Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oralair 100IR & 300IR sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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.) .....100 IR* or 300 IR* per sublingual tablet.

* IR (Index of Reactivity): The unit IR has been defined to measure the allergenicity of an allergen extract. The allergen extract contains 100 IR/ml when, on a skin prick-test using a Stallerpoint®, it induces a wheal diameter of 7 mm in 30 patients sensitized to this allergen, (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive skin prick-test to either 9% codeine phosphate or 10 mg/ml histamine dihydrochloride. The IR unit of Stallergenes is not comparable to the units used by other allergen manufacturers.

Excipient with known effect:

One sublingual tablet of 100 IR contains 83.1 – 83.6 mg of lactose monohydrate.
One sublingual tablet of 300 IR contains 81.7 – 83.2 mg of lactose monohydrate.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet

The tablets of 100 IR are slightly speckled white to beige, engraved "100" on both surfaces.
The tablets of 300 IR are slightly speckled white to beige, engraved "300" on both surfaces.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to one of the grass pollen from the Pooideae grass homologous group[1].

[1] *Pooideae (temperate) grass homologous group: Phleum pratense (Timothy grass), Anthoxanthum odoratum (Sweet vernal grass), Avena sativa (Oat), Dactylis glomerata (Orchard grass/Cocksfoot), Festuca spp. (Meadow fescue), Holcus lanatus (Velvet grass/Yorkshire fog), Hordeum vulgare (Barley), Lolium perenne (Perennial ryegrass), Poa pratensis (Kentucky bluegrass), Secale cereale (Cultivated rye), Triticum aestivum (Cultivated wheat).*

4.2 Posology and method of administration

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.

The first tablet of ORALAIR should be taken under medical supervision and the patient should be monitored for 30 minutes.

Posology
The treatment is composed of an initiation phase (including a 3-day dose escalation) and a maintenance phase.

Initiation treatment

The dose of ORALAIR should be increased over a three-day period to reach the maintenance dose, according to the following scheme:

Day 1	1 tablet of 100 IR
Day 2	2 tablets of 100 IR simultaneously
Day 3	1 tablet of 300 IR

The dose-escalation period could be prolonged, when considered necessary by the physician according to the patient's condition.

Maintenance treatment
The dose for adults, adolescents and children is 300 IR daily.

The maintenance treatment should be continued with one ORALAIR 300 IR sublingual tablet per day until the end of the pollen season.

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

Treatment duration

International treatment guidelines refer to a treatment period of a minimum of 3 years for allergen immunotherapy (AIT) to achieve long-term efficacy after treatment discontinuation.

If no relevant improvement of symptoms is obtained during the first pollen season, there is no indication for continuing the treatment.

In general, if treatment is interrupted for less than 7 days, it is to be continued. Should the interruption period be longer than 7 days, it is recommended to continue the treatment under medical supervision.

Special populations

Clinical experience on immunotherapy with ORALAIR in patients older than 65 years is lacking.

Paediatric population

The safety and efficacy of ORALAIR in children below the age of 5 years have not been established.
No data on treatment with ORALAIR in children beyond one grass pollen season are available.

The posology to be used in adolescents and children from 5 years onwards is the same as in adults.

Method of administration

Tablets should be placed under the tongue until complete dissolution (at least 1 minute) and then swallowed.
It is recommended to take the tablets during the day, in an empty mouth. Food and beverage should not be taken for the following 5 minutes.

4.3 Contraindications

- Hypersensitivity to any of the excipients listed in Section 6.1;
- Severe uncontrolled or unstable asthma (FEV1 < 80% of predicted value) or severe exacerbation of asthma within the previous 3 months;
- Patients with active or poorly controlled autoimmune disease, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance;
- Severe oral inflammations (such as oral lichen planus, oral ulcerations or oral mycosis);
- Initiation of allergen immunotherapy treatment during pregnancy is contra-indicated (See Section 4.6).

4.4 Special warnings and precautions for use

Severe allergic reactions

As with any allergen immunotherapy, severe allergic reactions including severe laryngopharyngeal disorder or systemic allergic reactions (i.e., acute onset of an illness with involvement of the skin, mucosal tissue, or both, respiratory compromise, persistent gastrointestinal symptoms, or reduced blood pressure and/or associated symptoms) can occur. Inform patients of the associated signs and symptoms and have them seek immediate medical care and discontinue therapy should these occur. Treatment should only be resumed at the instruction of a physician.

