

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ACTAIR Initiation Treatment Sublingual Tablets 100 IR & 300 IR

Mixture of American (*D. farinae*) and European (*D. pteronyssinus*) House dust mite allergen extracts

ACTAIR Continuation Treatment Sublingual Tablets 300 IR

Mixture of American (*D. farinae*) and European (*D. pteronyssinus*) House dust mite allergen extracts

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A 50% mixture of House dust mite allergen extracts from: European house dust mites (*Dermatophagoides pteronyssinus*) and American house dust mites (*Dermatophagoides farinae*), 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[®], 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.

Excipients with known effects: Lactose monohydrate

One sublingual tablet of 100 IR contains 82.8 – 83.3 mg Lactose monohydrate.

One sublingual tablet of 300 IR contains 80.8 – 82.3 mg Lactose monohydrate

For full list of excipients, see section 6.1 LIST OF EXCIPIENTS

3. PHARMACEUTICAL FORM

Sublingual tablet.

ACTAIR sublingual tablet is a round, biconvex, white to beige, brown 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 house dust mites allergen extract (50% mixture from European house dust mites and American house dust mites).

Two dose strengths are available:

- 100 IR
- 300 IR

ACTAIR 100 IR sublingual tablets are engraved “SAC” on one side and 100 on the other.

ACTAIR 300 IR sublingual tablets are engraved “SAC” on one side and 300 on the other.

The tablets are to be taken whole. They cannot be halved.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ACTAIR is indicated for the treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults, adolescents and children 5 years and over diagnosed with house dust mite allergy.

4.2 Dosage and method of administration

Treatment with ACTAIR should only be prescribed and initiated by physicians with adequate training and experience in the treatment of allergic diseases. In case of treatment of adolescent and paediatric patients 5 years and over, the physicians should have the corresponding training and experience in patients in this age group.

It is recommended that the first tablet of ACTAIR is taken under medical supervision and that the patient is monitored for 30 minutes.

Do not halve the tablet. Tablet is to be taken whole.

Method of administration

Precautions to be taken before handling or administering the medicine

It is recommended to take the tablets during the day in an empty mouth. Tablets should be placed under the tongue until complete disintegration (at least 2 minutes) and then swallowed. Food or beverage should not be taken for the following 5 minutes. On the first day, one 100 IR tablet should be taken. On the second day of treatment two 100 IR tablets should be placed under the tongue simultaneously.

Dose regimen in adults, adolescents and children 5 years and over:

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

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.

Continuation treatment

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

Study 1 (VO57.07) has shown that, after one year of ACTAIR treatment in adults, efficacy is demonstrated during the subsequent treatment free year.

Duration of treatment

Post treatment efficacy data after 12 months of treatment with ACTAIR are available (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Discontinuation should be considered if no improvement is observed during the first year of treatment with ACTAIR.

Paediatric population

The posology is the same for adults, adolescents and children (5 years and over).
The efficacy of ACTAIR in children below the age of 5 years has not been established.

Discontinuation of therapy

In general, if treatment is interrupted for less than 7 days, treatment can be resumed. Should the interruption period be longer than 7 days, it is recommended to contact a physician before resuming the treatment.

4.3 Contraindications

- Hypersensitivity to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS);
- 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 or immunosuppression or malignant neoplasia 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 FERTILITY, PREGNANCY AND LACTATION).

4.4 Special warnings and precautions for use

Identified precautions

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. Severe allergic reactions may be treated with adrenaline (epinephrine). In case of severe allergic reactions, patients should discontinue the treatment and seek immediate medical care. The treatment should only be resumed upon instruction of a physician.

Previous systemic allergic reaction to allergen immunotherapy

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

Asthma

The asthma status should be carefully evaluated before starting therapy (see Section 4.3 CONTRAINDICATIONS).

Asthma is a known risk factor for severe systemic allergic reactions. 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 to allergen immunotherapy. 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 reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of adrenaline (epinephrine).

MAOIs, tricyclic antidepressants and COMT inhibitors

Allergen immunotherapy in patients treated with mono amine oxidase inhibitors (MAOIs) or tricyclic antidepressants or COMT inhibitors should be considered carefully as these treatments could potentiate the effect of adrenaline (epinephrine).

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 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, ACTAIR should be prescribed with caution.

Lactose

Due to the presence of 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 ACTAIR in patients older than 65 years is lacking.

Paediatric use

The safety and efficacy of ACTAIR in children below the age of 5 years have not been demonstrated.

Effects on laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interaction

No interaction studies have been performed.

