PRODUCT MONOGRAPH

[Pr]ORALAIR

Grass Pollen Allergen Extract

100 IR and 300 IR Sublingual Tablets

Allergenic Substance

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ORALAIR

Sublingual Tablet of grass pollen allergen extract

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Sublingual	Sublingual tablets of 100 IR and 300 IR	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Each sublingual ORALAIR tablet contains 100 IR and 300 IR respectively, of the allergen extract composed of the following grass pollen: Cocksfoot (*Dactylis glomerata* L.), Sweet vernal grass (*Anthoxanthum odoratum* L.), Rye grass (*Lolium perenne* L.), Meadow grass (*Poa pratensis* L.) and Timothy (*Phleum pratense* L.)

The strength of ORALAIR is expressed in IR (Index of Reactivity). The unit IR has been defined to measure the allergenicity of an allergen extract. An allergen extract is said to have a titer of 100 IR/ml if a prick-test performed using a Stallerpoint® in 30 subjects sensitized to that allergen produces a wheal of 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with codeine phosphate 9% or 10 mg/ml histamine dihydrochloride. **The IR unit of Stallergenes is not comparable to the units used by other allergen manufacturers.**

The drug substance is prepared by the extraction of the 5 grass pollens, which are then purified, freeze dried and sieved, before incorporation in the final dosage form. The characterization of the allergenic components includes identification of relevant allergens based on technique using sera from allergic patients.

INDICATIONS AND CLINICAL USE

ORALAIR (sublingual tablet of grass pollen extract) is indicated for the treatment of symptoms of moderate to severe seasonal grass pollen allergic rhinitis with or without conjunctivitis in patients 5 to 50 years of age, confirmed by clinically relevant symptoms, a positive cutaneous test and a positive titre of the specific IgE to *Poaceae* grass pollen, who have suffered from allergic rhinitis with or without conjunctivitis for at least two pollen seasons and have not adequately responded to, or tolerated, conventional pharmacotherapy.

Treatment with ORALAIR should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases. In case of paediatric treatment, the physicians should have the corresponding training and experience in children.

For previously untreated patients, prior to the initiation of therapy, clinical sensitivity to the standardized grass pollen extract should be established by careful evaluation of the patient's history confirmed by diagnostic skin testing and IgE titres. Hyposensitization should not be prescribed for sensitivities to allergens which can easily be avoided.

Special Populations:

Immunotherapy with ORALAIR has not been studied in patients under 5 years or over 50 years of age.

CONTRAINDICATIONS

Immunotherapy with specific antigens is not indicated in those individuals who do not exhibit positive cutaneous test and clinical history of disease to the particular antigens (see **WARNINGS AND PRECAUTIONS**). A patient should not be immunized with preparations of allergens to which the patient has not demonstrated symptoms, IgE antibodies, positive skin tests, or properly controlled challenge testing. In most cases, immunotherapy is not indicated for those allergens that can be eliminated or minimized by environmental control.

ORALAIR should not be used in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Patients with extreme sensitivity to the specific allergen determined from previous anaphylaxis following exposure.
- Patients on beta-blockers as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction (also see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).
- Patients treated with ACE inhibitors as greater risk of a more serious reaction to allergen immunotherapy may exist.

- Patients with severe and/or unstable asthma (FEV_1 < 70% of predicted value).
- Patients with severe immune deficiency or auto-immune disease. Individuals with autoimmune disease may be at risk, due to the possibility of routine immunizations exacerbating symptoms of the underlying disease. Hyposensitization should be given cautiously to patients with this predisposition.
- Patients with malignant diseases (e.g. cancer).
- Patients who have oral inflammations (such as oral lichen planus, oral ulcerations or oral mycosis).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Treatment with ORALAIR should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases. In case of paediatric treatment, the physicians should have the corresponding training and experience in children.
- The first tablet of ORALAIR must be taken at the physician's office under medical supervision and the patient must be monitored for at least 30 minutes.
- Extra precautions must be taken while treating paediatric patients, including: each administration of ORALAIR must be given under direct adult supervision for at least 30 minutes.
- When treated with ORALAIR the patient is exposed to the allergen that causes the allergic symptoms. Therefore, mild or moderate local allergic reactions are to be expected during the treatment period.
- Patients should be instructed in recognizing adverse reactions and their possible severity. If the patient experiences moderate local adverse reactions from the treatment, anti-allergic medication (e.g. antihistamines) should be considered.
- Hypersensitivity, diarrhoea and angioneurotic oedema have occurred during clinical trials within the first year of treatment with ORALAIR. If severe systemic reactions occur, emergency medical treatment should be sought immediately and treatment with ORALAIR should be discontinued.

General

No data are available on the effect of vaccination in patients receiving ORALAIR treatment. Vaccination may be given without interrupting treatment with ORALAIR after medical evaluation of the general condition of the patient.

Severe allergic reactions such as anaphylactic shock should be treated with epinephrine. Effects of epinephrine may be potentiated in patients treated with tricyclic antidepressants and

monoamine oxidase inhibitors (MAOIs) with possible fatal consequences; this should be taken into consideration prior to initiating specific immunotherapy.

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or clinically significant milk (lactose) allergies should not take this medication.

Carcinogenesis and Mutagenesis

No carcinogenicity studies were conducted based on the fact that there is no cause for concern with regard to carcinogenicity. Also, the grass pollen allergen extract tested in the *in vitro* and *in vivo* studies evidenced no risk of mutagenic effect (see **Part II, TOXICOLOGY**).

Gastrointestinal

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy. During treatment with ORALAIR, if severe or persistent gastroesophageal symptoms including dysphagia or chest pain occur, ORALAIR should be interrupted and the patient evaluated by their physician. Treatment should only be resumed upon instruction of the physician.

Peri-Operative Considerations

In case of oral surgery, including dental extraction or any intervention affecting oral mucosa, treatment with ORALAIR should be stopped until complete healing. Thereafter, treatment may be restarted at the dosage of last intake. Should the interruption period be longer than 7 days, it is recommended to restart the treatment at the dosage of last intake, under medical supervision.

Psychomotor Impairment

ORALAIR has no known influence on the ability to drive and operate machinery.

Special Populations

Pregnant Women:

There are no adequate and well controlled studies on the use of ORALAIR in pregnant women.

ORALAIR should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus and mother.

No specific fertility study was conducted with the grass pollen allergen extract. However, the histopathological examination from 26-week and 13-week repeat-dose toxicology studies in rat and hamster, respectively, revealed no relevant finding on reproductive organs.

No adverse effect on embryofoetal development was observed following the oral administration of grass pollen allergen extract at doses up to 795 IR/kg/day in mated female Sprague-Dawley

rats and at doses up to 885 IR/kg/day in mated New Zealand White rabbits. The NOAEL's (No Observed Adverse Event Level) of 795 and 885 IR/kg/day correspond to approximately 159-fold and 177-fold the maximal therapeutic dose in women.

No pre- and post-natal development study was conducted and was not deemed necessary based on the fact that no toxicity was observed in repeat-dose toxicity studies in adult rats, in juvenile rats and in embryofoetal developmental studies in pregnant female rats and rabbits at doses up to 910 IR/kg/day, 1445 IR/kg/day, 795 IR/kg/day and 885 IR/kg/day, respectively.

Nursing Women:

No clinical data are available for the use of ORALAIR during lactation. No effects on the breastfed infants are anticipated.

ORALAIR should be used during lactation only if the potential benefit justifies the potential risk to the foetus.

Paediatrics (< 5 years of age):

Immunotherapy with ORALAIR has not been studied in young children (< 5 years).

Geriatrics (> 50 years of age):

Immunotherapy with ORALAIR has not been studied in patients over 50 years of age.

Monitoring and Laboratory Tests

The first tablet of ORALAIR should be administered under medical supervision and patients should be monitored for 30 minutes so that any adverse reaction can be observed and properly handled.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

During treatment with ORALAIR, patients are exposed to allergens that may cause local and/or systemic allergic symptoms. Mild to moderate local allergic reactions (i.e. oral swelling or discomfort) may therefore be expected during the period of therapy. Fifty percent (50%) of these reactions occur during the first three days of treatment (dose escalation).

If the patient experiences severe local adverse reactions during therapy, symptomatic treatment (e. g. with antihistamines) should be considered.

Uncommonly, stronger allergic reactions can occur, including severe laryngo-pharyngeal

disorders (sensation of swelling in the throat, difficulty swallowing or breathing or voice changes). In such cases, a physician has to be consulted immediately and the treatment has to be discontinued immediately. Treatment may only be resumed on the physician's advice.

Serious adverse events including hypersensitivity, diarrhoea and angioneurotic oedema have occurred during clinical trials. If severe systemic reactions occur, emergency medical treatment should be sought immediately and treatment with ORALAIR should be discontinued.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The overall safety evaluation of ORALAIR sublingual immunotherapy (SLIT) in adult and paediatric patients is based primarily on 5 clinical studies; one trial had sites in North America, but the majority of patients were in Europe.

In the placebo-controlled pivotal trials, a total of 569 adult and 139 paediatric patients with grass pollen rhinoconjunctivitis received at least one treatment with 300 IR ORALAIR sublingual tablets. In addition, 157 and 160 adult patients received 100 IR and 500 IR, respectively of ORALAIR in pivotal Study VO34.04.

