.

8. ADVISORY COMMITTEE MEETING

An APAC meeting was not held for this supplement, as there were no issues or concerns that presented during the course of review of the supplement that required consult from the advisory committee.

9. OTHER RELEVANT REGULATORY ISSUES

There are no additional relevant regulatory issues in addition to the discussions in this summary.

10. LABELING

The ORALAIR package insert (PI) was updated to include safety data from Study 140224. To comply with the 2014 Final Rule, *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, also known as the Pregnancy and Lactation Labeling Rule (PLLR), a request was made to the Applicant to submit a Package Insert (PI) revision to include language to comply with the PLLR. The proposed PI was primarily reviewed by the Clinical, Statistical and Advertising and Promotional Labeling Branch reviewers, and revisions were made to Section 2 Dosage and Administration, Section 6 Adverse Reactions, Section 8 Use in Specific Populations, Section 10 Overdosage, and Section 14 Clinical Studies. All labeling issues were satisfactorily resolved through communication with Stallergenes, SAS.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The safety data submitted to this supplement from Study 140244 (Protocol SL74.14), in conjunction with the efficacy data from Study V052.06, support licensure of ORALAIR in children 5 through 9 years of age. With respect to efficacy, the pre-licensure data from V052.06 were considered representative of children and adolescents 5 through 17 years of age. Post hoc subgroup analysis of efficacy data from Study V052.06 did not reveal any age-based differences or suggest that efficacy is different in younger children than in older children or adolescents. Taken together, the safety and effectiveness data provided in this supplement support the use of ORALAIR as immunotherapy in persons 5 years of age and older 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.

b) Risk/ Benefit Assessment

The risk-benefit profile for the use of ORALAIR is favorable. No safety signals for serious adverse events were identified. Most of the adverse reactions were local reactions, namely throat irritation, oral pruritus, and oral paresthesia. The postmarketing safety data submitted in this BLA efficacy supplement adequately addressed the concerns raised during the review of the original BLA regarding safety in the 5 through 9 year-old age group.

c) Recommendation for Postmarketing Activities

There is no recommendation for postmarketing activities. Based on a review of the submitted clinical data, the review committee concurs with continued routine

safety surveillance.