

## SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

### 1. NAME OF THE MEDICINAL PRODUCT

ACTAIR 100 IR & 300IR sublingual tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Standardised house dust mite allergen extracts from: *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in equal parts, 100 IR\* or 300 IR\* per sublingual tablet.

\*IR (Index of Reactivity): The IR unit 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<sup>®</sup>, 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

Each sublingual tablet of 100 IR contains 82.8 – 83.3 mg of lactose monohydrate.

Each sublingual tablet of 300 IR contains 80.8 – 82.3 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 white to beige, round and biconvex, brown speckled, engraved “SAC” on one side and “100” on the other.

The tablets of 300 IR are white to beige, round and biconvex, brown speckled, engraved “SAC” on one side and “300” on the other.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

ACTAIR is indicated in adolescents (12-17 years) and adults for treatment of moderate to severe house dust mite-induced allergic rhinitis or rhinoconjunctivitis, diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE).

## 4.2 Posology and method of administration

### Posology

#### *Initiation treatment*

The dose of ACTAIR 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 and adolescents is 300 IR daily.

#### *Treatment duration*

Onset of the clinical effect is expected about 8-16 weeks after treatment initiation.

International treatment guidelines refer to a treatment period of 3 years for allergen immunotherapy to achieve disease modification, but only efficacy data over 12 months of treatment with ACTAIR are available for adolescents (12-17 years) and adults (see section 5.1). Interruption should be considered if no improvement is observed during the first year of treatment with ACTAIR.

#### *Paediatric population*

The posology is the same for adolescents (12-17 years) and adults. The efficacy of ACTAIR in children below the age of 12 years has not been established. Available data are described in sections 4.8 and 5.1.

#### *Elderly population*

Clinical experience on immunotherapy with ACTAIR in adults >65 years of age has not been established. ACTAIR is not intended for use in adults >65 years of age (see section 5.1).

### Method of administration

ACTAIR is to be prescribed to patients with a documented diagnosis and initiated by physicians experienced in the treatment of allergic diseases.

Physician should give to the patient appropriate information on the treatment as well as education on possible side effects.

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

ACTAIR should be administered during the day, in an empty mouth.

ACTAIR should be placed and kept under the tongue until tablet dissolution before swallowing. Food and beverage should not be taken for the following 5 minutes.

### Discontinuation of therapy

If treatment with ACTAIR is interrupted for a period up to 7 days, treatment can be resumed by the patient. If the treatment is interrupted for more than 7 days, it is recommended to contact a physician before resuming the treatment.

### 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 sublingual allergen immunotherapy, severe allergic reactions including severe laryngopharyngeal disorders, or systemic allergic reactions may occur.

Patients should be made aware of the signs and symptoms of severe allergic reactions. In case of severe allergic reactions, patients should discontinue the treatment and seek immediate medical care where measures to treat severe allergic reactions should be available. The treatment should only be resumed upon the instruction of a physician.

#### Previous systemic allergic reaction to allergen immunotherapy

Initiation of ACTAIR 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 4.3).

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

Patients with concomitant 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 increased risk in case of systemic allergic reactions. This should be taken into consideration prior to initiating ACTAIR.

#### Beta-adrenergic blockers

Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of adrenaline used to treat serious systemic reaction, including anaphylaxis. Specifically, beta-adrenergic blockers antagonise 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 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 ACTAIR should be postponed and ongoing treatment should be interrupted until complete healing of the oral cavity.

### Eosinophilic oesophagitis

Cases of eosinophilic oesophagitis have been reported in association with ACTAIR treatment. If severe or persistent gastroesophageal symptoms including dysphagia or chest pain occur, ACTAIR should be interrupted and the patients 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, ACTAIR should be prescribed with caution.

### Lactose

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

## **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

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.

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

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

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There is a limited amount of data on the use of house dust mite allergen extracts in pregnant women. Performed animal studies do not indicate increased risk to the foetus. Relevance of these animal studies for the human application is, however, limited, as the application route in the test species differed from the sublingual administration in humans.