Adverse events in adult patients

Study VO53.06

Study VO53.06 was conducted to evaluate the efficacy and safety of ORALAIR compared to placebo in adult patients for 3 consecutive pollen seasons. Patients with seasonal grass pollen-induced allergic rhinoconjunctivitis were randomized to either placebo or ORALAIR 300 IR given sublingually once daily for up to 4 months before and then during the pollen season in years 1 to 3. In this study, 633 patients were randomized and treated in Year 1; 508 in Year 2 and 465 in Year 3.

Study VO34.04

Study VO34.04 was a Phase IIb/III study assessing the efficacy and safety of ORALAIR administered at 3 different doses as once daily tablet to adult patients suffering from grass pollen rhinoconjunctivitis for at least 2 years. A total of 628 patients were randomized to receive a maintenance dose of 100IR, 300IR or 500IR of ORALAIR sublingual tablets or placebo.

In the above-mentioned pivotal studies conducted in adult patients, the adverse events most

commonly observed during the first year of treatment with ORALAIR 300IR were reported up to the following incidences: oral pruritus (43% vs. 12.8% with placebo), throat irritation (25.6% vs. 5.5% with placebo), ear pruritus (11.6% vs. 1.4% with placebo), mouth oedema (9.7% vs. 1.4% with placebo).

Other very commonly reported adverse events were sneezing (15.0%), rhinorrhoea (15.5%), nasopharyngitis (13.5%), eye pruritus (13.0%), nasal congestion (12.6%), nasal discomfort (12.6%) and cough (10.6%). During the first year of treatment, three patients experienced an event that was deemed serious and drug-related. The events were the following: hypersensitivity, diarrhoea and angioneurotic oedema.

Based on results from the pivotal studies in adult patients, treatment duration had no cumulative impact on the overall safety profile of ORALAIR 300 IR following one pollen season treatment. Results from Studies VO34.04 and VO53.06 showed no significant relationship between the profile or frequency of adverse events and the 3 different ORALAIR doses (100 IR, 300 IR, and 500 IR) or with the duration of the pre-seasonal period (2M and 4M), except for a non significant trend in some gastrointestinal events that slightly increase with dose or pre-seasonal treatment duration.

Approximately 4% of actively treated adults (vs. 0-2.3% of those treated with placebo) prematurely withdrew from the pivotal studies due to TEAEs, primarily related to gastrointestinal disorders, during Years 1 and 2, with most cases occurring during Year 1. The age or gender of the patients was not shown to impact the safety profile of ORALAIR.

No event of anaphylactoid and/ or anaphylactic reactions was reported during the clinical development of ORALAIR.

Table 1 lists the treatment-emergent adverse events, regardless of causality, reported in Studies VO53.06 and VO34.04 after one treatment pollen season by at least 1% of patients treated with ORALAIR 300 IR in at least one of the studies.

Table 1: Treatment-emergent adverse events reported in studies VO53.06 and VO34.04 after one treatment pollen season with ORALAIR and at a frequency of ≥ 1 % in at least one of the studies

System Organ Class **Preferred Term**	**VO53.06** **(Year 1)**		**VO34.04**	
	ORALAIR Dose			
	Placebo **(N=219)** **n (%)**	**300 IR (4M)** **(N=207)** **n (%)**	**Placebo** **(N=156)** **n (%)**	**300 IR** **(N=155)** **n (%)**
Blood and lymphatic system disorders	**1 (0.5)**	**0**	**0**	**4 (2.6)**
Lymphadenopathy	0	0	0	3 (1.9)

System Organ Class Preferred Term	VO53.06 (Year 1)		VO34.04	
	ORALAIR Dose			
	Placebo (N=219) n (%)	300 IR (4M) (N=207) n (%)	Placebo (N=156) n (%)	300 IR (N=155) n (%)
Ear and labyrinth disorders	**4 (1.8)**	**24 (11.6)**	**1 (0.6)**	**7 (4.5)**
Ear pruritus	3 (1.4)	24 (11.6)	1 (0.6)	5 (3.2)
Eye disorders	**75 (34.2)**	**53 (25.6)**	**6 (3.8)**	**6 (3.9)**
Eye pruritus	39 (17.8)	27 (13.0)	3 (1.9)	2 (1.3)
Lacrimation increased	26 (11.9)	14 (6.8)	0	0
Conjunctivitis	11 (5.0)	12 (5.8)	1 (0.6)	2 (1.3)
Conjunctivitis allergic	19 (8.7)	10 (4.8)	1 (0.6)	0
Chalazion	0	2 (1.0)	0	0
Gastrointestinal disorders	**41 (18.7)**	**126 (60.9)**	**18 (11.5)**	**64 (41.3)**
Oral pruritus	28 (12.8)	89 (43.0)	8 (5.1)	40 (28.5)
Oedema mouth	3 (1.4)	20 (9.7)	0	7 (4.5)
Dyspepsia	0	11 (5.3)	2 (1.3)	5 (3.2)
Oral discomfort	1 (0.5)	9 (4.3)	0	4 (2.6)
Paraesthesia oral	1 (0.5)	8 (3.9)	1 (0.6)	4 (2.6)
Tongue oedema	0	8 (3.9)	0	4 (2.6)
Glossodynia	1 (0.5)	7 (3.4)	0	2 (1.3)
Lip oedema	0	6 (2.9)	0	0
Hypoaesthesia oral	1 (0.5)	6 (2.9)	0	1 (0.6)
Stomatitis	0	4 (1.9)	0	0
Abdominal pain upper	0	4 (1.9)	0	4 (2.6)
Swollen tongue	0	3 (1.4)	0	5 (3.2)
Vomiting	0	3 (1.4)	1 (0.6)	1 (0.6)
Diarrhoea	5 (2.3)	2 (1.0)	4 (2.6)	3 (1.9)
Nausea	3 (1.4)	2 (1.0)	3 (1.9)	2 (1.3)
Lip swelling	1 (0.5)	2 (1.0)	0	0
Toothache	0	2 (1.0)	0	2 (1.3)
Abdominal pain	0	2 (1.0)	2 (1.3)	2 (1.3)
Oral pain	0	2 (1.0)	0	1 (0.6)

System Organ Class Preferred Term	VO53.06 (Year 1)		VO34.04	
	ORALAIR Dose			
	Placebo (N=219) n (%)	300 IR (4M) (N=207) n (%)	Placebo (N=156) n (%)	300 IR (N=155) n (%)
Dysphagia	0	2 (1.0)	0	0
Gastro-oesophageal reflux disease	1 (0.5)	2 (1.0)	0	0
Buccal mucosal roughening	0	2 (1.0)	0	0
Stomach discomfort	0	2 (1.0)	0	0
Glossitis	0	1 (0.5)	0	3 (1.9)
Dry mouth	2 (0.9)	0	0	2 (1.3)
General disorders and administration site conditions	**6 (2.7)**	**6 (2.9)**	**8 (5.1)**	**5 (3.2)**
Chest discomfort	0	3 (1.4)	1 (0.6)	0
Fatigue	3 (1.4)	2 (1.0)	0	0
Pyrexia	2 (0.9)	1 (0.5)	2 (1.3)	2 (1.3)
Sensation of a foreign body	0	0	1 (0.6)	2 (1.3)
Immune system disorders	**12 (5.5)**	**6 (2.9)**	**1 (0.6)**	**1 (0.6)**
Seasonal allergy	5 (2.3)	5 (2.4)	0	0
Infections and infestations	**75 (34.2)**	**64 (30.9)**	**36 (23.1)**	**35 (22.6)**
Nasopharyngitis	29 (13.2)	28 (13.5)	11 (7.1)	13 (8.4)
Rhinitis	12 (5.5)	15 (7.2)	3 (1.9)	5 (3.2)
Gastroenteritis	2 (0.9)	4 (1.9)	2 (1.3)	0
Influenza	6 (2.7)	3 (1.4)	4 (2.6)	4 (2.6)
Upper respiratory tract infection	2 (0.9)	3 (1.4)	1 (0.6)	0
Acute tonsillitis	6 (2.7)	3 (1.4)	1 (0.6)	0
Pharyngitis	8 (3.7)	2 (1.0)	7 (4.5)	3 (1.9)
Herpes simplex	4 (1.8)	2 (1.0)	0	3 (1.9)
Viral infection	0	2 (1.0)	3 (1.9)	4 (2.6)
Tonsillitis	1 (0.5)	2 (1.0)	0	3 (1.9)
Respiratory tract infection viral	2 (0.9)	2 (1.0)	0	1 (0.6)