Previous systemic allergic reaction to allergen immunotherapy

Initiation of ORALAIR in patients who have previously had a systemic allergic reaction to previous allergen immunotherapy should be carefully considered, and measures to treat potential reactions should be available.

Asthma

Asthma is a known risk factor for severe systemic allergic reactions. The asthma status should be carefully evaluated before starting therapy (See Section 4.3).

Patients with associated asthma should be controlled at the initiation and during all the duration of ORALAIR treatment. Abrupt discontinuation of asthma controller medication after initiation of ORALAIR treatment is not recommended.

Patients with concomitant asthma should be informed of the need to seek medical attention immediately if their asthma deteriorates suddenly.

In patients with asthma experiencing an acute respiratory tract infection, initiation of ORALAIR treatment should be postponed until the infection has resolved.

Cardiovascular diseases

Patients with cardiovascular disease may be at increased risk in case of systemic allergic reactions. This should be taken into consideration prior to initiating ORALAIR.

Beta-adrenergic blockers

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

MAOIs, tricyclic antidepressants and COMT inhibitors

Allergen immunotherapy in patients treated with monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants or catechol-O-methyltransferase (COMT) inhibitors should be considered carefully as these treatments could potentiate the effect of adrenaline.

Mild to moderate local allergic reactions

The treatment consists of exposure to allergens to which the patient is allergic. Therefore, mild or moderate local allergic reactions in the oropharyngeal area (e.g., oral pruritus, throat irritation, ear pruritus) may be expected. If the patient experiences significant application site reactions, symptomatic treatment (e.g., antihistamines) may be considered.

Oral lesions

In case of oral surgery, including dental extraction, initiation of ORALAIR should be postponed and ongoing treatment should be interrupted until complete healing of the oral cavity.

Eosinophilic oesophagitis

Eosinophilic oesophagitis has been reported in association with ORALAIR. During treatment with ORALAIR, if severe or persistent gastro-oesophageal 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.

Autoimmune diseases in remission

In patients with autoimmune disease in remission, ORALAIR should be prescribed with caution.

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies have been performed.
No interactions were reported in clinical trials with ORALAIR, during which patients were able to take medications to treat allergic symptoms (antihistamines, steroids).

There are no data available on possible risks of simultaneous immunotherapy with other allergens during treatment with ORALAIR.

Concomitant therapy with symptomatic anti-allergic medications or anti-IgE medications e.g. omalizumab may increase the tolerance level of the patient to immunotherapy. This should be considered at discontinuation of such medications.

Clinical experience in relation to simultaneous vaccination and treatment with ORALAIR is missing. Vaccination may be given without interrupting treatment with ORALAIR after medical evaluation of the general condition of the patient.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no clinical data from the use of ORALAIR in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (See Section 5.3).
Treatment with ORALAIR should not be initiated during pregnancy (See Section 4.3) due to potential risk of serious systemic allergic reactions (anaphylactic reactions).
If pregnancy occurs during treatment, the use of ORALAIR may continue, if necessary, but with close supervision.

Breastfeeding
It is unknown whether 5 grass pollen allergen extract is excreted in milk.
As a precautionary measure, it is preferable to avoid initiating allergen immunotherapy during breast-feeding.
However, since the systemic exposure of a breast-feeding woman to ORALAIR active substance is negligible, use of ORALAIR may be considered during breast-feeding taking into account the benefit of therapy for the woman and the benefit of breast-feeding for the child.

Fertility
There are no fertility data available in humans.
No animal fertility studies were conducted with ORALAIR active substance. However, histopathological examination of the male and female reproductive organs revealed no adverse findings in repeat-dose toxicity studies with 5 grass pollen allergen extract.

4.7 Effects on ability to drive and use machines

ORALAIR has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
During treatment with Oralair, patients are exposed to allergens that may cause application site reactions and/or systemic allergic symptoms.
Application site reactions (e.g. oral pruritus and throat irritation) may therefore be expected during the period of therapy.
If a patient experiences an application site reaction, symptomatic treatment (e.g. with antihistamines) may be considered.