Treatment with ACTAIR should not be initiated during pregnancy (See Section 4.3). If pregnancy occurs during treatment, the treatment may continue after evaluation of the general condition of the patient and reactions to previous administration of ACTAIR.

### Breastfeeding

No clinical data are available for the use of ACTAIR during lactation. No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to ACTAIR is assumed negligible.

### Fertility

No human data on the effect of ACTAIR on fertility are available.

No animal fertility studies were conducted with ACTAIR active substances. However, in a repeat-dose toxicity study with mite allergen extracts, no effects were observed in the reproductive organs of both genders.

#### 4.7 Effects on ability to drive and use machines

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

#### 4.8 Undesirable effects

##### Summary of the safety profile

Assessment of adverse reactions from clinical study data is based on trials in which 3007 patients received at least one dose of house dust mite sublingual tablet. The most frequent adverse reactions were application site reactions: oral pruritus, mouth oedema, throat irritation and ear pruritus. Adverse reactions were generally mild or moderate. They mostly occurred within the first days of treatment and decreased over the next 3 months.

##### Tabulated list of adverse reactions

Among 1583 adults and adolescents with house dust mite-induced allergic rhinitis receiving ACTAIR in the 300 IR treatment group, 909 (57%) reported adverse reactions. These are listed below by system organ class and MedDRA frequency [ $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ )]; within each frequency group, undesirable effects are presented in order of decreasing seriousness:

<b>System Organ Class</b>	<b>Frequency</b>	<b>Adverse Drug Reactions</b>
Infections and infestations	<b>Uncommon</b>	Gastroenteritis, nasopharyngitis, oral candidiasis
	<b>Rare</b>	Bronchitis, periodontitis
Immune system disorders	<b>Uncommon</b>	Oral allergy syndrome
	<b>Rare</b>	Seasonal allergy
Psychiatric disorders	<b>Uncommon</b>	Anxiety
	<b>Rare</b>	Irritability
Nervous system disorders	<b>Common</b>	Dysgeusia
	<b>Uncommon</b>	Dizziness, headache, paraesthesia
	<b>Rare</b>	Disturbance in attention, hypoesthesia, somnolence, speech disorder, tremor
Eye disorders	<b>Common</b>	Eye pruritus
	<b>Uncommon</b>	Conjunctivitis, eye oedema, lacrimation increased
	<b>Rare</b>	Ocular hyperaemia, blepharitis, blepharospasm, eye irritation
Ear and labyrinth disorders	<b>Very common</b>	Ear pruritus
	<b>Uncommon</b>	Vertigo, ear pain, paraesthesia ear
	<b>Rare</b>	Ear congestion, tinnitus
Cardiac disorders	<b>Rare</b>	Tachycardia, palpitations
Respiratory, thoracic and mediastinal disorders	<b>Very common</b>	Throat irritation
	<b>Common</b>	Pharyngeal oedema, dyspnoea, cough

