Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORALAIR safely and effectively. See full prescribing information for ORALAIR.

ORALAIR® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract)
Tablet for Sublingual Use

Initial U.S. Approval: 2014

WARNING: SEVERE ALLERGIC REACTIONS
See full prescribing information for complete boxed warning

- **ORALAIR can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema. (5.1)**
- **Do not administer ORALAIR to patients with severe, unstable or uncontrolled asthma. (4)**
- **Observe patients in the office for at least 30 minutes following the initial dose. (5.1)**
- **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)**
- **ORALAIR may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)**
- **ORALAIR may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)**

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2018
Dosage and Administration (2.1)	11/2018

INDICATIONS AND USAGE

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.

DOSAGE AND ADMINISTRATION

For sublingual use only.

Age (years)	Dose		
	Day 1	Day 2	Day 3 and following
5-17	100 IR	2x 100 IR	300 IR
18-65	300 IR	300 IR	300 IR

- Initiate treatment 4 months before the expected onset of each grass pollen season and continue treatment throughout the season. (2.2)
- Place the tablet under the tongue for at least 1 minute, until complete dissolution and then swallow. (2.2)
- Administer the first dose of ORALAIR under the supervision of a physician with experience in the diagnosis and treatment of severe allergic reactions. Observe the patient for at least 30 minutes. (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets, 100 IR and 300 IR (3)

CONTRAINDICATIONS

- Severe, unstable or uncontrolled asthma (4)
- History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy (4)
- A history of eosinophilic esophagitis (4)
- Hypersensitivity to any of the inactive ingredients contained in this product (4)

WARNINGS AND PRECAUTIONS

- Inform patients of the signs and symptoms of severe allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. (5.1)
- In case of oral inflammation or wounds, stop treatment with ORALAIR to allow complete healing of the oral cavity. (5.5)

ADVERSE REACTIONS

Adverse reactions reported in ≥5% of patients were: oral pruritus, throat irritation, ear pruritus, mouth edema, tongue pruritus, cough, asthma, oropharyngeal pain, tonsillitis, and oral paresthesia (6)

To report SUSPECTED ADVERSE REACTIONS, contact Stallergenes at 1-855-274-1322 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for Patient Counseling Information and FDA approved Medication Guide

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SEVERE ALLERGIC REACTIONS

- **ORALAIR can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)**
- **Do not administer ORALAIR to patients with severe, unstable or uncontrolled asthma. (4)**
- **Observe patients in the office for at least 30 minutes following the initial dose. (5.1)**
- **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)**
- **ORALAIR may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)**
- **ORALAIR may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)**

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

For sublingual use only.

2.1 Dose

For adults 18 through 65 years of age, the dose is 300 IR (index of reactivity) daily. For children and adolescents 5 through 17 years of age, the dose is increased over the first three days as shown in Table 1.

Table 1. Dosage for Adults and Children for the Days 1-3 (and following)

Age (years)	Dose		
	Day 1	Day 2	Day 3 and following
5-17	100 IR	2x 100 IR	300 IR
18-65	300 IR	300 IR	300 IR

2.2 Administration

Administer the first dose of ORALAIR in a healthcare setting in which acute allergic reactions can be treated under the supervision of a physician with experience in the diagnosis and treatment of severe allergic reactions. After receiving the first dose of ORALAIR, observe the patient for at least 30 minutes 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.

Administer ORALAIR to children under adult supervision.

Remove the ORALAIR tablet from the blister just prior to dosing.

Place the ORALAIR tablet immediately under the tongue until complete dissolution for at least 1 minute before swallowing.

Wash hands after handling the ORALAIR tablet.

Do not take the ORALAIR tablet with food or beverage. To avoid swallowing allergen extract, food or beverage should not be taken for 5 minutes following dissolution of the tablet.

Initiate treatment 4 months before the expected onset of each grass pollen season and maintain it throughout the grass pollen season.