System Organ Class Preferred Term	VO53.06 (Year 1)		VO34.04	
	ORALAIR Dose			
	Placebo (N=219) n (%)	300 IR (4M) (N=207) n (%)	Placebo (N=156) n (%)	300 IR (N=155) n (%)
Pharyngotonsillitis	4 (1.8)	2 (1.0)	0	0
Bronchitis Acute	2 (0.9)	2 (1.0)	2 (1.3)	0
Injury, poisoning and procedural complications	**5 (2.3)**	**6 (2.9)**	**4 (2.6)**	**3 (1.9)**
Excoriation	0	2 (1.0)	0	0
Musculoskeletal and connective tissue disorders	**11 (5.0)**	**6 (2.9)**	**2 (1.3)**	**11 (7.1)**
Back pain	8 (3.7)	2 (1.0)	2 (1.3)	5 (3.2)
Neck pain	1 (0.5)	1 (0.5)	0	2 (1.3)
Nervous system disorders	**33 (15.1)**	**20 (9.7)**	**23 (14.7)**	**23 (14.8)**
Headache	30 (13.7)	17 (8.2)	21 (13.5)	22 (14.2)
Psychiatric disorders	**2 (0.9)**	**1 (0.5)**	**2 (1.3)**	**3 (1.9)**
Anxiety	1 (0.5)	0	1 (0.6)	2 (1.3)
Respiratory, thoracic and mediastinal disorders	**94 (42.9)**	**113 (54.6)**	**24 (15.4)**	**35 (22.6)**
Throat irritation	12 (5.5)	53 (25.6)	5 (3.2)	14 (9.0)
Rhinorrhoea	36 (16.4)	32 (15.5)	0	1 (0.6)
Sneezing	41 (18.7)	31 (15.0)	0	0
Nasal congestion	34 (15.5)	26 (12.6)	0	3 (1.9)
Nasal discomfort	37 (16.9)	26 (12.6)	0	0
Cough	23 (10.5)	22 (10.6)	3 (1.9)	1 (0.6)
Pharyngolaryngeal pain	10 (4.6)	12 (5.8)	6 (3.8)	6 (3.9)
Pharyngeal oedema	1 (0.5)	9 (4.3)	0	0
Rhinitis allergic	9 (4.1)	9 (4.3)	1 (0.6)	0
Pharyngolaryngeal discomfort	0	7 (3.4)	0	0
Dysphonia	0 (0.0)	6 (2.9)	0	0
Dyspnoea	5 (2.3)	6 (2.9)	6 (3.8)	3 (1.9)
Asthma	9 (4.1)	5 (2.4)	6 (3.8)	4 (2.6)

System Organ Class Preferred Term	VO53.06 (Year 1)		VO34.04	
	ORALAIR Dose			
	Placebo (N=219) n (%)	300 IR (4M) (N=207) n (%)	Placebo (N=156) n (%)	300 IR (N=155) n (%)
Pharyngeal hypoaesthesia	0	4 (1.9)	0	0
Wheezing	5 (2.3)	3 (1.4)	0	1 (0.6)
Throat tightness	0	2 (1.0)	0	1 (0.6)
Laryngeal oedema	1 (0.5)	2 (1.0)	0	0
Nasal oedema	4 (1.8)	2 (1.0)	0	0
Dry throat	0	2 (1.0)	0	3 (1.9)
Oropharyngeal swelling	0	0	0	3 (1.9)
Skin and subcutaneous tissue disorders	**14 (6.4)**	**11 (5.3)**	**4 (2.6)**	**15 (9.7)**
Swelling face	0	0	0	6 (3.9)
Eczema	3 (1.4)	3 (1.4)	1 (0.6)	1 (0.6)
Pruritus	6 (2.7)	2 (1.0)	1 (0.6)	3 (1.9)
Face oedema	0	0	1 (0.6)	3 (1.9)
Vascular Disorders	**4 (1.8)**	**2 (1.0)**	**3 (1.9)**	**2 (1.3)**
Hypertension	0	2 (1.0)	1 (0.6)	1 (0.6)

Adverse events in paediatric patients

Study VO52.06

Study VO52.06 was conducted to assess efficacy of ORALAIR compared to placebo in paediatric patients (5 to 17 years of age, inclusively) with grass pollen-related allergic rhinoconjunctivitis for at least 2 previous pollen seasons. A total of 278 patients were randomized to receive a maintenance dose of ORALAIR 300 IR or placebo sublingually once daily for one pollen season.

The following adverse events were the most commonly observed in the paediatric patients following treatment with ORALAIR 300 IR: oral pruritus (33.1% vs. 4.3% with placebo), throat irritation (9.4% vs. 5.0% with placebo), mouth oedema (12.9% vs. 0% with placebo) and lip swelling (5.0% vs. 0.7% with placebo).

Other very commonly reported adverse events were cough (25.2%), nasopharyngitis (13.7%),

eye pruritus (7.2%), nasal congestion (8.6%), headache (7.5%), asthmas (7.2%) and tonsillitis (6.5%). Two serious adverse drug reactions were reported in patients receiving 300 IR, namely exacerbation of asthma and Burkitt's lymphoma. Neither of these events was considered drug-related by the investigator.

In study VO52.06, 7 patients (5%) prematurely withdrew from the clinical trial due to adverse events.

Table 2 lists the treatment-emergent adverse events, regardless of causality, reported by at least 1% of patients in the 300 IR group in Study VO52.06.

Table 2: Treatment-emergent adverse events reported at a frequency of ≥ 1 % of patients in study VO52.06.

System Organ Class **Preferred Term**	**ORALAIR Dose**	
	Placebo **(N=139)** **n (%)**	**300 IR** **(N=139)** **n (%)**
Ear and labyrinth disorders	**2 (1.4)**	**7 (5.0)**
Ear pruritus	1 (0.7)	5 (3.6)
Eye disorders	**25 (18.0)**	**14 (10.1)**
Eye pruritus	12 (8.6)	10 (7.2)
Conjunctivitis	7 (5.0)	4 (2.9)
Lacrimation increased	8 (5.8)	2 (1.4)
Gastrointestinal disorders	**23 (16.5)**	**70 (50.4)**
Oral pruritus	6 (4.3)	46 (33.1)
Oedema mouth	0 (0.0)	18 (12.9)
Lip swelling	1 (0.7)	7 (5.0)
Swollen tongue	1 (0.7)	5 (3.6)
Abdominal pain upper	2 (1.4)	4 (2.9)
Diarrhoea	5 (3.6)	3 (2.2)
Nausea	1 (0.7)	3 (2.2)
Oral mucosal blistering	0 (0.0)	3 (2.2)
Stomatitis	0 (0.0)	3 (2.2)
Vomiting	0 (0.0)	3 (2.2)
Cheilitis	0 (0.0)	2 (1.4)
Glossitis	0 (0.0)	2 (1.4)
Oral discomfort	0 (0.0)	2 (1.4)
Abdominal pain	6 (4.3)	2 (1.4)
General disorders and administration site conditions	**6 (4.3)**	**11 (7.9)**
Pyrexia	5 (3.6)	5 (3.6)

System Organ Class **Preferred Term**	**ORALAIR Dose**	
	Placebo **(N=139)** **n (%)**	**300 IR** **(N=139)** **n (%)**
Chest discomfort	0 (0.0)	3 (2.2)
Asthenia	0 (0.0)	2 (1.4)
Infections and infestations	**58 (41.7)**	**55 (39.6)**
Nasopharyngitis	18 (12.9)	19 (13.7)
Tonsillitis	5 (3.6)	9 (6.5)
Pharyngitis	16 (11.5)	6 (4.3)
Upper respiratory tract infection	3 (2.2)	6 (4.3)
Rhinitis	6 (4.3)	4 (2.9)
Bronchitis acute	1 (0.7)	4 (2.9)
Bronchitis	6 (4.3)	3 (2.2)
Pneumonia	0 (0.0)	3 (2.2)
Viral infection	4 (2.9)	2 (1.4)
Otitis media	2 (1.4)	2 (1.4)
Viral rhinitis	1 (0.7)	2 (1.4)
Infectious mononucleosis	0 (0.0)	2 (1.4)
Influenza	0 (0.0)	2 (1.4)
Respiratory tract infection viral	0 (0.0)	2 (1.4)
Nervous system disorders	**24 (17.3)**	**12 (8.6)**
Headache	24 (17.3)	11 (7.9)
Dizziness	0 (0.0)	2 (1.4)
Respiratory, thoracic and mediastinal disorders	**70 (50.4)**	**74 (53.2)**
Cough	37 (26.6)	35 (25.2)
Throat irritation	7 (5.0)	13 (9.4)
Nasal congestion	9 (6.5)	12 (8.6)
Sneezing	11 (7.9)	11 (7.9)
Asthma	6 (4.3)	10 (7.2)
Wheezing	13 (9.4)	8 (5.8)
Rhinorrhoea	10 (7.2)	8 (5.8)
Nasal discomfort	9 (6.5)	7 (5.0)
Pharyngolaryngeal pain	3 (2.2)	4 (2.9)
Dysphonia	2 (1.4)	4 (2.9)
Epistaxis	9 (6.5)	3 (2.2)
Dyspnoea	6 (4.3)	3 (2.2)
Rhinitis allergic	3 (2.2)	3 (2.2)
Larynx irritation	0 (0.0)	3 (2.2)

