1 PRODUCT NAME

ORALAIR Initiation Treatment Sublingual Tablets 100 IR & 300 IR
(Allergen pollen extract of 5 grasses)

ORALAIR Continuation Treatment Sublingual Tablets 300 IR
(Allergen pollen extract of 5 grasses)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Grass pollen allergen extracts 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.

One sublingual tablet of 100 IR contains 83.1 – 83.6 mg Lactose monohydrate.
One sublingual tablet of 300 IR contains 81.8 – 83.1mg Lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sublingual tablets.

ORALAIR tablet is a round, biconvex, white to beige, slightly speckled tablet, with a diameter of 6 mm and a radius of curvature of 5 mm, for all dose strengths. Each tablet with a nominal mass of 100 mg contains grass pollen allergen extract.

Two dose strengths are available:
- 100 IR
- 300 IR

Oralair 100 IR sublingual tablets are engraved 100 on each face.
Oralair 300 IR sublingual tablets are engraved 300 on each face.

The tablets cannot be halved

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oralair is indicated for the 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 the grass pollen.

4.2 Dose and method of administration

Treatment should be initiated each year about 4 months before the expected onset of the pollen season (pre-seasonal) and must be maintained until the end of the pollen season (co-seasonal).

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 that the patient should be monitored for 30 minutes).

Method of administration
Tablets should be placed under the tongue until complete dissolution (at least 2 minutes) 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.

Dose regimen in adults, adolescents and children (above the age of 5):
The treatment is composed of a treatment initiation phase (including a 3-day dose escalation) and a treatment continuation phase (maintenance dose).

Treatment initiation

The dose of ORALAIR should be increased over a three-day period to reach the maintenance dose (300 IR) according to the following scheme (see table 1 below):

Table 1

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

Treatment continuation
The maintenance dose for adults, adolescents and children over 5 years of age is 1 tablet of 300 IR per day. Treatment with the maintenance dose should be continued until the end of the pollen season.

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.

If treatment is interrupted for more than 7 days, medical intervention is required before ORALAIR is continued. If treatment is to be continued, the initial dose of ORALAIR should be administered under medical supervision and the patient monitored for 30 minutes. The physician should review if re-dose escalation is required depending on the clinical circumstances of the individual patient.

The long term study, VO53.06, has shown that after pre- and co-seasonal treatment in adults, over 3 consecutive pollen seasons, efficacy is maintained during the subsequent treatment free pollen season.

An ORALAIR Initiation Treatment pack and an ORALAIR Continuation Treatment pack are available (see section 6.5). The ORALAIR Initiation Treatment pack includes 100 IR tablets and 300 IR tablets. This pack should be used for treatment initiation (i.e. the 3-day dose escalation) and for treatment continuation (after Day 3). The ORALAIR Continuation Treatment pack includes 300 IR tablets. This pack should be used after the Initiation Treatment pack for treatment continuation

Special Population:
Clinical experience on immunotherapy with ORALAIR in patients older than 65 years is lacking (see section 4.4).

Paediatric population
The safety and efficacy of ORALAIR in children below the age of 5 years is lacking.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe uncontrolled or unstable asthma (FEV1 < 70% of predicted value) or severe exacerbation of asthma within the previous 3 months.
- Patients with active or poorly controlled autoimmune disease, immune defects, immuno deficiencies, 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. Before starting therapy, patients who have a history of asthma should be reviewed and evaluated for their asthma control and recent asthma exacerbations (See Section 4.3). When starting ORALAIR in patients with asthma, the asthma should be well controlled when initiating treatment and throughout the duration of treatment. Abrupt discontinuation of asthma prevention medicines after initiation of ORALAIR treatment is not recommended. Patients with asthma should be informed of the need to seek medical attention immediately if their asthma deteriorates suddenly.

Cardiovascular diseases
Patients with cardiovascular disease may be at an increased risk of systemic allergic reactions with ORALAIR, and this should be reviewed before initiating ORALAIR in such patients.

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

MAOIs, tricyclic antidepressants and COMT inhibitors
Allergen immunotherapy in patients treated with mono amine 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
Oralair treatment consists of exposure to allergens to which the patient is allergic. Therefore, mild or moderate local allergic reactions in or around the application site of 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. In patients who are currently on treatment, treatment should be interrupted until complete healing of the oral cavity."

Eosinophilic oesophagitis
Eosinophilic esophagitis has been reported in association with ORALAIR. During treatment with ORALAIR, if severe or persistent gastrointestinal symptoms including dysphagia or chest pain occur, ORALAIR should be discontinued, and the patient evaluated by their physician. Treatment should only be resumed upon instruction of the physician, taking into consideration the risks and benefits of continued treatment.

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.