Data regarding the safety of starting treatment during the pollen season are not available. Data regarding the safety of restarting treatment after missing a dose of ORALAIR are not available.
It is recommended that auto-injectable epinephrine be made available to patients prescribed ORALAIR. Patients who are prescribed epinephrine while receiving immunotherapy should be instructed in the proper use of emergency self-injection of epinephrine [*See Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

ORALAIR tablets are available as follows:

- ORALAIR 100 IR tablets are round and biconvex, slightly speckled white to beige with “100” engraved on both sides
- ORALAIR 300 IR tablets are round and biconvex, slightly speckled white to beige with “300” engraved on both sides

4 CONTRAINDICATIONS

ORALAIR is contraindicated in patients with:

- Severe, unstable or uncontrolled asthma
- History of any severe systemic allergic reaction
- History of any severe local reaction to sublingual allergen immunotherapy
- A history of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients (mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and lactose monohydrate) contained in this product [*see Description (11)*]

5 WARNINGS AND PRECAUTIONS

5.1 Severe Allergic Reactions

ORALAIR can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, ORALAIR can cause severe local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening.

Patients who have a systemic allergic reaction to ORALAIR should stop taking ORALAIR.

Patients who have either escalating or persistent local reactions to ORALAIR should be reevaluated and considered for discontinuation of ORALAIR.

Administer the initial dose of ORALAIR in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or a severe local allergic reaction. Observe patients in the office for at least 30 minutes following the initial dose of ORALAIR.

Severe and serious allergic reactions may require treatment with epinephrine [*See Warnings and Precautions (5.2)*].

5.2 Epinephrine

Prescribe auto-injectable epinephrine to patients receiving ORALAIR. Instruct patients to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency self-injection of epinephrine and instruct patients to seek immediate medical care upon its use [*See Patient Counseling Information (17)*].

ORALAIR may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to: markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.

ORALAIR may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include:

Beta-adrenergic blockers: Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.

Alpha-adrenergic blockers, ergot alkaloids: Patients taking alpha-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, alpha-adrenergic blockers antagonize the vasoconstricting and hypertensive effects of epinephrine. Similarly, ergot alkaloids may reverse the pressor effects of epinephrine.

Tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors and certain antihistamines: The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and the antihistamines chlorpheniramine, and diphenhydramine.

Cardiac glycosides, diuretics: Patients who receive epinephrine while taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

5.3 Eosinophilic Esophagitis

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy [*see Contraindications (4) and Adverse Reactions (6.2)*]. Discontinue ORALAIR and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

5.4 Asthma

ORALAIR has not been studied in subjects with moderate or severe asthma or any subjects who required daily medication.
Immunotherapy with ORALAIR should be withheld if the patient is experiencing an acute asthma exacerbation. Reevaluate patients who have recurrent asthma exacerbations and consider discontinuation of ORALAIR.

5.5 Concomitant Allergen Immunotherapy

ORALAIR has not been studied in subjects receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.

5.6 Oral Inflammation

Stop treatment with ORALAIR to allow complete healing of the oral cavity in patients with oral inflammation (e.g., oral lichen planus, mouth ulcers or thrush) or oral wounds, such as those following oral surgery or dental extraction.

5.7 Initiation of ORALAIR Therapy during Grass Pollen Season

The risk of ORALAIR may be increased when treatment is initiated during the grass pollen season.

6 ADVERSE REACTIONS

Adverse reactions reported in ≥5% of patients were: oral pruritus, throat irritation, ear pruritus, mouth edema, tongue pruritus, cough, oropharyngeal pain.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

Adults

Overall, in 6 placebo-controlled clinical trials, 1,038 adults 18 through 65 years of age received at least one dose of ORALAIR 300IR, of whom 611 (59%) completed at least four months of therapy. Of study participants, 56% were male, 17% had a history of mild intermittent asthma at study entry, and 64% were polysensitized. Data on race and ethnicity were not systematically captured in the five European studies (N=805). In the US study (N=233), a limited number of patients reported their race as other than White/Caucasian (Black/African American: 5.6%, Asian: 2.6%, Other: 2.1%) or their ethnicity as Hispanic or Latino (3.0%). Adverse events were captured on a daily diary card that did not solicit for specific adverse events.

Across the six clinical studies, adverse reactions reported at an incidence of ≥2% of ORALAIR recipients and at a greater incidence than that in participants treated with placebo are listed in Table 2.