System Organ Class Preferred Term	ORALAIR Dose	
	Placebo (N=139) n (%)	**300 IR (N=139) n (%)**
Throat tightness	0 (0.0)	3 (2.2)
Skin and subcutaneous tissue disorders	**19 (13.7)**	**15 (10.8)**
Pruritus	5 (3.6)	3 (2.2)
Dermatitis atopic	1 (0.7)	5 (3.6)
Eczema	3 (2.2)	3 (2.2)
Urticaria	4 (2.9)	2 (1.4)
Rash	2 (1.4)	2 (1.4)
Surgical and medical procedures	**1 (0.7)**	**3 (2.2)**
Tooth extraction	0 (0.0)	3 (2.2)

The overall profile of adverse events between adult and paediatric patients was similar. In patients receiving 300 IR, the following adverse events were observed at a higher frequency in the paediatric population when compared to the adult population and to placebo:

- mouth oedema (12.9% in children *vs.* up to 9.7% in adults)
- lip swelling (5.0% in children *vs*. up to 1.0% in adults)
- upper respiratory tract infection (4.3% in children *vs*. up to 1.4% in adults)
- tonsillitis (6.5% in children *vs*. up to 1.9% in adults)
- cough (25.2% in children *vs*. up to 10.6% in adults)
- asthma (7.2% in children *vs*. up to 2.6% in adults)

Conversely, the following adverse events were observed at a higher frequency in the adult population receiving 300 IR when compared to the paediatric population and to placebo:

- dyspepsia (0.7% in children *vs*. up to 5.3% in adults)
- rhinitis (2.9% in children *vs*. up to 7.2% in adults)

Long-term safety

In Study VO53.06, a total of 299 adult patients were evaluated for safety following 3 consecutive pollen seasons treatment of daily ORALAIR dose at 300 IR. Safety and efficacy have not been studied in paediatric patients aged 5-17 years old for more than one season.

In Years 2 and 3, a decrease in the number of patients reporting adverse events was observed; however, the types of events reported are similar to the ones observed in Year 1. No serious drug-related adverse events were observed during Years 2 and 3. The events that were

consistently seen over the three years, but with a decreasing frequency, are the following: oral pruritus, nasopharyngitis and throat irritation.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events were reported in the administration of ORALAIR at a frequency <1% in the safety and efficacy studies (two studies in adults [VO53.06 and VO34.04] and one study in children [VO52.06]).

Blood and lymphatic system disorders: eosinophilia.

Ear and labyrinth disorders: ear congestion, ear discomfort, ear pain, tinnitus, vertigo.

Eye disorders: conjunctival hyperaemia, conjunctival oedema, dry eye, eyelid oedema, eyelids pruritus, foreign body sensation in eyes, lacrimal disorder, ocular hyperaemia.

Gastrointestinal disorders: abdominal discomfort, aphthous stomatitis, aptyalism, bowel sounds abnormal, colitis, enteritis, eructation, flatulence, gastritis, gastrooesphageal reflux disorder, gingival pruritus, gingivitis, hyperchlorhydria, lip blister, mouth ulceration, odynophagia, oesophageal discomfort, oesophageal pain, oesophagitis, palatal oedema, tongue blistering, tongue disorder, tongue ulceration, tooth fracture.

General disorders and administration site conditions: application site pain, chest pain, cyst, inflammation, local swelling, malaise, oedema peripheral, thirst.

Hepatobiliary disorders: biliary colic, gallbladder pain.

Immune system disorders: allergy to animal, food allergy, hypersensivity.

Infections and infestations: acute sinusitis, appendicitis, blister infected, brucellosis, conjunctivitis infective, croup infectious, ear infection, eyelid infection, fungal infection, fungal skin infection, gastrointestinal infection, herpes zoster, infection, laryngitis, localized infection, measles, meningococcal infection, otitis externa, respiratory tract infection, scarlet fever, sinusitis, streptococcal infection, tinea barbae, tinea vesicolour, tonsillitis streptococcal, tooth abscess, tooth infection, tracheitis, urinary tract infection, vaginitis, vaginal infection, vaginal mucosis, varicella, viral tonsillitis.

Injury, poisoning and procedural complications: arthropod sting, cervical vertebral fracture, concussion, contraceptive device complication, contusion, face injury, foreign body trauma, head injury, joint sprain, muscle strain, post procedural complication, radius fracture, road traffic accident, skeletal injury, wound, wrist fracture.

Investigations: weight increased.

Metabolism and nutrition disorders: anorexia, hypercholesterolaemia, latent tetany, lipid metabolism disorder.

Musculoskeletal and connective tissue disorders: coccydynia, growing pains, haemarthrosis, intervertebral disc protrusion, muscle spasm, musculoskeletal stiffness, myalgia, pain in extremity, synovial cyst, tendonitis, torticollis.

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Burkitt's lymphoma, lipoma, skin papilloma.

Nervous system disorders: ageusia, burning sensation, cervical rib syndrome, cervical root pain, cervicobrachial syndrome, convulsion, dysgeusia, hypoaesthesia, somnolence, syncope.

Pregnancy, puerperium and perinatal conditions: ectopic pregnancy, pregnancy.

Psychiatric disorders: insomnia, sleep disorder, stress symptoms.

Reproductive system and breast disorders: adnexa uteri pain, breast cyst, breast pain, genital pruritus female.

Respiratory, thoracic and mediastinal disorders: allergic cough, asthma exercise induced, bronchial obstruction, hoarseness, laryngeal disorder, nasal dryness, nasal septum deviation, paranasal sinus discomfort, productive cough, respiration abnormal, sinus congestion, upper respiration tract congestion.

Skin and subcutaneous tissue disorders: acne, alopecia areata, angioneurotic oedema, circumoral oedema, dermatitis, dry skin, hyperhidrosis, neurodermatitis, periorbital oedema, photodermatosis, pityriasis rosea, prurigo, pruritus generalized, rash pruritic, urticaria localised.

Surgical and medical procedures: tenotomy.

Vascular disorders: hypotension, varicose vein.

Abnormal Hematologic and Clinical Chemistry Findings

There were no clinically relevant findings in the mean values and mean changes in clinical laboratory data after any of the treatments.

Post-Market Adverse Drug Reactions

The following adverse events have been reported during the post marketing use of ORALAIR, and had not been previously observed in clinical trials. 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.

Cardiac disorders: palpitations, tachycardia.

Eye disorders: eyelid injury.

Gastrointestinal disorders: Crohn's disease, eosinophilic esophagitis.

General disorders and administration site conditions: chest pain.

Immune system disorders: anaphylactic reaction.

Infections and infestations: enterocolitis infectious.

Investigations: weight decreased.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps): acanthoma, plasmacytoma.

Nervous system disorders: paraesthesia, tremor.

Psychiatric disorders: nervousness.

Respiratory, thoracic and mediastinal disorders: analgesic asthma syndrome, aphonia.

Skin and subcutaneous tissue disorders: erythema, generalised erythema, skin sensitization.

Vascular disorders: circulatory collapse, pallor.

During the post-marketing use of ORALAIR, the following report of vascular disorder, which had characteristics consistent with a vasovagal reaction, was received. A 58-year-old female with previous medical history of myocardial infarction, arterial hypertension and diabetes mellitus, on lisinopril, hydrochlorothiazide, aspirin and diclofenac experienced marked decrease of blood pressure together with malaise, pallor and nausea without loss of consciousness 15 minutes after the first intake of ORALAIR 100 IR. This lasted 15 minutes and totally abated after treatment. ORALAIR was discontinued.

DRUG INTERACTIONS

Overview

There are no data on possible risks of simultaneous immunotherapy with other allergens during treatment with ORALAIR. No interaction was reported in clinical trials with ORALAIR.

Drug-Drug Interactions

No interactions were reported in clinical trials with ORALAIR, during which patients were able to take medications in case of unbearable symptoms (antihistamines, steroids).

No data are available on possible risk of simultaneous immunotherapy with other allergens during treatment with ORALAIR.

Drug-Food Interactions

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or clinically significant lactose (milk) allergy should not take this medicine.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Interactions with lifestyle drugs have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment with ORALAIR should only be prescribed and initiated by physicians with adequate training and experience in the treatment of allergic diseases. In case of paediatric treatment, the physicians should have the corresponding training and experience in children.

Treatment should be initiated about 4 months before the expected onset of the pollen season and must be maintained throughout the pollen season.

It is recommended that the first tablet of ORALAIR is taken under medical supervision and that the patient is monitored for 30 minutes. This also enables the patient and physician to discuss any side effects and their management.

For adult patients (18-50 years), clinical experience with treatment with ORALAIR is limited to three grass pollen seasons. If no improvement is noted after three seasons, treatment should be discontinued.

For paediatric patients (5-17 years), clinical experience with treatment with ORALAIR is limited to one grass pollen season.

Recommended Dose and Dosage Adjustment

Posology in adults and children five years of age and older:

In adults and children (above the age of 5), treatment is initiated with a 3-day dose escalation phase, followed by a maintenance treatment with one ORALAIR 300 IR sublingual tablet per day until the end of treatment. The 3-day dose escalation phase consists of the following:

Day 1: 1 x 100 IR tablet
Day 2: 2 x 100 IR tablets
Day 3: 1 x 300 IR tablet

Administration of ORALAIR

The tablet must be placed under the tongue until complete dissolution (for at least 1 minute) and then swallowed. During the second day of treatment, the patient should take 2 tablets of 100 IR. These 2 tablets must be placed under the tongue simultaneously and then swallowed.
It is recommended to take the tablet in the morning, in an empty mouth.