	<b>Uncommon</b>	Laryngeal oedema, pharyngeal disorder, asthma, bronchospasm, wheezing, throat tightness, dysphonia, epistaxis, laryngeal discomfort, pharyngeal paraesthesia, rhinitis (nasal congestion, nasal pruritus, rhinorrhoea, sneezing)
	<b>Rare</b>	Hyperventilation, larynx irritation, nasal discomfort, pharyngeal hypoaesthesia, sinus congestion
Gastrointestinal disorders	<b>Very common</b>	Oedema mouth, oral pruritus
	<b>Common</b>	Tongue oedema, lip oedema, mouth ulceration, stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia, nausea, oropharyngeal pain, oropharyngeal discomfort, paraesthesia oral, tongue pruritus, lip pruritus
	<b>Uncommon</b>	Eosinophilic oesophagitis, palatal oedema, gastritis, gastrooesophageal reflux disease, oropharyngeal blistering, oesophageal pain, cheilitis, dry mouth, dry throat, glossitis, glossodynia, hypoaesthesia oral, oral disorder, salivary gland disorder, vomiting
	<b>Rare</b>	Oesophageal oedema, mouth haemorrhage, irritable bowel syndrome, frequent bowel movements, breath odour, eructation, flatulence, odynophagia
Skin and subcutaneous tissue disorders	<b>Common</b>	Pruritus
	<b>Uncommon</b>	Angioedema, dermatitis, rash, urticaria
	<b>Rare</b>	Erythema multiforme, blister, erythema, prurigo
Musculoskeletal and connective tissue disorders	<b>Rare</b>	Muscle spasms, musculoskeletal discomfort
Renal and urinary disorders	<b>Rare</b>	Micturition urgency
Reproductive system and breast disorders	<b>Rare</b>	Breast pain
General disorders and administration site conditions	<b>Common</b>	Chest pain
	<b>Uncommon</b>	Face oedema, localised oedema, chest discomfort, lump feeling in throat, asthenia, malaise, thirst

Investigations

**Uncommon**

Laboratory test abnormal  
(haematologic, hepatic, uric  
acid)

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#### Description of selected adverse reactions

Severe allergic reactions including severe laryngopharyngeal disorder or systemic allergic reactions such as serious 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 (see section 4.4).

#### Paediatric population

ACTAIR is not indicated in children (< 12 years). The safety experience in the paediatric population is based on clinical trials enrolling 270 children from 5 to 11 years old with house dust mite-induced allergic rhinitis and who received ACTAIR at the 300 IR dose. Overall, the safety profile of ACTAIR in the paediatric population was similar to that in adults and adolescents.

In addition to the reactions listed in the Tabulated Summary, the following reactions were reported:

Uncommon: enterocolitis, eye pain, decrease appetite, pyrexia and seborrhoea

Moreover, the following reactions were reported at a higher incidence than in adults and adolescents:

Common: laryngeal discomfort, vomiting, urticaria and laboratory test abnormal (haematologic, hepatic, uric acid).

Uncommon: ocular hyperhaemia and larynx irritation.

#### Patients enrolled in studies of allergic asthma

The safety experience in patients with allergic asthma is based on clinical trials enrolling 589 patients from 6 to 50 years old with a medical history of house dust mite-induced allergic asthma controlled with asthma therapies consistent with GINA treatment Step 2, 3 or 4 with or without perennial rhinitis and who received ACTAIR at doses up to 2000 IR. Overall, the safety profile of ACTAIR in patients with house dust mite-induced allergic asthma was similar to that in patients with house dust mite-induced allergic rhinitis.

In addition to the reactions listed in the Tabulated Summary, the following reaction was reported with ACTAIR 300 IR:

Common: intranasal paraesthesia

#### Post-marketing

Cases of systemic allergic reactions, including serious anaphylactic reactions have been reported in post marketing and are considered a class effect.

#### 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 to HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: [www.hpra.ie](http://www.hpra.ie), e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## **4.9 Overdose**

Doses up to 1000 IR were administered to patients for up to 28 days and overdosing of at least 600 IR for up to 324 days was reported. No unexpected safety risk emerged in those patients. Doses up to 2000 IR in asthmatic patients have been investigated without any new safety concerns.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extract, house dust mites; ATC code: V01AA03

#### Mechanism of action and pharmacodynamic effects

ACTAIR is an allergen product for immunotherapy. Allergen immunotherapy is the repeated administration of allergens to allergic individuals with the purpose of inducing a sustainable modification of the immunological response to the allergen during subsequent natural allergen exposure.

The pharmacodynamic effects of allergen immunotherapy are exerted on the immune system, nevertheless the exact mechanism of action underlying clinical efficacy is not fully understood. Several studies have shown that the immunological response to allergen immunotherapy is characterized by an induction of allergen specific IgG<sub>4</sub> that competes with IgE for the binding to allergens, and thereby reduces activation of immune cells. Treatment with ACTAIR has been shown to induce a systemic antibody response towards house dust mite allergens, with an early and transient increase in specific IgE antibodies followed by a gradual decrease and an increase in specific IgG<sub>4</sub>.