Table 2. Adverse Reactions Reported by ≥2% of Adults Receiving ORALAIR 300 IR and at a Greater Incidence than that in Participants Treated with Placebo

Adverse Reactions	ORALAIR 300 IR (N=1,038)	PLACEBO (N=840)
Ear and labyrinth disorders		
Ear pruritus	8.4%	0.6%
Respiratory, thoracic and mediastinal disorders		
Throat irritation	22.0%	3.7%
Cough	7.3%	5.9%
Oropharyngeal pain	5.1%	3.7%
Pharyngeal edema	3.8%	0.1%
Gastrointestinal disorders		
Oral pruritus	25.1%	5.0%
Edema mouth	8.2%	0.6%
Tongue pruritus	7.9%	0.7%
Lip edema	4.4%	0.4%
Paraesthesia oral	4.3%	1.0%
Abdominal pain	4.2%	1.3%
Dyspepsia	3.9%	0.4%
Tongue edema	2.7%	0.1%
Hypoaesthesia oral	2.2%	0.1%
Stomatitis	2.1%	0.7%
Skin and subcutaneous tissue disorders		
Urticaria	2.3%	1.5%

Additional adverse reactions of interest that occurred in <2% of ORALAIR recipients include dysphagia, nausea, vomiting, esophageal pain, gastritis, and gastroesophageal reflux.

Children and Adolescents

Overall, in placebo-controlled clinical trials, 154 children and adolescents 5 through 17 years of age received ORALAIR 300 IR, of whom 147 were exposed for more than 3 months. Of study participants, 66% were male, and 21% had a history of mild intermittent asthma at study entry. Data on race and ethnicity were not systematically captured.

The safety profile in the pediatric population, was generally similar to that of adults. In pediatric patients receiving ORALAIR, additional adverse reactions reported at an incidence of ≥2% and at a greater incidence than that in participants treated with placebo are listed in Table 3.

Table 3. Additional Adverse Reactions Reported by ≥2% of Children and Adolescents Receiving ORALAIR 300 IR and at a Greater Incidence than that in Participants Treated with Placebo

Adverse Reactions	ORALAIR 300 IR (N=154)	PLACEBO (N=158)
Infections and infestations		
Tonsillitis	5.8%	3.2%
Upper respiratory tract infection	3.9%	1.9%
Respiratory, thoracic and mediastinal disorders		
Asthma	7.1%	3.8%
Dysphonia	2.6%	1.3%
Gastrointestinal disorders		
Lip pruritus	3.2%	0.0%
Skin and subcutaneous tissue disorders		
Atopic dermatitis	3.2%	0.6%

An open-label study was conducted to evaluate the 30-day safety profile of ORALAIR in 307 children 5 through 9 years of age. Of study participants, 71% were male and 36% had a history of mild intermittent asthma at study entry. Data on race and ethnicity were not systematically captured. Adverse reactions reported at an incidence of ≥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%).

Serious Adverse Reactions

At least 1 serious adverse event was reported in 22 of 1514 (1.5%) pediatric and adult subjects from randomized clinical trials who received ORALAIR at any dose, and 11 of 840 (1.1%) of placebo recipients. Of the 22 serious adverse events in the ORALAIR recipients, 2 were considered "definitely related" to ORALAIR.

The first subject was an adult who experienced a severe hypersensitivity reaction which began 5 minutes after administration of ORALAIR. The symptoms were violent coughing and marked dyspnea. The subject was treated with antihistamines, salbutamol and prednisolone and the reaction resolved without sequelae.

The second subject was an adult who experienced severe laryngeal edema. The subject was treated with prednisolone and event resolved without sequelae.

There was also one case of gastroenteritis with an onset on Day 93 of therapy that was possibly related to ORALAIR.

In the open-label study conducted in 307 children 5 through 9 years of age, 2 serious adverse events were considered "likely" related to ORALAIR.

The first subject was an 8-year-old subject with a history of allergic bronchial asthma who developed oral pruritus, conjunctivitis, urticaria and asthma exacerbation 15 minutes after administration of ORALAIR on Day 5. The subject was treated with antihistamines and inhaled salbutamol and the reactions fully resolved in 30 minutes. The subject continued ORALAIR.

The second subject was a 6-year-old subject who developed severe lip, eye and eyelid swelling after administration of ORALAIR on Day 26 of therapy. The subject was treated with intravenous antihistamines and prednisolone. Reactions fully resolved within 6 hours. Treatment with ORALAIR was discontinued.