Patients should be advised to wash their hands after taking the medicine in order to prevent inadvertent spreading.

Missed Dose

In case of a missed dose, the patient should resume treatment with the next scheduled dose and continue the regular dosing schedule. The patient should not take a double dose to make up for the forgotten dose.

If a patient has interrupted the treatment with ORALAIR during the continuation phase for less than one week, he can take up treatment where he left off. Should the interruption period be longer than 7 days, it is recommended to restart the treatment at the dosage of last intake, under medical supervision.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No case of overdosing has been reported.

If doses higher than the recommended daily dose are taken, the risk of undesirable effects, including systemic side effects or severe local adverse reactions, is increased. In the case of occurrence of severe symptoms, such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, a physician has to be consulted immediately.

In the event of an overdose, the adverse effects should be treated symptomatically.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ORALAIR is an allergen-specific immunotherapy product that is administered sublingually for treatment of patients with grass pollen-mediated seasonal allergic rhinitis with or without conjunctivitis.

Specific immunotherapy (SIT) is aimed at preventing allergic reaction by inducing immunologic tolerance (defined as a long-lived decrease in allergen-specific T-cell responsiveness). However, the complete and exact mechanism responsible for its clinical efficacy is continually being elucidated.

The immunologic response to SIT is characterized by decreases in the sensitivity of end organs and to changes in the humoral and cellular responses to the administered allergens. The reduction in end-organ response with SIT includes decreased early and late responses of the skin, conjunctiva, nasal mucosa and bronchi to allergen challenge; decrease allergen-induced eosinophil, basophil, and mast cell infiltration; blunting of mucosal priming; and reduction of nonspecific bronchial sensitivity to histamine.

Pharmacodynamics

Treatment with ORALAIR is associated with a transient increase in antigen-specific serum IgE and a prolonged increase in antigen-specific serum IgG_4, confirming the immunologic activity of the product.

Pharmacokinetics

The majority of allergens in ORALAIR are a mixture of proteins and glycoproteins. When administered by the sublingual route, the main part of the allergen extract is expected to be broken down to aminoacids and small polypeptides in the gastrointestinal tract and thus no direct bioavailability of intact allergens is measurable in blood. Therefore, no pharmacokinetic studies in animals or in humans have been carried out to investigate the pharmacokinetic profile and metabolism of ORALAIR.

STORAGE AND STABILITY

Store at room temperature (15°C to 30°C). Store in the original package in order to protect from moisture. The tablet should remain in the sealed blister until use.

Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

This drug product does not require any special temperature storage conditions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ORALAIR (sublingual tablet of grass pollen allergen extract) is formulated as a slightly speckled white to beige tablet available in two strengths, 100 IR and 300 IR, and showing the following distinguishable characteristics:

- 100 IR tablet is engraved "100" on both surfaces
- 300 IR tablet is engraved "300" on both surfaces

Each strength of ORALAIR tablet formulation also contains the following non-medicinal ingredients: colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, magnesium stearate, mannitol and microcrystalline cellulose.

ORALAIR is supplied in individually sealed blister packages. Each blister (Alu/alu) is composed of a film (polyamide/aluminium/polyvinyl chloride) on one side and a heat-sealed foil (aluminium) coated with a varnish (vinyl) on the other side.

ORALAIR is available in the following presentations as a carton containing a leaflet and:

- Blister pack containing 3 sublingual tablets of 100 IR;
- Two blister packs each containing 3 sublingual tablets of 300 IR (6 tablets);
- One blister pack containing 30 sublingual tablets of 300 IR;
- Three blister packs each containing 30 sublingual tablets of 300 IR (90 tablets).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

The IR unit expresses the allergenicity of ORALAIR: An allergen extract is said to have a titer of 100 IR/ml if a prick-test performed using a Stallerpoint® in 30 subjects sensitized to that allergen produces a wheal of 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with codeine phosphate 9% or 10 mg/ml histamine dihydrochloride. **This unit is not comparable to the units used by other allergen manufacturers.**

Drug Substance

The drug substance is the grass pollen allergen extract (as sieved freeze dried)

Proper name: Grass pollen allergen extract

All pollens included in the 5 grass preparation are part of plants belonging to the *Poaceae* family and the *Pooideae* subfamily.

- Cocksfoot (*Dactylis glomerata* L.)
- Sweet vernal grass (*Anthoxanthum odoratum* L.)
- Rye grass (*Lolium perenne* L.)
- Meadow grass (*Poa pratensis* L.)
- Timothy (*Phleum pratense* L.)

Molecular formula and molecular mass: Allergens of *Poaceae* family have a molecular weight between 10,000 and 60,000 Daltons.

Physicochemical properties: The drug substance is the grass pollen allergen extract (sieved and freeze dried). It is in a solid state form freely soluble in water.

Product Characteristics

The drug substance is prepared by the extraction of the 5 grass pollens, which are then purified, freeze dried and sieved, before incorporation in the final dosage form. The characterization of the allergenic components includes identification of relevant allergens based on technique using sera from allergic patients.

CLINICAL TRIALS

The efficacy data of ORALAIR is based on pivotal efficacy and safety studies VO34.04 and VO53.06 in adult patients suffering from grass pollen rhinoconjunctivitis, as well as on the pivotal study VO52.06 in paediatric patients.

Study design of pivotal clinical trials

Adult and paediatric patients included in pivotal studies had shown grass pollen-related rhinoconjunctivitis for at least 2 years (the last 2 pollen seasons). Diagnosis was confirmed by a positive skin prick test (SPT), a positive radioallergosorbent (RAST) (≥Class 2) and a Retrospective Rhinoconjunctivitis Total Symptom Score (RRTSS) score ≥12.

Evidence to demonstrate the efficacy of ORALAIR in clinical pivotal trials was based on various efficacy endpoints, including the measure of RTSS and the Rescue Medication Score (RMS). The RTSS ranged from 0 to 18 and was calculated as the sum of the 6 individual symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes) as evaluated by the study subject and using 4-point descriptor scales (0 = absent symptoms; 1 =mild symptoms; 2 =moderate symptoms; 3 = severe symptoms). The RMS was assigned to the different products used as rescue medication as follows: 0 = no rescue medication taken; 1 = patient took anti-histamine (oral and/or eye drops); 2 = patient took nasal corticosteroid; 3 = patient took oral corticosteroid. If a patient took two or more categories of rescue medication on the same day, the rescue medication category with the higher score was to be used for the RMS.

In studies VO34.04 and VO53.06, the demographic characteristics were similar in adult patients and baseline characteristics were well-balanced between the treatment groups in both studies. The age of the patients ranged from 18 to 51 years. More male than female patients participated in the studies with similar proportions of males and females between each treatment groups. In the various groups of these studies, the proportion of patients having asthma ranged between 10% and 14.2%; while the majority of patients expressed poly-sensitization (i.e. between 54% and 60%).

In the paediatric study VO52.06, the age of the patients ranged from 5 to 17 years, with one patient aged 4 years old. There were more male (65.5%) than female (34.5%) patients in the study. Other demographic and baseline characteristics were similar between the treatment groups. There were 46 patients with asthma and the majority of patients (60%) expressed polysensitization to grass pollen.

For each study, the analysis set (intent-to-treat set, ITT) included all assessable patients i.e. those who received at least one dose of the investigational product and had at least one RTSS during one pollen period while on treatment (whatever the year in Study VO53.06).

Study VO53.06 (adults)

Study VO53.06 was a randomized, multicenter, double-blind, placebo-controlled, Phase III study conducted to evaluate the efficacy and safety of sublingual tablets of ORALAIR in patients with seasonal grass pollen-induced allergic rhinoconjunctivitis for at least the 2 previous pollen seasons. Patients were randomized to one of the following treatment groups: placebo, ORALAIR 300 IR administered 2 months (2M) or 4 months (4M) before pollen season and then administered ORALAIR during 3 consecutive pollen seasons.

A total of 633 patients were randomized in Year 1, with a total of 508 and 465 patients who maintained their participation in Years 2 and 3, respectively.

The Year 3 efficacy analysis was based on a total of 583 assessable patients (placebo, n=206; ORALAIR 300 IR (4M), n=189; ORALAIR 300 IR (2M), n=188). The following patients (n=50 or 8%) were not assessable and therefore excluded from the efficacy analysis: placebo, n=13 (6%); ORALAIR 300 IR (4M), n=18 (9%) ORALAIR 300 IR (2M), n=19 (9%).

Study VO34.04 (Adults)

Study VO34.04 was a multicenter, randomized, double-blind, placebo-controlled study conducted to assess efficacy and safety of ORALAIR. The study included 628 patients with seasonal allergic rhinitis and/or conjunctivitis caused by grass pollens, as confirmed by cutaneous tests and/or a positive titre of the IgE specific to the grass pollens.

A total of 628 patients were randomized to 4 groups: placebo (n=156), ORALAIR 100 IR/day (n=157), ORALAIR 300 IR/day (n=155) and ORALAIR 500 IR/day (n=160). Treatment included an initiation period during which a starting dose of 100 IR was progressively increased over a 5-day period until 500 IR using 100 IR increments up to the target dose level for each study group.