Tabulated list of adverse reactions
During clinical trials, a total of 1038 adults and 154 paediatrics patients with grass pollen-associated allergic rhinoconjunctivitis were treated with ORALAIR 300 IR once daily in placebo-controlled clinical trials. The undesirable effects reported in these patients are summarized in the table below.
The majority of adverse reactions leading to premature study withdrawal were consistent with application site reactions. These were of mild or moderate severity and were non-serious.

Tabulated summary of adverse drug reactions by body system, frequency [Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥1/10,000, <1/1,000)]. Within each frequency category, adverse drug reactions are

presented by decreasing seriousness. Adverse drug reactions reported during post-marketing surveillance are presented in the table below with a frequency "not known".

System Organ Class / Frequency / Adverse Drug Reactions		
Infections and infestations		
	Common	Nasopharyngitis, rhinitis
	Uncommon	Oral herpes, otitis
Blood and lymphatic system disorders		
	Uncommon	Lymphadenopathy
Immune system disorders		
	Uncommon	Hypersensitivity, oral allergy syndrome
	Not known	Anaphylactic reaction
Psychiatric disorders		
	Uncommon	Depression
Nervous system disorders		
	Very common	Headache
	Uncommon	Dizziness, dysgeusia, somnolence
	Rare	Anxiety
Eye disorders		
	Common	Conjunctivitis, eye pruritus, lacrimation increased
	Uncommon	Eye oedema, ocular hyperaemia, dry eye
Ear and labyrinth disorders		
	Common	Ear pruritus
	Uncommon	Ear discomfort
Vascular disorders		
	Rare	Flushing
Respiratory, thoracic and mediastinal disorders		
	Very common	Throat irritation
	Common	Pharyngeal oedema, asthma, dyspnoea, cough, dysphonia, rhinitis allergic (nasal congestion, sneezing, rhinorrhea, nasal discomfort), sinus congestion
	Uncommon	Laryngeal oedema, wheezing, throat tightness, pharyngeal hypoesthesia
Gastrointestinal disorders		
	Very common	Oral pruritus
	Common	Oedema mouth, tongue oedema, lip oedema, oropharyngeal blistering, stomatitis, diarrhoea, vomiting, abdominal pain, dyspepsia, dysphagia, nausea, glossodynia, hypoaesthesia oral, paraesthesia oral, oropharyngeal pain, oropharyngeal discomfort, oral discomfort, tongue pruritus, lip pruritus, dry mouth, dry throat
	Uncommon	Palatal oedema, gastritis, gastro-oesophageal reflux, mouth ulceration, oesophageal pain, oral pain, cheilitis, eructation, gingivitis, glossitis, odynophagia, oral disorder, salivary gland enlargement, salivary hypersecretion, tongue disorder

	Not known	Eosinophilic oesophagitis
Skin and subcutaneous tissue disorders		
	Common	Urticaria, atopic dermatitis, pruritus
	Uncommon Rare	Angioedema, rash, acne Face oedema
General disorders and administration site conditions		
	Common	Chest discomfort
	Uncommon	Lump feeling in throat, asthenia, influenza like illness
Investigations		
	Rare	Eosinophil count increased
Injury, poisoning and procedural complications		
	Uncommon	Excoriation

Compared to adverse reactions reported during the first treatment period, fewer types and lower frequencies of adverse reactions were reported during the second and third treatment periods by adults who were treated with ORALAIR during three consecutive grass pollen seasons in a clinical study.

Description of selected adverse reactions
During treatment with ORALAIR, patients are exposed to allergens that may cause application site reactions and/or systemic allergic symptoms.

Application site reactions (e.g. oral pruritus and throat irritation) may therefore be expected during the period of therapy. If a patient experiences an application site reaction, symptomatic treatment (e.g. with antihistamines) may be considered.

As with any allergen immunotherapy, allergic reactions including severe laryngo-pharyngeal reactions or anaphylactic reactions (i.e., acute onset of an illness with involvement of the skin, mucosal tissue, or both, respiratory compromise, persistent gastrointestinal symptoms, or reduced blood pressure and/or associated symptoms) can occur. Inform patients of the associated signs and symptoms and have them seek immediate medical care and discontinue therapy should these occur. Treatment should only be resumed at the instruction of a physician.