6.2 Postmarketing Experience

Post Marketing Safety Studies

A total of 1728 individuals (808 adults; 920 children 5 through 17 years of age) received ORALAIR in post marketing safety studies. Reported adverse reactions included: anaphylactic reaction, oral allergy syndrome, flushing, dyspnea, laryngeal edema, and diarrhea.

Spontaneous Postmarketing Reports

In addition to adverse reactions reported in clinical and post marketing safety studies, the following adverse reactions have been identified during post approval use of ORALAIR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to

reliably estimate their frequency or establish a causal relationship to drug exposure: autoimmune thyroiditis, eosinophilic myocarditis, eosinophilic esophagitis, palpitations, tachycardia, hypotension, loss of consciousness, circulatory collapse, malaise, pallor, peripheral vascular disorder, stridor, angioedema, face edema, weight decreased, wheezing, exacerbation of asthma, chest discomfort, oropharyngeal paresthesia, oropharyngeal blistering, headache, dizziness, tinnitus, asthenia, somnolence, anxiety, rash, pruritus, salivary gland enlargement and/or hypersecretion, dry mouth, dry eye, influenza-like syndrome, lymphadenopathy, eosinophil count increased.

8 USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Available human data do not establish the presence or absence of ORALAIR-associated risks during pregnancy, labor and delivery.

Two developmental toxicity studies were performed in female rats and female rabbits given doses up to 250 IR/day and 3500 IR/day of ORALAIR, respectively, during gestation.

Data

In developmental toxicity studies, the effect of ORALAIR on embryo/fetal development was evaluated in female rats and female rabbits administered with doses up to 250 IR/day and 3500 IR/day of ORALAIR, respectively, by oral gavage on days 6-17 of gestation for rats, and days 6-18 of gestation for rabbits. The human dose is 300 IR/day. There were no ORALAIR-related fetal malformations or other evidence of teratogenesis noted in these studies.

8.2 Lactation

Risk Summary

Data are not available to assess the effects of ORALAIR on the breastfed child or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORALAIR and any potential adverse effects on the breastfed child from ORALAIR or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ORALAIR have not been established in children below 5 years of age.

8.5 Geriatric Use

ORALAIR has not been studied in persons over 65 years of age.

11 DESCRIPTION

ORALAIR (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) is a mixed allergen extract of the following five pollens: Sweet Vernal (*Anthoxanthum odoratum L*), Orchard (*Dactylis glomerata L*), Perennial Rye (*Lolium perenne L*), Timothy (*Phleum pratense L)*, and Kentucky Blue Grass (*Poa pratensis L*).

ORALAIR is available as a sublingual tablet in the following strengths:

- 100 IR equivalent to approximately 3000 BAU (bioequivalent allergy units)
- 300 IR equivalent to approximately 9000 BAU

Inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and lactose monohydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy are not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies were conducted in animals. There was no evidence of mutagenic or clastogenic activity in response to ORALAIR in the *in vitro* bacterial mutagenesis assay and mouse lymphoma thymidine kinase cell assay or the *in vivo* bone marrow micronucleus and unscheduled DNA synthesis tests in rats.

No fertility study was conducted with ORALAIR.

14 CLINICAL STUDIES

The efficacy of ORALAIR for the treatment of grass pollen-induced allergic rhinoconjunctivitis was investigated in five double-blind, placebo-controlled clinical trials: four natural field studies and an environmental exposure chamber study.

The natural field studies included these trials, each conducted over a single season (two in adults and one in adolescents and children) and one five-year study (adults). Participants received ORALAIR or placebo daily for four months prior to grass pollen season and throughout grass pollen season.

Study participants reported at least a two grass pollen season history of rhinoconjunctivitis symptoms. For the European studies, subjects had a positive skin prick test to 5-grass pollen extract and positive *in vitro* testing for timothy grass-specific serum IgE. For the US study, subjects had a positive skin prick test to Timothy grass pollen extract.

With the exception of those with mild intermittent asthma, patients with asthma were excluded. Approximately 16% had asthma at baseline and 65% were polysensitized (i.e., sensitized to the 5-grass pollen allergen extract and at least one other unrelated allergen). Overall, the mean age of study participants was 28 years and 56% were male.