No interactions were reported in clinical trials with ACTAIR, during which patients were able to take medications to treat allergic symptoms (antihistamines, corticosteroids).

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 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 (Category B2)

There are no adequate and well-controlled studies of ACTAIR in pregnant women.

There was no evidence of maternal and embryofetal development toxicity following oral administration of ACTAIR active substances to pregnant rats and rabbits, commencing on gestation day 6, at doses at least 76 times the 300 IR ACTAIR dose, based on body surface area. No perinatal toxicity study has been conducted.

Treatment with ACTAIR should not be initiated during pregnancy (see Section 4.3 CONTRAINDICATIONS). 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. Studies in animals to investigate excretion of ACTAIR into milk were not conducted.

No effects on the breastfed infants are anticipated. It is not recommended to initiate an immunotherapy during breast-feeding. However, if a patient is under treatment at delivery, she can breast-feed with close supervision.

Fertility

There are no fertility data available in humans.

Animal fertility studies have not been conducted with ACTAIR active substances. However, histopathological examination of the male and female reproductive organs revealed no adverse effects in the repeat-dose toxicity studies with mite allergen extracts.

4.7 Effects on ability to drive and use machines

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

4.8 ADVERSE EFFECTS (Undesirable effects)

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.

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

ADULTS AND ADOLESCENTS

In adults and adolescents with house dust mite-induced allergic rhinitis receiving ACTAIR (N=1583) or placebo (N=1588) once daily for up to 12 months, 1238 patients (78.2%) in the 300 IR treatment group reported adverse events as did 1036 (65.2%) in the placebo group.

Adverse events reported at an incidence of $\geq 5\%$ of patients receiving ACTAIR 300 IR compared to placebo in pooled study data are listed in Table 1.

Table 1 Adverse Events Reported by $\geq 5\%$ of Patients Receiving ACTAIR 300 IR

| System Organ Class Preferred Term | ACTAIR 300 IR (N=1583) | Placebo (N=1588) |
|--|----------------------------------|----------------------------|
| Gastrointestinal disorders | | |
| Oral pruritus | 20.8% | 3.5% |
| Oedema mouth | 16.4% | 0.4% |
| Abdominal pain | 7.6% | 3.0% |
| Tongue oedema | 6.5% | 0.3% |
| Lip oedema | 5.9% | 0.6% |
| Oropharyngeal pain | 5.6% | 3.8% |
| Nausea | 5.0% | 1.3% |
| Infections and infestations | | |
| Nasopharyngitis | 24.2% | 26.3% |
| Upper respiratory tract infection | 5.4% | 5.9% |
| Respiratory, thoracic and mediastinal disorders | | |
| Throat irritation | 19.8% | 4.1% |
| Ear and labyrinth disorders | | |
| Ear pruritus | 12.8% | 1.6% |
| Nervous system disorders | | |
| Headache | 8.0% | 10.5% |

Adverse events with an incidence $< 5\%$ and with causality assigned to ACTAIR are listed below according to the MedDRA convention by system organ class and by frequency common: $\geq 1/100$, $< 1/100$, uncommon: $\geq 1/1,000$, $< 1/100$, rare: $\geq 1/10,000$, $< 1/1,000$.

Infections and infestations

Uncommon: Gastroenteritis, oral candidiasis

Rare: Bronchitis, periodontitis

Immune system disorders

Uncommon: Oral allergy syndrome

Rare: Seasonal allergy

Psychiatric disorders

Uncommon: Anxiety

Rare: Irritability

Nervous system disorders

Common: Dysgeusia

Uncommon: Dizziness, paraesthesia

Rare: Disturbance in attention, hypoaesthesia, somnolence, speech disorder, tremor

Eye disorders

Common: Eye pruritus

Uncommon: Conjunctivitis, eye oedema, lacrimation increased

Rare: Ocular hyperaemia, blepharitis, blepharospasm, eye irritation

Ear and labyrinth disorders

Uncommon: Vertigo, ear pain, paraesthesia ear

Rare: Ear congestion, tinnitus

Cardiac disorders

Rare: Tachycardia, palpitations

Respiratory, thoracic and mediastinal disorders

Common: Pharyngeal oedema, dyspnoea, cough

Uncommon: Laryngeal oedema, pharyngeal disorder, asthma, bronchospasm, wheezing, throat tightness, dysphonia, epistaxis, laryngeal discomfort, pharyngeal paraesthesia, rhinitis (nasal congestion, nasal pruritus, rhinorrhoea, sneezing)