#### Clinical efficacy and safety

ACTAIR works by addressing the cause of house dust mite respiratory allergic disease, and clinical effect during treatment has been demonstrated. The underlying protection provided by ACTAIR leads to improvement in disease control and improved quality of life demonstrated through severity of symptom reduction as well as reduced need for symptomatic medications (oral antihistamines or intranasal corticosteroids).

Since no data are available for more than 12 months of treatment, no long-term efficacy and disease modifying effect have been established.

Efficacy of ACTAIR was demonstrated in two double-blind, randomised, placebo-controlled natural field studies. A total of 2116 patients with house dust mite allergic rhinitis were randomised in those trials.

#### Study SL75.14

Adolescents (aged  $\geq 12$ ) and adults with moderate-to-severe diagnosed HDM-induced allergic rhinitis were included in an international, double-blind, placebo-controlled, randomised phase III trial of approximately 12 months of treatment with placebo or 300 IR HDM sublingual tablet.

A total of 1607 participants were randomised. Approximately 38% of patients had concomitant mild controlled asthma at inclusion and 46% were poly-sensitised.

The primary endpoint was the average Total Combined Score during 4 weeks at the end of the treatment period.

SL75.14	ACTAIR 300 IR  LS Mean	Placebo  LS Mean	Absolute difference from placebo	Relative* difference from placebo	p- value**
<b>Primary endpoint (modified FAS)</b>	<b>N=586</b>	<b>N=676</b>			
Total Combined Score <sup>1</sup> (Range: 0-15)	3.62	4.35	-0.74	-16.9%	<0.0001
<b>Key secondary endpoints</b>					
<b>Modified FAS</b>	<b>N=586</b>	<b>N=676</b>			
Combined Symptom and Medication Score <sup>2</sup> (Range: 0-6)	1.19	1.45	-0.26	-18.0%	<0.0001
Rhinitis Total Symptom Score <sup>3</sup> (Range: 0-12)	3.16	3.79	-0.64	-16.8%	<0.0001

Rhinoconjunctivitis Total Symptom Score <sup>4</sup> (Range: 0-18)	4.22	5.04	-0.81	-16.1%	0.0002
Rescue Medication Score (Range: 0-3)	0.21	0.30	-0.09	-29.7%	0.0004
PSCD <sub>2-0</sub> <sup>5</sup>	<b>Mean/median</b> 31.82/4.35	<b>Mean/median</b> 25.44/0.00	-	-	0.0082
<b>FAS</b>	<b>N=711</b>	<b>N=765</b>			
	<b>n</b> <b>LS Mean</b>	<b>n</b> <b>LS Mean</b>			
Rhinoconjunctivitis Quality of Life Questionnaire Overall Score <sup>6</sup> (Range: 0-6)	625      1.42	678      1.62	-0.19	-12.0%	0.0004
Global evaluation of treatment efficacy by the patient <sup>7</sup>	Number of patients reporting symptom improvement (%)				
	529 (80.8%)	522 (72.4%)	-	-	0.0003

FAS: Full Analysis Set; LS Mean: Least Squares mean; Modified FAS: Patients within the FAS who had an evaluation for the concerned variable during the primary evaluation period; N: Number of patients in each treatment group; n: Number of patients with data available for the analysis

\*Relative difference: Absolute difference / placebo

\*\*p-value ANCOVA on absolute values for all scores, Wilcoxon rank-sum test for PSCD<sub>2-0</sub> and Chi-Square test for Global evaluation of treatment efficacy

<sup>1</sup>The Total Combined Score is the sum of the symptom score (the sum of sneezing, rhinorrhoea, nasal pruritus and nasal congestion scores) and the rescue medication score.

<sup>2</sup>The Combined Symptom and Medication Score is equally balancing the symptom score and the rescue medication score.