Natural Field Studies

In the natural field studies, efficacy of ORALAIR as immunotherapy to treat symptoms of allergic rhinoconjunctivitis due to the grass pollens included in ORALAIR was assessed via daily recording of symptoms and rescue medication use. The daily Combined Score (CS, range: 0-3) equally weights symptoms and rescue medication use. The daily Rhinoconjunctivitis Total Symptom Score (RTSS, range 0-18) is the total of the six individual symptom scores (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes) each graded by participants on a 0 (no symptoms) to 3 (severe symptoms) scale. The daily Rescue Medication Score (RMS, range 0-3) grades the intake of rescue medication as 0 = absent, 1 = antihistamine, 2 = nasal corticosteroid, 3 = oral corticosteroid. In case of multiple medications, the higher score is retained. Least Squares (LS) means are within-group means adjusted for the covariates in the statistical models (i.e., analyses of covariance for average scores and linear mixed models with repeated measures for daily scores). The Relative Difference is the LS mean difference between ORALAIR and Placebo divided by the LS mean of Placebo, expressed as a percentage.

US Study

In this study, 473 adults aged 18 through 65 years received ORALAIR or placebo, starting approximately four months prior to the expected onset of the grass-pollen season and continuing for the duration of the pollen season. The results of the analysis of the daily Combined Score (CS), daily Rhinoconjunctivitis Total Symptom Score (RTSS), and daily Rescue Medication Score (RMS) are summarized in Table 4.

Table 4. Daily Combined Score (CS), Daily Rhinoconjunctivitis Total Symptom Score (RTSS), and Daily Rescue Medication Score (RMS) during the Grass Pollen Period (US study)

Efficacy endpoint	ORALAIR (N=208) LS[c] Mean	Placebo (N=228) LS Mean	LS Mean Difference ORALAIR - Placebo	Relative Difference	
				Estimate	95% CI
Daily CS[a]	0.32	0.45	-0.13	-28.2%	[-43.4%;-13.0%]
Daily RTSS[b]	3.21	4.16	-0.95	-22.9%	[-38.2%;-7.5%]
Daily RMS[b]	0.11	0.20	-0.09	-46.5%	[-73.9%;-19.2%]

[a] Primary efficacy analysis
[b] Secondary efficacy analysis
[c] LS: Least Squares

European Study

In study, adults aged 18 to 45 years received one of 3 different doses of 5-grass pollen extract sublingual tablet or placebo. A total of 311 subjects received ORALAIR or placebo starting approximately 4 months prior to the expected onset of the grass pollen season and continuing for the duration of the grass pollen season. The results of the analysis of the daily CS, daily RTSS and daily RMS for ORALAIR (300 IR) are shown in Table 5.

Table 5. Daily Combined Score (CS), Daily Rhinoconjunctivitis Total Symptom Score (RTSS), and Daily Rescue Medication Score (RMS) during the Grass Pollen Period (European study)

Efficacy endpoint	ORALAIR (N=136) LS[a] Mean	Placebo (N=148) LS Mean	LS Mean Difference ORALAIR - Placebo	Relative Difference	
				Estimate	95% CI
Daily CS	0.50	0.70	-0.21	-29.6%	[-43.1%;-16.1%]
Daily RTSS	3.48	4.91	-1.44	-29.2%	[-43.4%;-15.1%]
Daily RMS	0.41	0.59	-0.18	-30.1%	[-49.5%;-10.6%]

[a] LS: Least Squares

Long Term Study

In this study, adults received ORALAIR or placebo according to two different treatment regimen. A total of 426 subjects received ORALAIR or placebo starting approximately 4 months prior to the grass pollen season and continuing for the entire season. Subjects were treated for three consecutive grass pollen seasons (Year 1 to Year 3). The primary evaluation was the Year 3 pollen period. Participants then entered two years of immunotherapy-free follow-up (Year 4 and Year 5). The results of the analysis of the daily Combined Score for ORALAIR (4M) for treatment Years 1-3 are summarized in Table 6. Data are insufficient to demonstrate efficacy for one or two years after discontinuation of ORALAIR.