Paediatric population
Overall, the safety profile in the paediatric population is similar to that of adults. The following reactions listed in the tabulated summary were reported at a higher incidence in the paediatric population than in adults: cough, nasopharyngitis, mouth oedema (very common), oral allergy syndrome, cheilitis, glossitis, lump feeling in throat, ear discomfort (common).

In addition to the tabulated summary, the following reactions were reported in children and adolescents who received ORALAIR: tonsillitis, bronchitis (common), chest pain (uncommon).

Post-marketing

The following adverse reactions have been reported during post-marketing surveillance in adults, adolescents and children: asthma exacerbation, systemic allergic reaction, eosinophilic oesophagitis.
The frequency of these reactions to treatment with ORALAIR is not known.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extracts, grass pollen,
ATC code: V01AA02

Mechanism of actionand pharmacodynamic effects
ORALAIR is used for treatment of patients with specific IgE-mediated allergy symptoms of allergic rhinitis with or without conjunctivitis caused by grass pollen.

The immune system is the target for the pharmacodynamic effect. The aim is to induce an immune response against the allergen with which the patient is treated. The complete and exact mechanism of action regarding clinical effect of specific immunotherapy is not fully understood and documented. Treatment with ORALAIR has shown to induce a systemic competitive antibody response towards grass and induces an increase in specific IgG. The clinical relevance of these findings has not been established.

Clinical efficacy and safety
Study VO34.04
A European, multicentre, multinational, randomised, double-blind, placebo-controlled study was conducted. The study included 628 adults with seasonal allergic rhinitis and/or rhinoconjunctivitis caused by grass pollens, as confirmed by cutaneous tests and/or a positive titre of the IgE specific to the grass pollens.

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).

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. Analysis of the results 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 efficacy was determined according to the Rhinoconjunctivitis Total Symptom Score RTSS (see details below) during this one pollen season.

Results of this study showed a comparable efficacy of 500 and 300 IR, with safety data in favour of 300 IR, leading to a recommended dose of 300 IR per day.

The efficacy of the 300 IR group versus the placebo group (number of subjects included in the Intent to Treat (ITT) population were 136 and 148, respectively) showed the following results:

VO34.04 study efficacy results (during one pollen season)

Primary endpoint

VO34.04 study	**ORALAIR 300 IR Mean (SD)** *Median*	**Placebo Mean (SD)** *Median*	**Absolute Adjusted Diff Mean [CI 95%]**	**Relative Mean Diff.* %**	**p-value****
Rhinoconjunctivitis symptom score [A]	3.58 (2.98) *2.91*	4.93 (3.23) *4.62*	-1.39 [-2.09; -0.69]	27.3%	0.0001

*Relative Mean Difference: Absolute Difference / Placebo
** p-value ANCOVA

[A] Symptom Score: Average daily total rhinoconjunctivitis symptom scores for each patient during the grass pollen season. Rhinoconjunctivitis symptoms included sneezing, runny nose, itchy nose, nasal congestion, watery eyes and itchy eyes (0-18 range of score,the upper value of 18 indicates permanent very severe level in all six symptoms).

Secondary endpoints

VO34.04 study	**ORALAIR 300 IR Mean (SD)** *Median*	**Placebo Mean (SD)** *Median*	**Absolute Adjusted Diff Mean [CI 95%]**	**Relative Mean Diff.* %**	**p-value****
Rescue Medication use [B]	19.7% (24.8) *10.6%*	27.9% (29.3) *19.7%*	-	-	-
Quality of life score [C]	1.08 (0.96) *0.89*	1.37 (1.01) *1.20*	-0.25 [-0.47; -0.04]	21.1%	=0.0199

*Relative Mean Difference: Absolute Difference / Placebo

** p-value ANCOVA

[B] Rescue medication use: Percentage of days per patient with at least one rescue medication intake, p-value 0.0194 NS (Wilcoxon).

[C] Quality of life was assessed at the peak of the pollen season by the Rhinoconjunctivitis Quality of Life Questionnaire RQLQ (0-7 range of score,a higher score is reflecting a worse quality of life range).

Global evaluation of the efficacy of the treatment by the patient: 119/136 patients (88%) in the ORALAIR 300 IR group and 108/148 patients (73%) in the placebo group noted slight to moderate or good to excellent improvement relative to their recollection of the previous pollen season.