Each patient received a sublingual dose once a day for about 4 months before the start of the pollen season, and continuing throughout one pollen season. The efficacy analysis was based on 569 assessable patients (placebo, n=148; ORALAIR 100 IR, n=142; ORALAIR 300 IR, n=136; ORALAIR 500 IR, n=143). The following patients (n=59 or 9%) were not assessable and therefore excluded from the efficacy analysis: placebo, n=8 (5%); ORALAIR 100 IR, n=15 (10%); ORALAIR 300 IR, n=19 (12%), ORALAIR 500 IR, n=17 (11%).

Study VO52.06 (Paediatric Population)

Study VO52.06 was a multicenter, randomized, double-blind, placebo-controlled study conducted to assess the efficacy and safety of ORALAIR in the paediatric population. The study included 278 patients aged 5 to 17 years suffering from seasonal allergic rhinitis and/or rhinoconjunctivitis caused by grass pollens, as confirmed by cutaneous tests and a positive titre of the IgE specific to the grass pollens.

A total of 278 patients were randomized to 2 groups: placebo (n=139) or ORALAIR 300 IR/day (n= 139). Each patient received a sublingual dose once a day for about 4 months before the start of the pollen season, and continuing throughout one pollen season. An incremental dosing scheme was followed for the first 3 days of the treatment phase, where the dose was escalated by 100 IR per day from a starting dose of 100 IR up to daily dose of 300 IR. The efficacy analysis of the results was based on 266 assessable patients (placebo, n=135; ORALAIR 300 IR, n=131). The following patients (n=12 or 4%) were not assessable and therefore excluded from the efficacy analysis: placebo, n=4 (3%); ORALAIR 300 IR, n=8 (6%).

Efficacy results

Daily measurements of RTSS and RMS observed during the pollen period while on treatment were analyzed using a longitudinal linear mixed effects model.

Adult patients aged 18- 50 years: One season treatment duration (VO34.04)

Rhinitis Total Symptom Score (RTSS)

There was a statistically significant difference in RTSS compared to Placebo for the ORALAIR 300 IR group (p=0.0006).

Table 3: VO34.04 – Daily RTSS - Repeated measures (ITT)

				LS Mean difference vs. Placebo			Relative LS mean difference (%)	
Treatment	**n**	**LS Mean**	**SE**	**Point Estimate**	**[95% CI]**	**p-value**	**Point Estimate**	**[95% CI]**
500 IR	143	3.40	0.304	-1.12	[-1.79;-0.45]	0.0011	-24.8%	[-39.7%;-9.9%]
300 IR	136	3.31	0.307	-1.20	[-1.88;-0.52]	0.0006	-26.7%	[-41.7%;-11.6%]
100 IR	142	4.40	0.306	-0.11	[-0.79;0.56]	0.7379	-2.5%	[-17.4%;12.4%]
Placebo	148	4.52	0.306					

Covariates used in the linear mixed model: Asthma Status, Pooled Centre, Sensitization Status
Type I error=5%. The control of the Type I error rate using a step-down procedure has been applied.

Rescue Medication Score (RMS)

A relative LS mean difference of -29.5% was observed for RMS in the 300 IR group versus Placebo.

Table 4: VO34.04 – Daily RMS – Repeated measures (ITT)

Treatment	n	LS Mean	SE	LS Mean difference vs. Placebo	Relative LS mean difference (%)
500 IR	143	0.46	0.051	-0.09	-16.1%
300 IR (4M)	136	0.39	0.052	-0.16	-29.5%
100 IR	142	0.55	0.052	0.00	-0.5%
Placebo	148	0.55	0.052		

Covariates used in the linear mixed model: Asthma Status, Pooled Centre, Sensitization Status

Adult patients aged 18- 50 years: Multiple season treatment duration (VO53.06)

Rhinitis Total Symptom Score (RTSS)

The efficacy analysis based on the last available pollen period for each patient (at Year 1, Year 2 or Year 3) showed a statistically significant difference in RTSS compared to Placebo for the ORALAIR 300 IR (4M) group ($p<0.0001$).

Table 5: VO53.06 – Daily RTSS- Repeated measures (ITT)

				LS Mean difference vs. Placebo			Relative LS mean difference (%)	
Treatment	n	LS Mean	SE	Point Estimate	[95% CI]	p-value	Point Estimate	[95% CI]
300 IR (4M)	189	3.08	0.293	-1.25	[-1.81;-0.69]	<0.0001	-28.8%	[-41.8%;-15.9%]
300 IR (2M)	188	3.28	0.300	-1.05	[-1.62;-0.49]	0.0003	-24.4%	[-37.3%;-11.4%]
Placebo	206	4.33	0.287					

Covariates used in the linear mixed model: Age, Asthma Status, Pooled Centre, Sensitization Status, Gender
Type I error=5%. The control of the Type I error rate using a step-down procedure has been applied.

Rescue Medication Score (RMS)

The efficacy analysis based on the last available pollen period for each patient (at Year 1, Year 2 or Year 3) showed a relative LS mean difference of -28.4% was observed for RMS in the 300 IR (4M) group versus Placebo.

Table 6: VO53.06 – Daily RMS - Repeated measures (ITT)

Treatment	n	LS Mean	SE	LS Mean difference vs. Placebo	Relative LS mean difference (%)
300 IR (4M)	189	0.35	0.040	-0.14	-28.4%
300 IR (2M)	188	0.33	0.041	-0.15	-31.6%
Placebo	206	0.48	0.039		

Covariates used in the linear mixed model: Age, Asthma Status, Pooled Centre, Sensitization Status, Gender

Paediatric patients aged 5-17 years: One season treatment duration (VO52.06)

Rhinitis Total Symptom Score (RTSS)

There was a statistically significant difference in RTSS compared to Placebo for the ORALAIR 300 IR group (p=0.0002).

Table 7: VO52.06 – Daily RTSS - Repeated measures (ITT)

				LS Mean difference vs. Placebo			Relative LS mean difference (%)	
Treatment	n	LS Mean	SE	Point Estimate	[95% CI]	p-value	Point Estimate	[95% CI]
300 IR (4M)	131	2.44	0.275	-1.07	[-1.61;-0.52]	0.0002	-30.4%	[-46.0%;-14.7%]
Placebo	135	3.51	0.270					

Covariates used in the linear mixed model: Age, Asthma Status, Pooled Centre, Sensitization Status, Gender
Type I error=5%.

Rescue Medication Score (RMS)

A relative LS mean difference of -24.7% was observed for RMS in paediatric patients for the 300 IR group versus Placebo.

Table 8: VO52.06 – Daily RMS - Repeated measures (ITT)

Treatment	n	LS Mean	SE	LS Mean difference vs. Placebo	Relative LS mean difference (%)
300 IR	131	0.51	0.029	-0.17	-24.7%
Placebo	135	0.67	0.028		

Covariates used in the linear mixed model: Age, Asthma Status, Pooled Centre, Sensitization Status, Gender

DETAILED PHARMACOLOGY

Animal pharmacology

No animal studies were conducted to demonstrate the pharmacological and pharmacodynamic effects of the allergen extract included in ORALAIR. Actually, no animal model fully mimics the allergic rhinitis, because symptoms score applied in clinical trials are not applicable to animals and because no fully relevant biomarkers are available in humans.

No specific safety pharmacology studies were conducted because no or low tissue distribution of the extract is expected, and the grass pollen allergen extract has been used in medical practice for many years by sublingual route, without relevant safety concern which could lead to conduct a dedicated animal study.

Human Pharmacology

A randomized, double-blind, placebo-controlled study was conducted in an allergen exposition chamber to assess the effect and time course of sublingual immunotherapy administered in adults suffering from grass pollen rhinoconjunctivitis for at least 2 years.

A total of 89 adult out-patients (18 to 50 years of age) were randomized to receive 1 tablet of 300 IR allergen-based tablets or placebo once daily during a 4 months Treatment Phase. Allergen challenges were performed at screening and after 1 week and 1, 2, and 4 months of treatment. The allergen challenge to grass pollen took place in an allergen exposition chamber over a 2-hour period during the qualification session at baseline and a 4-hour period for the subsequent sessions.

The primary pharmacodynamic analysis of VO56.07A was to compare the Average Rhinoconjunctivitis Total Symptom Score (ARTSS) [0-4 hours] during the 4-hour allergen challenge at endpoint between subjects receiving active treatment and those receiving placebo. The (ARTSS) [0-4 hours] was calculated as the mean of the RTSSs at all timepoints (16 timepoints, from 15 minutes to 4 hours) during the allergen exposure in the allergen chamber at endpoint.

Study results showed that the ARTSS [0-4 hours] at endpoint was statistically lower in the ORALAIR group compared to the Placebo group with relative improvements of 29.3% for the mean and 33.3% for the median. The adjusted mean ARTSS [0-4 hours] at endpoint was lower in the ORALAIR group when compared to the Placebo group and the difference was statistically significant (p=0.0003). Similar results were observed at each visit.

TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity, local tolerance, embryofoetal and juvenile development.