Rare: Hyperventilation, larynx irritation, nasal discomfort, pharyngeal hypoaesthesia, sinus congestion

Gastrointestinal disorders

Common: Mouth ulceration, stomatitis, diarrhoea, dyspepsia, dysphagia, oropharyngeal discomfort, paraesthesia oral, tongue pruritus, lip pruritus

Uncommon: 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

Rare: Oesophageal oedema, mouth haemorrhage, irritable bowel syndrome, frequent bowel movements, breath odour, eructation, flatulence, odynophagia

Skin and subcutaneous tissue disorders

Common: Pruritus

Uncommon: Angioedema, dermatitis, rash, urticaria

Rare: Erythema multiforme, blister, erythema, prurigo

Musculoskeletal and connective tissue disorders

Rare: Muscle spasms, musculoskeletal discomfort

Renal and urinary disorders

Rare: Micturition urgency

Reproductive system and breast disorders

Rare: Breast pain

General disorders and administration site conditions

Common: Chest pain

Uncommon: Face oedema, localised oedema, chest discomfort, lump feeling in throat, asthenia, malaise, thirst

Investigations

Uncommon: Laboratory test abnormal (haematologic, hepatic, uric acid)

Paediatric population (5 to 11 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 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 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://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Overdoses of up to 1000 IR for up to 28 days and overdosing of at least 600 IR for up to 324 days were reported in patients receiving ACTAIR. No unexpected safety risk emerged in those patients. Doses up to 2000 IR for 10 days in asthmatic patients have been investigated without any new safety concerns. Higher doses may be associated with reduced tolerability and may potentially increase the risk of serious allergic reactions.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Immunologic changes associated with immunotherapy are complex, and the exact mechanism(s) responsible for its clinical efficacy are unknown.

The allergic reaction is dependent on the presence of allergen-specific Immunoglobulin E (IgE) antibodies bound to specific receptors on mast cells and basophils. Upon interaction of allergens with such cell-bound IgE antibodies, histamine and other mediators are released and produce local or systemic responses in atopic individuals.

Several studies have shown that the immunological response to allergen immunotherapy is characterized by an induction of allergen specific IgG4 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 IgG4.

Pharmacodynamic effects

Treatment with Actair has been shown to induce a systemic antibody response towards house dust mite allergens, with an increase in specific IgG₄ antibodies in some patients. These immunoglobulins may compete with IgE for allergen binding, thereby decreasing allergen capture and presentation.

Clinical trials

Clinical experience in adults: Study 1-VO57.07

During a European, multicenter, multinational, randomized, double-blind, placebo-controlled study conducted over 2 years, 509 patients received either the 300 IR dose (n=170) or the 500 IR dose (n=169) sublingual tablet of house dust mites allergen extract or placebo (n=170) daily for 12 months and were followed up during the subsequent treatment-free year.

Study patients had allergic rhinitis caused by house dust mites, confirmed by positive skin tests and *in vitro* testing for dust mites-specific IgE antibodies. Patients with intermittent asthma were included. Approximately 30% had asthma at baseline and 52% were poly-sensitized (i.e., sensitized to house dust mites allergens and at least one of the other allergens tested).

Efficacy was assessed via daily recording of rhinitis symptoms and rescue medication use by patients.

Patients receiving the 300 IR dose had a lower Average Adjusted Symptom Score over the last 3 months of treatment by 17.9% than those receiving placebo.

The results of the primary efficacy analysis are presented in the table below:

Table 2 Average Adjusted Symptom Score¹ study VO57.07

| Dosage | N | Average Adjusted Symptom Score | Difference from placebo | p-value | Relative difference from placebo |
|---------|-----|--------------------------------|-------------------------|---------|----------------------------------|
| 300 IR | 141 | 3.18 | -0.69 | 0.0150 | -17.9% |
| Placebo | 153 | 3.87 | — | — | — |

N = number of subjects with data

¹The Average Adjusted Symptom Score adjusts the symptom score (the sum of sneezing, rhinorrhoea, nasal pruritus and nasal congestion scores, using a score from 0 to 3) for rescue medication use (i.e., antihistamines and corticosteroids). It ranges from 0 to 12.

Patients receiving the 300 IR dose had a lower Average Rhinitis Total Symptom Score by 18.5% than those receiving placebo. There was no difference in the Average Rescue Medication Score between the active and placebo treatment groups.

The individual symptom scores for sneezing, nasal pruritus, nasal congestion, rhinorrhoea and ocular itching were reduced in the 300 IR group by 19.0%, 21.2%, 20.7%, 12.2% and 20.5%, respectively, compared to the placebo group.