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

Paediatric use
The safety and efficacy in younger children < 5 years has 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

4.5 Interaction with other medicines and other forms of interaction

No interaction 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 (for example 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 medicines or anti-IgE medicines e.g. omalizumab may increase the tolerance level of the patient to immunotherapy. This should be considered at discontinuation of such medicines.

Clinical experience in relation to simultaneous vaccination and treatment with ORALAIR is not available. 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

Effects on 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 in repeat-dose toxicity studies with the 5 grasses pollen extract of ORALAIR revealed no adverse findings.

Use in Pregnancy (Category B2)

For ORALAIR no clinical data on exposed pregnancies are available.
Treatment with ORALAIR should not be initiated during pregnancy (See section 4.3 Contraindications). If pregnancy occurs during treatment, the treatment may continue, if necessary, but with close supervision.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Use in Lactation

No clinical data are available for the use of ORALAIR during lactation. No effects on the breastfed infants are anticipated. It is preferable to avoid initiating allergen immunotherapy during breast-feeding. However, if a patient is under treatment at delivery, she can breast-feed with close supervision.
Studies in animals to investigate excretion of ORALAIR into milk were not conducted.

4.7 Effects on ability to drive and use machines

ORALAIR has no known influence on the ability to drive and use machines

4.8 Undesirable effects

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

A total of 1038 adults and 154 children 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.

Adults, adolescents and children

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.

Table 2

System Organ Class / Frequency / Adverse Drug Reactions		
Infections and infestations		
	Common	Nasopharyngitis, rhinitis
	Uncommon	Oral herpes, otitis (media and externa),
Blood and lymphatic system disorders		
	Uncommon	Lymphadenopathy
Immune system disorders		
	Uncommon	Hypersensitivity, oral allergy syndrome
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, dyspnea, 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	mouth oedema, tongue oedema, lip oedema, oropharyngeal blistering, stomatitis, diarrhea, 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, gastroesophageal reflux, mouth ulceration, oesophageal pain, oral pain, cheilitis, eructation, gingivitis, glossitis, odynophagia, oral disorder, salivary gland enlargement, salivary hypersecretion, tongue disorder
Skin and subcutaneous tissue disorders		
	Common	Urticaria, atopic dermatitis, pruritus
	Uncommon	Angioedema, rash, acne
	Rare	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

Application site reactions (e.g. oral pruritus and throat irritation) may 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

Additionally, the following adverse reactions have been reported during post-marketing surveillance: in adults, adolescents and children: asthma exacerbation, systemic allergic reaction and eosinophilic esophagitis.
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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (https://pophealth.my.site.com/carmreportnz/s/)

4.9 Overdose
No case of overdose 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 should be consulted immediately.

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

Contact the Poisons Information Centre (telephone 0800 POISON or 0800 764 766) or go to accident and emergency at your nearest hospital for advice on the management of an overdose.
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Allergen extract, grass pollen
ATC code: V01AA02

Mechanism of action
ORALAIR is used for treatment of patients with specific IgE-mediated allergy symptoms such as 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 pollen and induces an increase in specific IgG. The clinical relevance of these findings has not been established.

Clinical efficacy and safety

VO34.04 study:
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 pollen.

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 the 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).

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 sensitisation status (poly/mono-sensitised) and the presence or absence of associated asthma have no impact on the results.

During the first season, 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

Table 3

VO34.04 study	**ORALAIR 300IR 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 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 a severe level in all six symptoms).

Secondary endpoints

Table 4

VO34.04 study	**ORALAIR 300IR Mean (SD)** *Median*	**Placebo Mean (SD)** *Median*	**Absolute Adjusted Diff Mean [CI 95%]**	**Relative 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 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). A higher score is reflecting a worse quality of life.

Global evaluation of the efficacy of the treatment by the patient: 119/136 (88%) of patients in the ORALAIR 300IR group and 108/148 (73%) of patients in the placebo group noted improvement (moderate to excellent) 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 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 highest difference as compared to placebo was observed on nasal congestion and itchy eyes.

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

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 the placebo group.

VO53.06 study

A long-term, multicentre, multinational, randomised, double-blind, placebo-controlled study was conducted. The study included 633 adults with seasonal allergic rhino conjunctivitis caused by grass pollen, as confirmed by cutaneous tests and a positive titre of the IgE specific to the grass pollen.

Patients were randomized to 3 groups: placebo (n=219), ORALAIR 300 IR (4M) (n= 207), and ORALAIR 300 IR (2M) (n=207). [4M = 4 months pre-seasonal treatment: 2M = 2 months pre-seasonal treatment]

In the 4M group, each patient received a sublingual dose once a day for about 4 months before the start of the pollen season and continuing throughout the pollen season for 3 consecutive pollen seasons.