Repeated dose toxicity

A repeat-dose toxicity study was conducted in Sprague Dawley rats treated daily by the oral route with grass pollen allergen extract for 26 weeks at the dose levels of 0, 155, 525 and 910 IR/kg/day. No compound-related death or premature euthanasia was observed during the study. No clinical sign related to the allergen extract was observed during the study. No effect of treatment was observed on body weight and food consumption. No relevant ophthalmological finding was observed in any group. No difference in haematological, blood chemistry and urinalysis parameter was observed between treated and control groups. At final euthanasia, none of the necropsy findings were considered to be compound-related and histopathogical examination did not reveal any abnormal finding in relation with treatment. Consequently, the NOEL (No Observed Effect Level) observed in this study was considered to be 910 IR/kg/day.

A 13-week repeat-dose tolerance study was also performed with grass pollen allergen extract in male and female hamsters. Hamsters were administered one tablet of grass pollen allergen extract in the cheek pouch on a daily basis at doses of 0, 100, 300 and 500 IR/animal. There was no effect on body weight and clinical condition, and no change in haematological, blood chemical and urinary parameters related to the administration of allergen extract.

Both above mentioned studies were conducted at high doses when compared to the proposed clinical dose (300 IR, corresponding to 5 IR/kg on the basis of an adult body weight of 60 kg).

Local Tolerance

In a 14-day study, Syrian hamsters were administered one tablet of grass pollen allergen extract in the cheek pouch on a daily basis at doses of 0, 100, 300 or 500 IR/animal. There was no macroscopic finding of local irritation in the cheek pouch at the end of the treatment period.

In the pivotal 13-week repeat-dose toxicity study described above, no histopathological findings related to the allergen extract, in particular in the cheek pouch, were noted in control and high dosed animals when allergen extracts were administered in the cheek pouch of male and female hamsters at doses up to 500 IR.

Reproduction Toxicity

Fertility and early embryonic development

No specific fertility study was conducted with the grass pollen allergen extract. Nevertheless, the 26-week rat and 13-week hamster studies allowed the evaluation of the potential effect on fertility. The 13-week and 26-week duration of the toxicology studies corresponds to more than one and 3 full sequences of man spermatogenesis (63 days/sequence), respectively. The histopathological examination of the animals following the repeat-dose studies revealed no relevant findings on reproductive organs. Therefore, there is no cause for concern with regard to fertility with grass pollen allergen extract.

Embryofoetal development

Embryofoetal development toxicity studies were conducted in rats and rabbits by oral route (gavage) with grass pollen allergen extract.

Mated female Sprague-Dawley rats were administered the freeze dried extract of grass pollen allergens on a daily basis from Day 6 to Day 17 of gestation at doses of 0, <10, 185 and 795 IR/kg/day. There was no unscheduled death or compound-related clinical sign during the study. There was no effect of treatment with the allergen extract on maternal body weight or food consumption. The mean numbers of corpora lutea, implantation sites and foetuses observed in the treatment groups were comparable to the control animals at all dose levels. There was no effect on foetal body weight or sex and no compound-related external, soft tissue or skeletal malformation or variation. Based on this study, the maternal and foetal NOEL (No Observed Effect Level) in the rats was considered to be 1000 IR/kg/day.

Mated female New Zealand White rabbits were administered the grass pollen allergen extract on a daily basis from Day 6 to Day 18 of gestation at doses of 0, 66, 210 and 885 IR/kg/day. There was no unscheduled death during the study and no adverse clinical sign was noted in dams. There was no compound-related effect on maternal body weight or food consumption and no compound-related macroscopic finding. The number of implantation sites and foetuses was unaffected by treatment, as well as foetal body weight and sex ratio. Foetal malformations

(gastroschisis, omphalocele and absent gonads) were observed at very low incidences (one foetus) and therefore a relationship to treatment was considered unlikely. In the high-dose group, there was a slight increase in the number of foetuses with incomplete ossification of the 1st to 4th sternebrae and unossified 5th sternebra. This finding was not considered as being clinically significant. Based on this study, the maternal and foetal NOAELs (No Observed Adverse Effect Level) were considered to be 1000 IR/kg/day.

Juvenile animals

Male and female juvenile rats were treated with the grass pollen allergen extract daily for 10 weeks at doses of 0, 326, 636 and 1356 IR/kg/day. There was no compound-related death or clinical sign and no effect of treatment on body weight or food consumption. Tests of pre- and post-weaning development [tibia growth, physical development, motor activity and learning and memory (water T-maze), reproductive development] indicated no effects of the allergen extract. No adverse change was noted at laboratory investigations. The animals in the treatment groups did no show difference from the control group for mating, fertility and hysterectomy parameters at any dose-level. The NOAEL was thus considered to be 1500 IR/kg/day.

This study was conducted at high doses when compared to the proposed clinical dose (300 IR, corresponding to 15 IR/kg on the basis of a paediatric body weight of 20 kg).

Prenatal and postnatal development

No pre- and postnatal development study was conducted and deemed necessary based on the results of repeat-dose, embryofoetal development and juvenile studies, showing no toxicity at doses up to 910, 795, 885 and 1356 IR/kg/day administered in adult rats, in pregnant rats, in pregnant rabbits and in juvenile rats, respectively.

Genotoxicity and Carcinogenicity

***In vitro* genotoxicity studies**

A mammalian *in vitro* test conducted with the 5 grasses pollen extract showed no mutagenic effect of the extract at the limit concentration of 5000 µg/mL, corresponding to 3653 IR/mL.

Bacterial tests were performed using 5 strains of Salmonella typhimurium (TA 98, TA 100, TA 102, TA 1535 and TA 1537) with 5 grasses pollen extracts. In all studies, the bacterial tests conducted showed no mutagenic effect of the 5 grasses pollen extract at the limit concentration of 5000 µg/plate, corresponding to at least 3406 IR/plate.

In vivo genotoxicity studies

A micronucleus test was conducted on rats at 500, 1000 and 2000 mg/kg/day with the total freeze dried 5 grasses pollen extract (corresponding to 116 300, 232 600 and 465 200 IR/kg, respectively) and showed no clastogenic or aneugenic activity of the extract.

Moreover, an *in vivo* unscheduled DNA synthesis (UDS) assay was performed using rat hepatocytes after administration of total freeze dried extract of 5 grasses pollen at doses of 1000 and 2000 mg/kg (corresponding 232 600 and 465 200 IR/kg, respectively). No increases in primary DNA damage were noted.

Carcinogenicity studies

No carcinogenicity studies were conducted with the grass pollen allergen extract.

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PART III: CONSUMER INFORMATION

[Pr] ORALAIR

Sublingual Tablets of Grass Pollen Allergen Extract

This leaflet is part III of a three-part "Product Monograph" published when ORALAIR™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ORALAIR. Contact your physician or pharmacist if you have any questions about the drug.

Keep this leaflet; you may need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:

ORALAIR is used for the treatment of patients with a history of allergy to a specific grass pollen. Grass pollen allergy is characterised by rhinitis (sneezing, runny or itchy nose, nasal congestion) with or without conjunctivitis (itchy and watery eyes).

Before the treatment, your allergy will be confirmed by a physician with adequate training and experience in allergic diseases, who will perform appropriate skin and/or blood tests.

There is no experience with ORALAIR in children younger than 5 years and in patients over 50 years of age.

What it does:

ORALAIR reduces symptoms associated with exposure to specific grass allergens. It contains an allergen extract that helps to make you less sensitive to the grass pollens you are allergic to.

When it should not be used:

Do not use ORALAIR if:

- you are allergic (hypersensitive) to any of the other ingredients of ORALAIR (see **What the nonmedicinal ingredients are**);
- you are taking beta-blockers and ACE inhibitors (medicines prescribed for heart conditions and cardiovascular diseases, for example high blood pressure);
- you suffer from severe and/or unstable asthma;
- your immune system is very weakened or if you suffer from a disease that attacks your own immune system;
- you suffer from a malignant disease (for example cancer);
- you have any inflammation in your mouth

What the medicinal ingredient is:

Grass pollen allergen extract from: Cocksfoot (*Dactylis glomerata* L.), Sweet vernal grass (*Anthoxanthum odoratum* L.), Rye grass (*Lolium perenne* L.), Meadow grass (*Poa pratensis* L.) and Timothy (*Phleum pratense* L.).

What the nonmedicinal ingredients are:

Colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, magnesium stearate, mannitol and microcrystalline cellulose.

What dosage forms it comes in:

ORALAIR sublingual tablets are available in two strengths, each containing either 100 IR or 300 IR of grass pollen allergen extract. The IR (index of reactivity) expresses the potency (strength) of the tablets.

ORALAIR (100 IR and 300 IR) is supplied in blister cards, divided into blister units that contain individual tablets. The tablets of 100 IR are white to beige, engraved "100" on both surfaces. The tablets of 300 IR are white to beige, engraved "300" on both surfaces.