The ANCOVA results on each of the six individual mean symptom scores ranging from 0 to 3 showed a difference in favour of the 300 IR tablet as compared to placebo for sneezing (-0.19), runny nose (-0.23), itchy nose (-0.23), nasal congestion (-0.28), itchy eyes (-0.24) and watery eyes (-0.21).

The proportion of patients not using rescue medication were 35.3% in the 300 IR group and 27.0% in the placebo group (NS).

Post-hoc endpoints (performed after unblinding):

VO34.04 study	**ORALAIR 300 IR Mean (SD)** *Median*	**Placebo Mean (SD)** *Median*	**Absolute Adjusted Diff Mean [CI 95%]**	**Relative Mean Diff.* %**	**p-value**
Average Adjusted Symptom Score [D]	4.17 (3.39) *3.57*	5.88 (3.82) *5.26*	-1.84 [-2.66; -1.02]	29.1%	<0.0001**
Average Rescue Medication Score [E]	0.31 (0.43) *0.16*	0.48 (0.53) *0.31*	-0.17 [-0.29; -0.05]	35.0%	0.0047**
$PSCD_{2-0}$ [F]	43.5% (33.8) *38.6*	28.7% (30.7) *17.1*	-	-	0.0001***
PSFD [G]	25.3% (30.2) *10.9*	14.9% (23.6) *0.0*	-	-	0.0006***

*Relative Mean Difference: Absolute Difference / Placebo

** p-value ANCOVA/*** p-value Wilcoxon

[D] Average Adjusted Symptom Score (AASS): Average symptom scores adjusted for rescue medication use (for each patient, using daily symptom scores and daily rescue medication use).

[E] Average Rescue Medication Score: Average daily rescue medication score for each patient during the grass pollen season. Medications used were scored as follows: no rescue medication = 0, antihistamines (oral and/or ocular) = 1, nasal corticosteroids = 2 and oral corticosteroids = 3.

[F] Percentage of Symptom Controlled Days ($PSCD_{2-0}$): Percentage of days with a symptom score not higher than 2 and without rescue medication.

[G] Proportion of Symptom and rescue medication–Free days (PSFD): Percentage of days without symptoms and without intake of rescue medication.

Sixty-one patients (45%) in the 300 IR group had presented more than 50% Symptom Controlled Days (with a symptom score not higher than 2 and without rescue medication) over the grass pollen season, versus 40 patients (27%) in Placebo group.

<u>Paediatric population</u>

Study VO52.06

A European, multicentre, multinational, randomised, double-blind, placebo-controlled study (VO52.06 study) was conducted. 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.

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. Analysis of the results was based on 266 assessable patients (placebo, n=135 and Oralair 300 IR, n=131). The efficacy was determined according to the Rhinoconjunctivitis Total Symptom Score RTSS (see details below) during this one pollen season.

The efficacy analysis of the 300 IR group versus the placebo group (number of subjects included in the Intent to Treat ITT population were 131 and 135 respectively) showed the following results:

VO52.06 study: efficacy results (during one pollen season):

Primary endpoint

VO52.06 study	**ORALAIR 300 IR Mean (SD)** *Median*	**Placebo Mean (SD)** *Median*	**Absolute Adjusted Diff Mean [CI 95%]**	**Relative Mean Diff.* %**	**p-value****
Rhinoconjunctivitis symptom score [A]	3.25 (2.86) *2.48*	4.51 (2.93) *4.08*	-1.13 [-1.80; -0.46]	28.0%	0.001

*Relative Mean Difference: Absolute Difference / Placebo

** p-value ANCOVA

[A] Symptom Score: Average daily total rhinoconjunctivitis symptom scores for each patient during the grass pollen season. Rhinoconjunctivitis symptoms included sneezing, runny nose, itchy nose, nasal congestion, watery eyes and itchy eyes (0-18 range of score, the upper value of 18 indicates permanent very severe level in all 6 symptoms).