The fourth pollen season was a treatment-free follow-up phase.
The efficacy was determined according to the primary endpoint: the Average Adjusted Symptom Score AASS at year 3 (see details below). The daily Adjusted Symptom Score (ASS) is a symptom score adjusted for daily rescue medication use. The average ASS (AASS) is the average of the daily Adjusted Symptom Score over the evaluation period.

Results of this study demonstrated a sustained and favourable clinical effect for the 300 IR (4M) treatment group after 3 consecutive treatment periods with a pre- and co-seasonal administration scheme (4 months before the pollen season until the end of the pollen season). The clinically relevant efficacy shown during the first three years was maintained during the first treatment-free follow-up year indicating post-treatment long-term efficacy.

The efficacy of the 300 IR (4M) group versus the placebo group (number of subjects included in the Full analysis set (FAS) population were respectively 188 and 205 in the first year, 160 and 172 in the second year, 149 and 165 in the third year, 143 and 155 in the fourth year) was as follows:

Primary and secondary endpoints

Table 5

VO53.06 study	**ORALAIR 300 IR (4M)** LS Mean	**Placebo** LS Mean	**ORALAIR 300 IR (4M) vs. Placebo**		
			Absolute LS Mean Difference [CI 95%]	**Relative LS Mean difference**	**p-value***
Average Adjusted Symptom Score [A]					
Year 1	5.74	6.99	-1.25 [-1.98,-0.53]	-17.9%	0.0007
Year 2	4.03	5.92	-1.89 [-2.67,-1.11]	-31.9%	<0.0001
Year 3	3.39	5.21	-1.82 [-2.61, -1.02]	-34.9%	<0.0001
Year 4**	3.85	5.00	-1.14 [-2.03, -0.26]	-22.9%	0.0114

* p-value ANCOVA

[A] 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).

** Treatment-free follow-up period

Secondary endpoints

Table 6

VO53.06 study	ORALAIR 300 IR (4M) LS Mean	Placebo LS Mean	ORALAIR 300 IR (4M) vs. Placebo		
			Absolute LS Mean difference [CI 95%]	Relative LS Mean difference	p-value*
Rhinoconjunctivitis Symptom Score[B]					
Year 1	4.49	4.97	-0.48 [-1.04, 0.08]	-9.6%	0.0913
Year 2	3.22	4.42	-1.20 [-1.83,-0.56]	-27.1%	0.0002
Year 3	2.67	4.03	-1.37 [-2.03, -0.71]	-33.9%	<0.0001
Year 4**	3.07	3.89	-0.82 [-1.55, -0.09]	-21.0%	0.0282
Average Rescue Medication Score[C]					
Year 1	0.60	0.74	-0.14 [-0.24, -0.05]	-19.4%	0.0042
Year 2	0.35	0.58	-0.23 [-0.33,-0.13]	-39.6%	<0.0001
Year 3	0.31 (	0.47	-0.16 [-0.25, -0.06]	-33.5%	0.0011
Year 4**	0.36	0.48	-0.12 [-0.22, -0.02]	-24.6%	0.0184
Quality of Life Score [D]					
Year 1	1.36	1.66	-0.31 [-0.50, -0.12]	-18.5%	0.0015
Year 2	1.06 (	1.46	-0.39 [-0.61,-0.17]	-27.0%	0.0005
Year 3	0.94	1.36	-0.41 [-0.64, -0.19]	-30.5%	0.0003
Year 4**	0.95	1.41	-0.46 [-0.70, -0.23]	-32.8%	0.0001

*p-value ANCOVA

** Treatment-free follow-up period

[B] 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, with 0 indicating no symptoms and 18 indicating all six symptoms being severe).

[C] 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.

[D] 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: the first year, 139 patients (74%) in the ORALAIR 300 IR (4M) group and 127 patients (62%) in the placebo group noted slight to moderate or marked improvement relative to their recollection of the previous pollen season.

The proportions of patients not using rescue medication were 18.1 % in the 300 IR (4M) group and 10.7 % in the placebo group in the first year, 31.9 % in the 300 IR (4M) group and 12.8 % in the placebo group in the second year, 43.6 % in the 300 IR (4M) group and 20.0 % in the placebo group in the third year, 36.4 % in the 300 IR (4M) group and 21.9 % in the placebo group in the fourth year.

Paediatric population

VO52.06 study:

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 pollen.

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 the 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).

The sensitisation status (poly/mono-sensitised), the presence or absence of associated asthma and the age group (children 5-11 years versus adolescents 12-17 years) have no impact on the results.

During the first 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

Table 7

VO52.06 study	**ORALAIR 300IR 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 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.