ORALAIR is supplied in blisters of 3 sublingual tablets of 100 IR, blisters of 3 sublingual tablets of 300 IR (cartons with 6 tablets) and blisters of 30 sublingual tablets of 300 IR (cartons with 30 or 90 tablets).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- ORALAIR is intended for use only by physicians with adequate training and experienced in the treatment of allergic diseases. With prescription for children, the doctor should also have the relevant experience.
- The first tablet of ORALAIR must be taken at the physician's office; your physician will also ask you to stay on site for 30 minutes to monitor and discuss possible side effects to the treatment you may have.
- The administration of ORALAIR to children must be supervised by an adult for at least 30 minutes after each dose.
- Because ORALAIR contains grass pollen extracts, you may therefore expect mild to moderate local allergic reactions (such as swelling of the mouth or a discomfort feeling in the mouth) during treatment. Your physician will explain to you the type of reactions you may experience and what to do about it.
- If you experience, stronger allergic reactions with a feeling of swelling in the throat, difficulty swallowing or breathing and voice changes, contact your physician immediately. The treatment has to be stopped immediately until your physician advises otherwise.

BEFORE you use ORALAIR talk to your physician or pharmacist if:

- You have intolerance to some sugars or severe allergies to milk as ORALAIR contains lactose.

- You have to undergo surgery in the mouth or if you are having a tooth pulled. You should stop the treatment with ORALAIR for 7 days to allow your oral cavity to heal. Thereafter, restart the treatment with the previous dosage. If you stopped the treatment for more than 7 days, please ask your physician how you should restart the treatment.
- You have any history of eosinophilic esophagitis, symptoms of which can include: severe or persistent upper abdominal pain, swallowing difficulties or chest pain.
- **You are pregnant or planning to become pregnant.** At present there is no experience for the use of ORALAIR during pregnancy. Therefore, you should not start an immunotherapy if you are pregnant. If you become pregnant, speak to your physician about whether it is appropriate for you to continue the treatment.
- **You are breast feeding.** There is no experience for the use of ORALAIR during breast-feeding as well. No effects on infants who are breast-fed during the treatment are anticipated. However, you should not start an immunotherapy if you are breast-feeding. If you wish to breastfeed while on treatment, speak to your physician about whether it is appropriate for you to continue the treatment.

No effect on the capacity to drive or operate machinery has been observed with ORALAIR.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Your doctor will tell you if it is safe to take other medicines while you are using ORALAIR.

PROPER USE OF THIS MEDICATION

Always take ORALAIR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

You must take the first tablet under medical supervision at your physician's office. Your physician will also ask you to stay on site for 30 minutes to monitor and discuss possible side effects to the treatment you may have.

It is recommended to take ORALAIR in the morning, in an empty mouth.

The administration of ORALAIR to children must be supervised by an adult for at least 30 minutes after each dose.

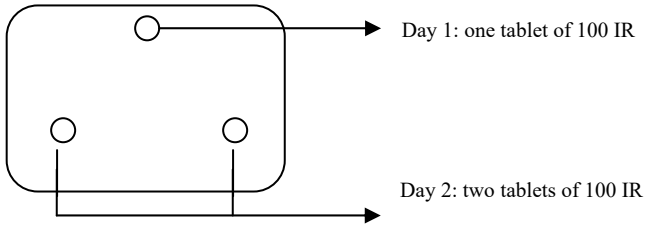
Usual dose:

Adults and children above the age of 5

The therapy is done as follows:

- the dose is increased over the first 3 days of treatment from 100 IR to 300 IR;
- the treatment is then continued with an ORALAIR dose of 300 IR per day.

When you begin the treatment with ORALAIR, use the small blister which contains 3 tablets of 100 IR during the first 2 days of treatment:



Starting on Day 3 and onwards, take 1 tablet of 300 IR once a day until the end of the treatment duration.

Method of administration

Keep the tablet (or the 2 tablets on day 2) under your tongue until complete dissolution. Swallow the tablet after about 1 minute.

Duration of treatment

Start your ORALAIR treatment on the day determined by your physician. The treatment starts about 4 months before the first expected appearance of the pollen and continues until the end of the pollen season.

General information about the safe and effective use of ORALAIR

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

It is recommended to wash your hands after taking ORALAIR to prevent inadvertent spreading.

If necessary, your physician may at the same time prescribe medications to treat the possible allergic reactions.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you take more ORALAIR than you should, you may experience allergic symptoms including local symptoms from mouth and throat. If you experience severe symptoms, immediately contact your physician.

Missed Dose:

If you miss one dose of ORALAIR, skip the missed dose and continue with the next scheduled dose. Do not take a double dose to make up for forgotten dose.

If you stop taking ORALAIR

If you stop taking ORALAIR, you may not have an effect of the treatment.

If you interrupt the treatment with ORALAIR during the continuation phase for less than one week, you can take up treatment where you left off. If you stopped the treatment for more than 7 days, please ask your physician how you should restart the treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ORALAIR can cause side effects, although not everybody gets them.

During treatment with ORALAIR, you will be exposed to substances that may cause local allergic reactions and/or allergic reactions that could affect your whole body. You may therefore expect mild to moderate local allergic reactions (such as swelling of the mouth or a discomfort feeling in the mouth) during this time. About half or fifty percent (50%) of those reactions occur during the first three days of treatment. The reactions are temporary and will go down.

Significant side effects or symptoms you should look out for, and measures to be taken if you are affected:

Uncommonly, stronger allergic reactions can occur, with a feeling of swelling in the throat, difficulty swallowing or breathing and voice changes.

In these cases please contact your physician immediately. The treatment has to be stopped immediately until your physician advises otherwise.

During treatment, if you have severe or persistent upper abdominal pain, swallowing difficulties or chest pain, please contact your doctor who may reconsider your treatment.

Other possible side effects

The following side effects were reported by adults who were treated with ORALAIR in a clinical study:

Very common (seen in at least 1 in 10 patients):
Itching in the mouth and/or eyes and/or ears, irritation of the throat, runny nose, blocked nose, sneezing, cough.

Common (seen in at least 1 in 100 patients, but in less than 1 in 10 patients):
Headache, general feeling of tingling or numbness, watery eyes, swelling and/or irritation inside the nose, shortness of breath, swelling in the mouth and/or throat and/or lips, dry throat, inflammation and/or burning of the tongue and/or mouth, swollen tongue, blisters in the mouth, mouth tingling, numbness and/or pain, dry mouth, facial swelling, itching, nettle-rash, tiredness, foreign body sensation in the mouth, stomach pain, feeling sick, indigestion, diarrhoea, throat swelling and/or tightness, pain in the throat and voice box area, gullet pain, difficulty in swallowing, acid stomach, chest discomfort, anxiety, mouth and/or tooth pain, altered voice, vomiting, nausea.

Uncommon (seen in at least 1 in 1,000 patients, but in less than 1 in 100 patients):
Abnormal sense of taste, itching and/or swelling of the eyelids, dizziness, irritation of the voice box, dry nose, diarrhoea, inflammation of the mouth, overproduction of saliva, belching, tongue blistering, problems with the tongue, lip blister, local swelling, swelling of the ankles, feet or fingers, allergic reaction, fatigue, thirst, noises in the ear, dry eyes.

The following side effects were reported by children and adolescents who were treated with ORALAIR in a clinical study:

Very common (seen in at least 1 in 10 patients):
Itching in the mouth, collection of fluid in the mouth tissue, cough.

Common (seen in at least 1 in 100 patients, but in less than 1 in 10 patients):
Itchy eyes, itching in the ears, irritation of the throat, blocked nose, asthma, sneezing, uncomfortable feeling in the nose, shortness of breath, irritation of the voice box, throat tightness, swollen lips, swollen tongue, formation of blisters in the mouth, inflammation of the mouth, vomiting, dry and/or cracked lips, inflammation of the tongue and/or lips, uncomfortable feeling in the mouth, allergic inflammation of the skin, itching, chest discomfort, headache, runny nose, voice alteration, stomach pain, painful swallowing, inflammation of the nose, throat and/or tonsils, bronchitis, influenza, shortness of breath, rash, watery eyes, abdominal pain, diarrhoea, nausea, dizziness, nose bleeding.

Uncommon (seen in at least 1 in 1,000 patients, but in less than 1 in 100 patients):
A feeling that the ear is blocked, uncomfortable feeling in the ear, swelling of the voice box and the throat, feeling sick, indigestion, difficult swallowing, reduced sensitivity in the mouth, pain in the mouth, swelling of the tongue and/or mouth, inflammation of the skin, growing pains, weakness, chest pain, allergic reaction.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your physician or pharmacist		Call your physician immediately and stop taking drug
		Only if severe	In all cases	
Uncommon	Stronger allergic reactions with a feeling of swelling in the throat, difficulty swallowing or breathing or voice changes.			√
Common	Swelling and/or irritation inside the nose, swelling in the mouth and/or throat, blocked and/or runny nose, facial swelling, itching.	√		
	Shortness of breath.			√
	Dry throat, sneezing, inflammation and/or burning of the tongue, swollen tongue, blisters in the mouth, mouth tingling.	√		
Rare	Severe allergic reactions and asthma	**Seek emergency medical care immediately**		

This is not a complete list of side effects. For any unexpected effects while taking ORALAIR, contact your physician or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store at room temperature (15°C to 30°C). Store in the original package in order to protect from moisture. The tablet should remain in the sealed blister until use.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about ORALAIR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp).

This full document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Stallergenes Canada Inc. at ca.medicalinformation@stallergenes.com

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