An overall improvement of 23.0% was demonstrated in the Rhinoconjunctivitis Quality of Life Questionnaire score in the 300 IR group versus the placebo group in the first year. The improvement was also observed for each of the 7 domains: activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional.

At the end of treatment, the proportion of patients reporting marked improvement was higher in the 300 IR group (36.9%) than in the placebo group (18.0%). A higher proportion of patients in the 300 IR group reported treatment success (80.5% versus 59.6% for placebo).

Clinical experience in adults and adolescents (12-17): Study 2-1207D1731

During a multicenter, randomized, double-blind, placebo-controlled study conducted in Japan over one treatment year, 968 adults and adolescents aged 12 to 64 years received either a 300 IR dose (n=322) or a 500 IR dose (n=324) of sublingual tablet of house dust mites allergen extract or placebo (n=322) daily for 12 months.

Study patients had allergic rhinitis caused by house dust mites, confirmed by positive nasal provocation test and *in vitro* testing for dust mites-specific IgE antibodies. Patients with intermittent or mild asthma were included.

Patients receiving the 300 IR dose had a lower Average Adjusted Symptom Score over the last 2 months of treatment by 18.2% than those receiving placebo.

The results of the primary efficacy analysis are presented in the table below:

Table 3 Average Adjusted Symptom Score¹ study 1207d1731

| Dosage | N | Average Adjusted Symptom Score | Difference from placebo | p-value | Relative difference from placebo |
|---------|-----|--------------------------------|-------------------------|---------|----------------------------------|
| 300 IR | 315 | 5.00 | -1.11 | <0.0001 | -18.2% |
| Placebo | 316 | 6.11 | — | — | — |

N = number of subjects with data

¹The Average Adjusted Symptom Score adjusts the symptom score (the sum of sneezing, rhinorrhoea and nasal congestion scores, using a score from 0 to 4, and nasal pruritus using a score from 0 to 3) for rescue medication use (i.e., antihistamines and corticosteroids). It ranges from 0 to 15.

In the subset of adolescents (aged 12 to 17 years), patients receiving the 300 IR dose had a lower Average Adjusted Symptom Score by 26.9% than those receiving placebo.

Patients receiving the 300 IR dose had a lower Average Rhinitis Total Symptom Score by 17.7% and a lower Average Rescue Medication Score by 41.6% than those receiving placebo.

The individual symptoms scores for sneezing, rhinorrhoea, nasal pruritus, nasal congestion and eye tearing were reduced in the 300 IR group by 11.4%, 17.8%, 17.7%, 22.8% and 18.1%, respectively, compared to the placebo group.

For each of the domains of the Japanese Rhinoconjunctivitis Quality of Life Questionnaire score (i.e., “Nasal and Eye symptoms,” “QOL-related Questionnaire” and “General State”), a numerically superior improvement was demonstrated at the end of the treatment in patients receiving 300 IR compared to those receiving placebo.

At the end of treatment, the proportion of patients reporting marked improvement was higher in the 300 IR group (22.2%) than in the placebo group (9.7%).

Clinical experience in paediatric population (5-16): Study 3-1501D1732

During a multicenter, randomized, double-blind, placebo-controlled study conducted in Japan over one treatment year, 438 children and adolescents aged 5 to 16 years received either a 300 IR dose (n=219) of sublingual tablet of house dust mites allergen extract or placebo (n=219) daily for 12 months.

Study patients had allergic rhinitis caused by house dust mites, confirmed by positive nasal provocation test and *in vitro* testing for dust mites-specific IgE antibodies. Patients with intermittent or mild asthma were included.

Patients receiving the 300 IR dose had a lower Average Adjusted Symptom Score over the last 4 weeks of treatment by 13.1% than those receiving placebo.

The results of the primary efficacy analysis are presented in the table below:

Table 4 Average Adjusted Symptom Score¹ for study 1501D1732

| Dosage | N | Average Adjusted Symptom Score | Difference from placebo | p-value | Relative difference from placebo |
|---------|-----|--------------------------------|-------------------------|---------|----------------------------------|
| 300 IR | 205 | 6.32 | -0.95 | 0.0005 | -13.1% |
| Placebo | 217 | 7.27 | — | — | — |

N = number of subjects with data

¹The Average Adjusted Symptom Score adjusts the symptom score (the sum of sneezing, rhinorrhoea and nasal congestion scores, using a score from 0 to 4, and nasal pruritus using a score from 0 to 3) for rescue medication use (i.e., antihistamines and corticosteroids). It ranges from 0 to 15.