Table 6. Analysis of Daily Combined Score for Each Grass Pollen Period (Long Term study)

Year	ORALAIR (4M)		Placebo		LS Mean Difference ORALAIR - Placebo	Relative Difference	
	N	LS[a] Mean	N	LS Mean		Estimate	95% CI
Year 1	188	0.56	205	0.67	-0.11	-16.4%	[-27.0%;-5.8%]
Year 2	160	0.35	172	0.56	-0.21	-38.0%	[-53.4%;-22.6%]
Year 3	149	0.31	165	0.50	-0.19	-38.3%	[-54.7%;-22.0%]

[a] LS: Least Squares

Pediatric Study

In this study, 278 children and adolescents 5 through 17 years of age received ORALAIR or placebo starting approximately 4 months prior to the grass-pollen season and continuing for the duration of the pollen season. The results of the daily CS, daily RTSS, and daily RMS are summarized in Table 7.

Table 7. Daily Combined Score (CS), Daily Rhinoconjunctivitis Total Symptom Score (RTSS), Daily Rescue Medication Score (RMS) during the Grass Pollen Period (Pediatric study)

Efficacy endpoint	ORALAIR (N=131) LS[a] Mean	Placebo (N=135) LS Mean	LS Mean Difference ORALAIR - Placebo	Relative Difference	
				Estimate	95% CI
Daily CS	0.44	0.63	-0.19	-30.1%	[-46.9%;-13.2%]
Daily RTSS	2.52	3.63	-1.11	-30.6%	[-47.0%;-14.1%]
Daily RMS	0.46	0.65	-0.19	-29.5%	[-50.9%;-8.0%]

[a] LS: Least Squares

Allergen Environmental Chamber Study

In an allergen environmental chamber study, 89 adults with grass pollen-associated allergic rhinoconjunctivitis were challenged with four of the five grass pollens contained in ORALAIR at baseline and after 4 months of treatment with ORALAIR (n=45) or placebo (n=44). The average Rhinoconjunctivitis Total Symptom Score (RTSS) of each group during the 4 hours of the allergen challenge was assessed; use of rescue medication was not permitted. The results of this study are shown in Table 8.

Table 8. Average Rhinoconjunctivitis Total Symptom Score (RTSS) during Grass Pollen Allergen Challenge in an Environmental Exposure Chamber after 4 months of ORALAIR or placebo

Efficacy endpoint	ORALAIR (N=45) LS[b] Mean	Placebo (N=44) LS Mean	LS Mean Difference ORALAIR - Placebo	Relative Difference	
				Estimate	95% CI
Average RTSS[a]	4.88	6.84	-1.97	-28.7%	[-43.7%;-13.7%]

[a] Primary efficacy analysis
[b] LS: Least Squares

16 HOW SUPPLIED/STORAGE AND HANDLING

ORALAIR is available as a sublingual tablet equivalent to 100 IR and 300 IR of five grass mixed pollens allergen extract.

	Description	**NDC Number**
Children and Adolescents Sample Kit (5 to 17 years of age)	One box of the 100 IR Starter Pack Two boxes of the 300 IR Sample Packs	NDC 59617-0020-1
Adult Sample Kit (18 to 65 years of age)	One box of 300 IR Starter Pack Two boxes of 300 IR Sample Packs	NDC 59617-0025-1
Children and Adolescents Starter Pack (5 to 17 years of age)	1 blister pack of three 100 IR tablets	NDC 59617-0010-1

Adult Starter Pack (18 to 65 years of age)	1 blister pack of three 300 IR tablets	NDC 59617-0016-1
Sample Pack	1 blister pack of three 300 IR tablets	NDC 59617-0015-3
Commercial Pack	1 blister pack of thirty 300 IR tablets	NDC 59617-0015-2

Storage: Store at controlled room temperature (20°C-25°C/68°F-77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Medication Guide).

- Keep ORALAIR out of the reach of children.

- Inform patients that ORALAIR is used for sublingual immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis and is not indicated for the immediate relief of allergy symptoms.

Severe Allergic Reactions

- Advise patients that ORALAIR may cause systemic allergic reactions, including anaphylactic reactions, and severe local allergic reactions [*See Warnings and Precautions (5.1)*].

- Educate patients about the signs and symptoms of a severe systemic allergic reaction and a severe local allergic reaction. The signs and symptoms of a severe allergic reaction may include: syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria [*See Warnings and Precautions (5.2)*].

- Ensure that patients have injectable epinephrine available and are appropriately trained in its use. Instruct patients who experience a severe allergic reaction to seek immediate medical care, discontinue therapy, and resume treatment only at the instruction of a physician [*See Warnings and Precautions (5.2)*].