<sup>3</sup>The Rhinitis Total Symptom Score is the sum of the four rhinitis symptom scores.

<sup>4</sup>The Rhinoconjunctivitis Total Symptom Score is the sum of the six individual rhinoconjunctivitis symptom scores.

<sup>5</sup>The Proportion of Symptom Controlled Days<sub>2-0</sub>: Percentage of days with a symptom score not higher than 2 and without rescue medication.

<sup>6</sup>The Rhinoconjunctivitis Quality of Life Questionnaire comprising 7 domains was assessed at the end of the treatment period.

<sup>7</sup>The Global evaluation of treatment efficacy by the patient was assessed at the end of the treatment period on a 15-point Likert scale.

The difference of -0.26 in the pre-defined secondary endpoint ACSMS (Average Combined Symptom and Medication Score) (0-6) (balanced score published by the European Society EAACI (European Academy of Allergy and Clinical Immunology)) demonstrates an effect of HDM tablet compared to placebo of one severity class in one symptom during the whole year, in the modified FAS population set.

In addition, a very similar effect has been demonstrated in a post-hoc analysis using a balanced ATCRS (Average Total Combined Rhinitis Score) (0-24) score (LS mean: -1.07 [-1.35; -0.79] in the modified FAS population set).

### Study VO57.07

Adults with diagnosed HDM-associated allergic rhinitis were randomised in a double-blind, placebo-controlled phase II/III trial to receive 500 IR HDM sublingual tablet, 300 IR tablet, or placebo administered once daily for 1 year and were followed for the subsequent year. 509 participants were randomised, and 427 continued in the immunotherapy-free year. Approximately 30% of the patients had asthma at baseline and 52% were poly-sensitised.

The primary endpoint was the average Adjusted Symptom Score over the last 3 months of Year 1.

<b>VO57.07</b>	<b>ACTAIR 300 IR</b>	<b>Placebo</b>	<b>Absolute difference</b>	<b>Relative* difference</b>	<b>p-value**</b>
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	LS Mean	LS Mean	from placebo	from placebo	
<b>Primary endpoint (modified FAS<sub>Y1</sub>)</b>	<b>N=141</b>	<b>N=153</b>			
Adjusted Symptom Score <sup>1</sup> (Range: 0-12)	3.18	3.87	-0.69	-17.9%	0.0150
<b>Key secondary endpoints</b>					
<b>Modified FAS<sub>Y1</sub></b>	<b>N=141</b>	<b>N=153</b>			
Rhinitis Total Symptom Score <sup>2</sup> (Range: 0-12)	2.71	3.33	-0.62	-18.5%	0.0067
Rescue Medication Score (Range: 0-3)	0.33	0.32	0.01	1.8%	0.9241
PSCD <sub>2-0</sub> <sup>3</sup>	<i>Mean/median</i> 51.49/57.78	<i>Mean/median</i> 41.83/38.04	-	-	0.0140
<b>FAS<sub>Y1</sub></b>	<b>N=153</b>	<b>N=163</b>			
	<b>n</b> <b>LS Mean</b>	<b>n</b> <b>LS Mean</b>			
Rhinoconjunctivitis Quality of Life Questionnaire Overall Score <sup>4</sup> (Range: 0-6)	135      1.05	144      1.37	-0.31	-23.0%	0.0040
Global evaluation of treatment efficacy by the patient <sup>5</sup>	Number of patients reporting symptom improvement (%)				
	120 (80.5%)	96 (59.6%)	-	-	0.0001

FAS<sub>Y1</sub>: Full Analysis Set Year 1; LS Mean: Least Squares mean; Modified FAS<sub>Y1</sub>: Patients within the FAS<sub>Y1</sub> who had an evaluation for the concerned variable during the Year 1 primary evaluation period; N: Number of patients in each treatment group; n: Number of patients with data available for the analysis

\*Relative difference: Absolute difference / placebo

\*\*p-value ANCOVA on absolute values for all scores, Wilcoxon rank-sum test for PSCD<sub>2-0</sub> and Cochran-Mantel-Haenszel test for Global evaluation of treatment efficacy

<sup>1</sup>The Adjusted Symptom Score adjusts the symptom score (the sum of sneezing, rhinorrhoea, nasal pruritus and nasal congestion scores) for rescue medication use (i.e. antihistamines and corticosteroids).