Patients receiving the 300 IR dose had a lower Average Rhinitis Total Symptom Score by 12.7% and a lower Average Rescue Medication Score by 8.5% than those receiving placebo.

The individual symptoms scores for sneezing, rhinorrhoea, nasal pruritus and nasal congestion were reduced in the 300 IR group by 14.4%, 9.9%, 12.1% and 15.0%, respectively, compared to the placebo group.

At the end of treatment, the proportion of patients reporting marked improvement was higher in the 300 IR group (19.7%) than in the placebo group (8.8%).

Study 3 included 282 children aged 5 to 11 years and 156 adolescents aged 12 to 17 years. Of these, 268 children (300 IR: 130, Placebo: 138) and 154 adolescents (300 IR: 75, Placebo: 79) were evaluable for efficacy. Although this study was not designed for efficacy analysis in the age subgroups, the treatment effect in children and in adolescents was consistently in favour of 300 IR as observed in the overall population. Children and adolescents receiving the 300 IR dose had a lower Average Adjusted Symptom Score by 12.4% and 13.6%, respectively, than those receiving placebo.

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). The patients were not sufficiently symptomatic to enable assessment of the efficacy of ACTAIR.

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; after swallowing, allergens that have not been captured within the sublingual mucosa are broken down into smaller polypeptides and amino acids in the

lumen of the gastrointestinal tract and in tissues. The extent of systemic absorption of the house dust mite extracts is assumed to be very low or negligible.

Therefore, no pharmacokinetic studies in animals or in humans have been carried out to investigate the pharmacokinetic profile and metabolism 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, toxicity to reproduction and development and local tolerance.

Carcinogenicity

Carcinogenicity studies have not been conducted with ACTAIR.

Genotoxicity

ACTAIR active substances revealed no evidence of mutagenic or clastogenic potential based on the results of in vitro genotoxicity tests (bacterial reverse mutation, mouse lymphoma thymidine kinase and micronucleus assays).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

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

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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:

Actair Initiation treatment sublingual tablets 100 IR and 300 IR (TT50-9711)

- Pack of 1 x 3 sublingual tablets of 100 IR in a small blister + 1 x 28 sublingual tablets of 300 IR in a blister.
- Pack of 1 x 3 sublingual tablets of 100 IR in a small blister + 88 sublingual tablets of 300 IR in 3 blisters (1 x 28, 1 x 30 and 1 x 30 sublingual tablets)
- -Pack of 1 x 3 sublingual tablets of 100 IR in a small blister + 1 x 7 sublingual tablets of 300 IR in a blister.

Actair Continuation treatment sublingual tablets 300 IR (TT50-9711-1)

1 x 30 sublingual tablets of 300 IR in a blister. Pack of 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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:
28 September 2017

10. DATE OF REVISION OF THE TEXT

06 April 2023

Summary table of changes

| Section changed | Summary of new information |
|--|---|
| 2. Qualitative and quantitative composition | Reference to 110 mg/mL histamine – corrected to histamine dihydrochloride |
| 4.1 Therapeutic Indications | Updated as per proposed expansion of indication into children 5 years and over |
| 4.2 –subheading: Method of administration | Adjustments made due to expanded indications. Under Method of administration: addition of instructions re the food intake, addition of information re the dose-escalation period. Update information re duration of treatment |
| 4.2 – subheading: Duration of treatment | Add statement of standard clinical practice for AIT for at least 3 years |
| 4.2 –subheading Paediatric population | Add new information related to paediatric use |
| 4.3 Contraindications | Addition of more info re the Asthma Updated to narrow the statement to “Active disease – as per general contraindications for oral AIT Added “severe” to oral inflammations Updated wording to further narrow contraindications to include poorly controlled autoimmune diseases |
| 4.4 Special warnings | Reorganized text, adding subheadings and updating information as per requests from authorities and updated publications. |
| 4.5 Interactions with other medicines and other forms of interaction | Addition of information re Concomitant therapy with symptomatic anti-allergic medications or anti-IgE medications e.g. omalizumab |

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|--|---|
| 4.6 Fertility, pregnancy and lactation | Precautions re pregnancy has been updated |
| 4.8 Adverse effects | Updated with new information due to additional clinical; data presented in paediatric population and further ADR's gathered |
| 4.0 Overdose | Updated with further information of higher doses used |
| 5.1 subheading clinical trials | Updated with new information related to new paediatric studies |
| 5.2 Pharmacokinetic properties | Reworded and expanded general information |