- Inform the patient that the first dose of ORALAIR is administered in a healthcare setting under the supervision of a physician and s/he will be monitored for at least 30 minutes to watch for signs and symptoms of a severe systemic or a severe local allergic reaction [*See Dosage and Administration (2.2)*].

- Inform parents/guardians that ORALAIR should be administered to children only under adult supervision [*See Dosage and Administration (2.2)*].

- Because of the risk of eosinophilic esophagitis, instruct patients with severe or persistent symptoms of esophagitis to discontinue ORALAIR and to contact their healthcare professional. [*See Warnings and Precautions (5.3)*]

Asthma

- Instruct patients with asthma that if they have difficulty breathing or if asthma becomes difficult to control, they are to stop taking ORALAIR and contact their healthcare professional immediately [*See Warnings and Precautions (5.3)*].

Administration Instructions

- Instruct patients to carefully remove the ORALAIR tablet from the blister just prior to dosing and to take the sublingual tablet immediately by placing it under the tongue where it will dissolve. Also instruct patients to avoid swallowing for about 1 minute, to wash their hands after handling the tablet, and to avoid food or beverages for 5 minutes after taking the tablet [*See Dosage and Administration (2.2)*].

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Stallergenes SAS
Antony, 92183, France
U.S. License # 1893

Distributed by:

GREER Laboratories, Inc.
Lenoir, N.C. 28645

MEDICATION GUIDE

ORALAIR® (OR-AL-AIR):(Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract)

Carefully read this Medication Guide before you or your child start taking ORALAIR and each time you get a refill. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment. Talk with your doctor or pharmacist if there is something you do not understand or you want to learn more about ORALAIR.

What is the Most Important Information I Should Know about ORALAIR?

ORALAIR can cause severe allergic reactions that may be life-threatening. Symptoms of allergic reactions to ORALAIR include:

- Trouble breathing
- Throat tightness or swelling
- Trouble swallowing or speaking
- Dizziness or fainting
- Rapid or weak heartbeat
- Severe stomach cramps or pain, vomiting, or diarrhea
- Severe flushing or itching of the skin

If any of these symptoms occur, stop taking ORALAIR and immediately seek medical care.

For home administration of ORALAIR, your doctor should prescribe auto-injectable epinephrine for you to keep at home for treating a severe reaction, should one occur. Your doctor will train and instruct you on the proper use of auto-injectable epinephrine.

What is ORALAIR

ORALAIR is a prescription medicine used for sublingual (under the tongue) immunotherapy prescribed to treat sneezing, runny or itchy nose, nasal congestion or itchy and watery eyes due to allergy to these grass pollens. ORALAIR may be prescribed for persons 5 to 65 years of age whose doctor has confirmed are allergic to any of the grass pollens contained in ORALAIR.

ORALAIR is taken for about four months before the expected start of the grass pollen season and is continued throughout the grass pollen season.

ORALAIR is NOT a medication that gives immediate relief of allergy symptoms.

Who Should Not Take ORALAIR

You or your child should not take ORALAIR if:

- You or your child has severe, unstable, or uncontrolled asthma
- You or your child had a severe allergic reaction in the past that included any of these symptoms:
  - Trouble breathing
  - Dizziness or fainting

- Rapid or weak heartbeat

- You or your child has ever had difficulty with breathing due to swelling of the throat or upper airway after using any sublingual immunotherapy before.
- You or your child has ever been diagnosed with eosinophilic esophagitis.
- You or your child is allergic to any of the inactive ingredients contained in ORALAIR
  - The inactive ingredients contained in ORALAIR are: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and lactose monohydrate

What Should I Tell My Doctor Before Taking ORALAIR

Your doctor may decide that ORALAIR is not the best course of therapy if:

- You or your child has asthma, depending on how severe it is.
- You or your child suffers from lung disease such as chronic obstructive pulmonary disease (COPD).
- You or your child suffers from heart disease such as coronary artery disease, an irregular heart rhythm, or you have hypertension that is not well controlled.
- You or your daughter is pregnant, plans to become pregnant during the time you will be taking ORALAIR, or is breast-feeding.
- You or your child is unable or unwilling to administer auto-injectable epinephrine to treat a severe allergic reaction to ORALAIR.
- You or your child is taking certain medicines that enhance the likelihood of a severe reaction, or interfere with the treatment of a severe reaction. These medicines include:
  - beta blockers and alpha-blockers (prescribed for high blood pressure)
  - cardiac glycosides (prescribed for heart failure or problems with heart rhythm)
  - diuretics (prescribed for heart conditions and high blood pressure)
  - ergot alkaloids (prescribed for migraine headache)
  - monoamine oxidase inhibitors or tricyclic antidepressants (prescribed for depression)
  - thyroid hormone (prescribed for low thyroid activity).