<sup>2</sup>The Rhinitis Total Symptom Score is the sum of the four rhinitis symptom scores.

<sup>3</sup>The Proportion of Symptom Controlled Days<sub>2-0</sub>: Percentage of days with a symptom score not higher than 2 and without rescue medication.

<sup>4</sup>The Rhinoconjunctivitis Quality of Life Questionnaire comprising 7 domains was assessed at the end of the treatment period.

<sup>5</sup>The Global evaluation of treatment efficacy by the patient was assessed at the end of the treatment period on a 5-point Likert scale.

After one year of treatment in adults, the effect of ACTAIR was maintained one year after the end of treatment.

### Paediatric population

Studies SL75.14, 1207D1731 and 1501D1732 included 341, 181 and 156 adolescents aged 12 to 17 years, respectively. Of these, 312 (300 IR: 155, Placebo: 157) adolescents in study SL75.14, 171 (500 IR: 55, 300 IR: 57, Placebo: 59) in study 1207D1731 and 154 (300 IR: 75, Placebo: 79) in study 1501D1732 were evaluable for efficacy. Although these studies were not powered to demonstrate efficacy in the age subgroups, the treatment effect in adolescents was consistently in favour of 300 IR as observed in the overall population with a relative difference from placebo in the Total Combined Score of -15.5% in study SL75.14, and a relative difference from placebo in the Adjusted Symptom Score of -26.9% and -13.6% in studies 1207D1731 and 1501D1732, respectively.

In another double-blind, placebo-controlled paediatric study VO64.08, 471 children and adolescents (5-17 years old) received ACTAIR at a dose up to 300 IR (n=241) or placebo (n=230). No significant treatment effect was observed for ACTAIR compared to placebo. Patients in both groups reported only few symptoms during and after treatment, and the study was early terminated for futility according to the recommendation of the Data and Safety Monitoring Board.

The European Medicines Agency has waived the obligation to submit the results of studies with ACTAIR in children under the age of 5 in house dust mite allergic rhinitis.

The clinical study VO64.08 in children and adolescents (5 - 12 years of age) planned in the paediatric development programme was performed. The European Medicines Agency has confirmed compliance with the paediatric development plan.

## **5.2 Pharmacokinetic properties**

The pharmacological effect of the active substances of house dust mite tablet is not related to blood allergen levels. Allergens are large molecules that can hardly pass through the biomembrane by passive diffusion and thus the extent of systemic absorption of the house dust mite extracts is assumed to be very low or negligible. Therefore, no PK studies in animals or in humans have been carried out to investigate the pharmacokinetic profile of ACTAIR.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity, and local tolerance. Sufficient data is not available for conclusions regarding toxicity to reproduction and development.

# **6. PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Microcrystalline cellulose  
Croscarmellose sodium  
Colloidal anhydrous silica  
Magnesium stearate  
Mannitol (E 421)  
Lactose monohydrate.

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

Orientated Polyamide (OPA)/Aluminium/PVC blister with an aluminium foil in outer carton.

Pack size: Pack of 3 sublingual tablets of 100 IR and 28 sublingual tablets of 300 IR

## **6.6 Special precautions for disposal**

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

STALLERGENES

6 rue Alexis de Tocqueville

92160 ANTONY

France

Tel. +33 (0) 1 55 59 20 00

Fax +33 (0) 155 59 21 68

## **8. MARKETING AUTHORISATION NUMBER(S)**

PA2113/002/002

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 8<sup>th</sup> October 2021

## **10. DATE OF REVISION OF THE TEXT**

March 2023