Secondary endpoints

VO52.06 study	**ORALAIR 300 IR Mean (SD)** *Median*	**Placebo Mean (SD)** *Median*	**Absolute Adjusted Diff Mean [CI 95%]**	**Relative Mean Diff.* %**	**p-value****
Average Rescue Medication Score [B]	0.60 (0.61) *0.39*	0.79 (0.65) *0.76*	-0.20 [-0.34; -0.06]	24.1%	0.0064
Rescue Medication use [C]	35.4% (33.2) *26.8%*	46.5% (34.6) *49.0%*	-	-	-

*Relative Mean Difference: Absolute Difference / Placebo

**p-value ANCOVA

[B] Average Rescue Medication Score: Average daily rescue medication score for each patient during the grass pollen season. Medications used were scored as follows: no rescue medication = 0, antihistamines (oral and/or ocular) = 1, nasal corticosteroids = 2 and oral corticosteroids = 3.

[C] Rescue medication use: Percentage of days per patient with at least one rescue medication intake, p-value 0.0146 NS (Wilcoxon).

Individual Symptom Scores: The ANCOVA results on each of the six individual mean symptom scores ranging from 0 to 3 showed a difference in favour of the 300 IR tablet as compared to placebo for runny nose (-0.16), nasal congestion (-0.26), itchy eyes (-0.33) and watery eyes (-0.21).

The proportion of patients not using rescue medication were 18.3% in the 300 IR group and 14.8% in the placebo group (NS).

Post-hoc endpoints (performed after unblinding):

VO52.06 study	**ORALAIR 300 IR Mean (SD)** *Median*	**Placebo Mean (SD)** *Median*	**Absolute Adjusted Diff Mean [CI 95%]**	**Relative Mean Diff.* %**	**p-value**
Average Adjusted	4.30 (3.57)	6.12 (3.85)	-1.64 [-2.51; -0.78]	29.8%	0.0002**

Symptom Score [D]	*3.33*	*5.28*			
$PSCD_{2-0}$ [E]	33.8% (30.0) *30.0*	23.7% (27.2) *12.2*	-	-	0.0107***
PSFD [F]	19.2% (24.9) *5.2*	10.5% (18.4) *0.0*	-	-	0.0037***

*Relative Mean Difference: Absolute Difference / Placebo
** p-value ANCOVA/*** p-value Wilcoxon
[D] Average Adjusted Symptom Score (AASS): Average symptom scores adjusted for rescue medication use (for each patient, using daily symptom scores and daily rescue medication use).
[E] Percentage of Symptom Controlled Days ($PSCD_{2-0}$): Percentage of days with a symptom score not higher than 2 and without rescue medication.
[F] Proportion of symptom and rescue medication-Free Days (PSFD): Percentage of days without symptoms and without intake of rescue medication.

Forty-four patients (34%) in the 300 IR group had presented more than 50% Symptom-Controlled Days (with a symptom score not higher than 2 and without rescue medication) over the grass pollen season, versus 26 patients (19%) patients in Placebo group.

5.2 Pharmacokinetic properties

The majority of allergens in ORALAIR are a mixture of proteins and glycoproteins. There is no direct bioavailability of intact allergens in the blood. Therefore, no pharmacokinetic studies in animals or in humans have been carried out to investigate the pharmacokinetic profile and metabolism of ORALAIR.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single-dose toxicity, repeated-dose toxicity, genotoxicity, local tolerance and embryofoetal development.
In juvenile toxicity study in rats, daily dosing for 10 weeks at the highest dose (300 times the Maximum Human Therapeutic Dose) was associated with significantly shortened APTT (Activated Partial Thromboplastin Time) in males only but neither clinical signs nor histopathological findings were found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose, microcrystalline;
- Croscarmellose sodium;
- Lactose monohydrate
- Magnesium stearate;
- Mannitol (E421);
- Silica, colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

These medicinal products do not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

100 IR and 300 IR
One small blister with 3 sublingual tablets of 100 IR and one blister with 28 sublingual tablets of 300 IR.
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. The blister cells are numbered.
Pack size: 31 sublingual tablets.

300 IR
One blister with 30 sublingual tablets of 300 IR.
The 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.
Pack sizes: 30 and 90 sublingual tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

STALLERGENES
6 rue Alexis de Tocqueville
92160 Antony
France

8 MARKETING AUTHORISATION NUMBER

PA2113/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th February 2010
Date of last renewal: 23rd June 2013

10 DATE OF REVISION OF THE TEXT

April 2024