Secondary endpoints

Table 8

VO52.06 study	**ORALAIR 300IR 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 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 showed a difference in favour of the 300 IR tablet with a statistical significance (p-values ≤ 0.0380) for runny nose (-0.16), nasal congestion (-0.26), itchy eyes (-0.33) and watery eyes (-0.21). The highest difference as compared to placebo was observed on watery eyes, nasal congestion and itchy eyes.

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

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 the 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.

Genotoxicity

The purified 5 grasses pollen extract contained in ORALAIR showed no mutagenic or clastogenic potential in a series of in vitro assays (mouse lymphoma TK cells and bacterial reverse mutation).

Moreover, the same less purified extract of five grasses was not genotoxic in vivo in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, at IP or SC doses resulting in exposures markedly greater than the maximum clinical exposure.

Carcinogenicity

No carcinogenicity studies were conducted in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, Microcrystalline cellulose, Croscarmellose sodium, Colloidal anhydrous silica, Magnesium stearate and Lactose monohydrate.

6.2 Incompatibilities

There is no information available.

6.3 Shelf life
36 Months.

6.4 Special precautions for storage
Store below 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
The following pack sizes are available:
Initiation treatment
1 x 3 sublingual tablets of 100 IR in a small blister + 1 x 28 sublingual tablets of 300 IR in a blister and pack of 1 x 3 sublingual tablets of 100 IR in a small blister + 1 x7 sublingual tablets of 300 IR in a blister. 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.

Continuation treatment
1 x 30 sublingual tablets of 300 IR in a blister (alu/alu) 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 of 30, 90 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MEDICINE SCHEDULE
PRESCRIPTION

8 SPONSOR
Stallergenes Greer New Zealand Limited
Level 1, 24 Manukau Road,
Epsom, Auckland 1023
Ph: 0800 824 166

9 DATE OF FIRST APPROVAL
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
1 September 2011

10 DATE OF REVISION OF THE TEXT

9 May 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
3	Editorial changes as follows: - Inclusion of some words in Caps - Addition of brackets
4.2	- Update the text to "should" instead of recommended - Modification in "Method of administration" paragraph: • In the sentence "Tablets must be placed under the tongue until complete dissolution …etc.", "must" is replaced with "should • Addition of the sentence "Food and beverage should not be taken for the following 5 minutes" - Restructuring the method of administration instructions in a new table - The instructions to place the tables under the tongue at least 2 minutes has been added in separate paragraph. - Addition of the title "maintenance treatment" - Addition of the sentence "The dose for adults, adolescents and children is 300 IR daily". - Replacement of the sentence "From the 2nd month onwards, the continuation treatment must be continued with one ORALAIR 300 IR sublingual tablet per day until the end of the pollen season." with the sentence "The maintenance treatment should be continued with one ORALAIR 300 IR sublingual tablet per day until the end of the pollen season.". - Deletion of the blister scheme - Moving some texts from other sections and reposition texts within the same section
4.3	- Replacement of sentence "Severe immune deficiency or auto-immune disease" and "Malignant diseases (e.g., cancer);" with "Patients with active or poorly controlled autoimmune disease, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance;" - Addition of "Severe" before the sentence "Oral inflammations (such as oral lichen planus, oral ulcerations or oral mycosis). - Addition of "Initiation of allergen immunotherapy treatment during pregnancy is contra-indicated (See Section 4.6)"
4.4	- Warning on severe allergic reactions moved from section 4.8 - Addition of the previous systemic allergic reaction as a warning - Warning on asthma added as class effect for AIT - Addition of the subtitle "cardiovascular diseases". - Addition of subheading "Beta-adrenergic blockers - Addition of "MAOIs, tricyclic antidepressants and COMT inhibitors" and rewording of the text - Replacement of the sentence "In case of oral surgery, including dental extraction, treatment with ORALAIR should be stopped until complete healing." with the sentence "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.”. - Information regarding interruption moved to section 4.2 DOSE AND METHOD OF ADMINISTRATION - Text in relation to the vaccination is moved from this section to section 4.5. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION - Addition of autoimmune disease in remission under warnings and precautions - General: reposition texts within the same section, removal of repeated texts and expand texts for clarity
4.5	Addition of info re “Concomitant therapy” with Omalizumab
4.6	Minor editorial changes including expanding text for clarity and addition to reference to section 4.3 under “use in pregnancy”
4.8	- Deletion of text regarding the sever allergen reactions to section 4.4 - Update heading of the tabulated summary to include “adolescents and children” - The ADR listed in the table have been updated to be presented by decreasing seriousness - Low level term “Eye redness” changed by the Preferred Term “Ocular hyperaemia” - Description of selected adverse reactions is added - Other typo corrections
5.1	- Editorial changes as follows: • Inclusion of reference to safety under clinical trials being a safety as well as efficacy studies • Correction of typos and adjustment of figures
5.3	- Inclusion of text regarding the pre-clinical safety data based on evaluated and approved data