You should tell your doctor if you or your child is taking or has recently taken any other medicines, including medicines obtained without a prescription and herbal supplements. Keep a list of them and show it to your doctor and pharmacist each time you get a new supply of ORALAIR. Ask your doctor or pharmacist for advice before taking ORALAIR.

Are there any reasons to stop taking ORALAIR?

Stop ORALAIR and contact your doctor if you or your child:

- has any type of a serious allergic reaction
- develops throat tightness or swelling of the tongue or throat that causes trouble speaking, breathing or swallowing after taking ORALAIR
- has trouble breathing or asthma or another breathing condition that gets worse
- experiences dizziness or fainting
- develops rapid or weak heartbeat
- experiences severe stomach cramps or pain, vomiting, or diarrhea
- develops severe flushing or itching of the skin

- has heartburn, difficulty swallowing, pain with swallowing, or chest pain that does not go away or worsens
- has any mouth surgery procedures (such as tooth removal), develops any mouth infections, ulcers or cuts in the mouth or throat

How should I take ORALAIR?

Take ORALAIR exactly as your doctor tells you.

ORALAIR is a prescription medicine that is placed under the tongue.

- Remove the ORALAIR tablet from the blister just prior to dosing.
- Place the ORALAIR tablet immediately under the tongue until complete dissolution for at least 1 minute before swallowing.
- Do not take ORALAIR with food or beverage. Food and beverage should not be taken for the following 5 minutes.
- Wash hands after handling the tablet.

Take the first tablet of ORALAIR in your doctor's office. After taking the first tablet, you or your child will be observed for at least 30 minutes for symptoms of a serious allergic reaction.

- The first dose for children will be one 100 IR tablet.
- The first dose for adults will be one 300 IR tablet.

If you or your child tolerates the first dose of ORALAIR, you or your child will continue daily ORALAIR therapy at home.

- The first dose at home for children is two 100 IR tablets.
- The first dose at home for adults is one 300 IR tablet.
- After the first dose at home, the dose for children and adults is one 300 IR tablet each day.

Children should be given each dose of ORALAIR by an adult who will watch for any symptoms of a serious allergic reaction.

Take ORALAIR as prescribed by your doctor until the end of the treatment course. If you forget to take ORALAIR, do not take a double dose. Take the next dose at your normal scheduled time the next day. If you don't take ORALAIR for more than one day, contact your health provider before restarting.

What are the possible side effects of ORALAIR?

In children and adults, the most commonly reported side effects were itching of the mouth, lips, tongue or throat. These side effects, by themselves, are not dangerous or life-threatening.

ORALAIR can cause severe allergic reactions that may be life-threatening. Symptoms of allergic reactions to ORALAIR include:

- Trouble breathing
- Throat tightness or swelling
- Trouble swallowing or speaking
- Dizziness or fainting
- Rapid or weak heartbeat

- Severe stomach cramps or pain, vomiting, or diarrhea
- Severe flushing or itching of the skin

For additional information on the possible side effects of ORALAIR, talk with your doctor or pharmacist. You may report side effects to the US Food and Drug Administration (FDA) at 1-800-FDA-1088 or www.fda.gov/medwatch.

How should I store ORALAIR?

Keep ORALAIR out of the reach of children.

Throw away any unused ORALAIR after the expiration date which is stated on the carton and blister pack after "EXP."

Store ORALAIR in a dry place at room temperature, 20ºC to 25ºC (68ºF to 77ºF), in the original package.

General information about ORALAIR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ORALAIR for a condition for which it was not prescribed. Do not give ORALAIR to other people, even if they have the same symptoms. It may harm them.

This Medication Guide summarizes the most important information about ORALAIR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ORALAIR that was written for healthcare professionals. For more information go to www.ORALAIR.com or call Greer Laboratories at 1-855-752-5046.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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