The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

28 March 2012

The opinion adopted by the Transparency Committee on 18 January 2012 was the subject of a hearing on 28 March 2012.

**ORALAIR 300 IR, sublingual tablet**
B/30 (CIP code: 368 952-2)

**ORALAIR 300 IR, sublingual tablet**
B/90 (CIP code: 368 953-9)

**ORALAIR 100 IR & 300 IR, sublingual tablet**
B/3 tablets of 100 IR and B/28 tablets of 300 IR (CIP code: 368 951-6)

Applicant: STALLERGENES SA

Allergenic extract of the following grass pollens:
- cocksfoot (*Dactylis glomerata* L.)
- sweet vernal (*Anthoxanthum odoatum* L.)
- rye (*Lolium perenne* L.)
- meadow (*Poa pratensis* L.)
- timothy (*Phleum pratense* L.)

ATC code: V01A A 02

List I

Date of Marketing Authorisation: 18 March 2010 (mutual recognition procedure)

**Reason for request:** Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health assessment Division
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Allergenic extract of the following grass pollens (100 IR\(^1\) or 300 IR per tablet):
- cocksfoot (*Dactylis glomerata* L.)
- sweet vernal (*Anthoxanthum odoatum* L.)
- rye (*Lolium perenne* L.)
- meadow (*Poa pratensis* L.)
- timothy (*Phleum pratense* L.)

1.2. Indication
“Treatment of allergic rhinitis, with or without conjunctivitis, caused by grass pollens, in adults, adolescents and children (above the age of 5), with clinically relevant symptoms, confirmed by a positive skin test and/or the presence of IgE specific for the grass pollens.”

1.3. Dosage
“ORALAIR treatment should only be prescribed and initiated by doctors trained and experienced in the treatment of allergic diseases. Treatment in children should be conducted by doctors trained and experienced in the treatment of allergic diseases in children.

The first tablet of ORALAIR should be taken under medical supervision for 30 minutes in order to take appropriate measures in the event of any undesirable effects occurring.

Treatment consists of an initiation phase (consisting in a 3-day gradual dose escalation) and a continuation phase.

The box of ORALAIR intended for the treatment in the initiation phase contains medicines for the first month of treatment, including ORALAIR 100 IR and ORALAIR 300 IR in 2 different blisters:

Small blister:
- Day 1 1 x 100 IR tablet
- Day 2 2 x 100 IR tablet

Large blister:
- Day 3 1 x 300 IR tablet
- Day 4 1 x 300 IR tablet
- Day 5 1 x 300 IR tablet
- ...
- Day 30 1 x 300 IR tablet

The box of ORALAIR intended for the continuation treatment contains only ORALAIR 300 IR tablets and will be used from the second month, the continuation treatment continuing with one ORALAIR 300 IR sublingual tablet per day. This dosage will be maintained until the end of the pollen season.

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\(^1\) IR: Index of Reactivity. The IR unit was defined to measure the allergenicity of an allergen extract. The allergen extract contains 100 IR/ml when, on a skin prick-test using a standardised lancet (Stallerpoint®), it induces a wheal diameter of 7 mm (geometric mean) in 30 subjects sensitised to this allergen. The cutaneous reactivity of these subjects is simultaneously demonstrated by a positive skin-prick test to either 9% codeine phosphate or 10 mg/ml histamine. The IR unit of Stallergenes is not comparable with units used by other allergen manufacturers.
Method of administration:
Administered orally. The sublingual tablet should be placed under the tongue until complete dissolution (for at least 1 minute) and then swallowed. On the second day of treatment, the two 100 IR tablets must be placed under the tongue simultaneously and then swallowed. It is recommended to take the tablet in the morning, on an empty stomach. Treatment should be initiated about 4 months before the estimated start of the pollen season and maintained throughout the pollen season. There are no data currently available regarding the efficacy of ORALAIR beyond one pollen season. If there is no significant improvement in the symptoms during the first pollen season, treatment should not be continued the following year. Clinical experience with allergenic immunotherapy using ORALAIR in young children (< 5 years) and in patients over 45 years of age is lacking."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)
V: Various
V01: Allergens
V01A: Allergens
V01A A: Allergen extracts
V01A A 02: Grass pollen

2.2. Medicines in the same therapeutic category
Strictly comparator medicines:
Another proprietary medicinal product used in oral immunotherapy:
GRAZAX 75 000 SQ-T: timothy pollen oral lyophilisate (low actual benefit [Transparency Committee’s opinion of 22 July 2009]).

Not strictly comparator medicines:
Allergens prepared for a single individual (APSIs) governed by the decree of 23 February 2004 are not classed as proprietary medicinal products. APSIs may be administered either subcutaneously or sublingually (not evaluated by the Transparency Committee – 65% reimbursement).

2.3. Medicines with a similar therapeutic aim
Symptomatic treatment for rhinitis with or without conjunctivitis features oral antihistamines, local or oral corticosteroids, sometimes cromones, and decongestants.
The pharmaceutical company provided 3 randomised double-blind studies versus placebo:
- 2 studies in adults: one short-term (1 pollen season of treatment), the other long–term (3 years of treatment and 2 years of follow-up) the results of which at 4 years are available
- 1 short-term study (1 pollen season of treatment) in children and adolescents.

### 3.1. Efficacy

#### Efficacy in adults

**Short-term study (VO34.04)**
Randomised, double-blind study comparing the efficacy and tolerance of 3 dosages of ORALAIR (100 IR, 300 IR and 500 IR) with those of placebo during one pollen season on the reduction in allergy symptoms and the consumption of rescue medications in adults suffering from rhinitis with or without allergic conjunctivitis triggered by grass pollens. This multicentre study was conducted in 10 European countries, including France.

Patients had to be aged between 18 and 45 years and have rhinitis with or without allergic conjunctivitis for at least the past 2 pollen seasons, with an RTSS\(^2\) score \(\geq 12\) during the preceding pollen season (retrospective RTSS): the patient had to recall having a level of symptom intensity during the preceding pollen season corresponding to a score of \(\geq 12\).

Among the non-inclusion criteria:
- allergic rhinoconjunctivitis caused by an allergen other than grass pollen;
- asthma requiring treatment other than with inhaled beta-2-agonists (patients with intermittent asthma not requiring treatment with nasal or systemic corticosteroids could be included);
- oral corticosteroids in the 12 weeks prior to the inclusion visit;
- desensitisation treatment to grass pollens or to other allergens during the past 5 years.

Patients were distributed into 4 groups:
- ORALAIR 100 IR/day (n = 157)
- ORALAIR 300 IR/day (n = 155)
- ORALAIR 500 IR/day (n = 160)
- Placebo (n = 156)

Patients could have recourse to the following rescue medications: antihistamines, nasal corticosteroids and systemic corticosteroids.

Only the results for the 300 IR dose will be presented in comparison with those for placebo, as that is the dosage referred to in the marketing authorisation.

**Study design:**
After they were selected, patients received the treatment for about 4 months prior to the start of the pollen season and until its end (about 30 days). Patients were followed up for 2 weeks after the end of the treatment.

\(^2\) "Rhinoconjunctivitis Total Symptoms Score": sum of the scores of 6 symptoms, each scored between 0 (no symptoms) and 3 (severe intensity). The symptoms assessed are: sneezing, runny nose, itchy nose, nasal congestion, itchy eyes and watery eyes.
Primary efficacy endpoint: the mean of the daily RTSS scores evaluated during the pollen season.
An a posteriori analysis was performed on the RTSS endpoint, adjusted for the consumption of rescue medications (AAdSS).³

Secondary endpoints evaluated during the pollen period:
- use of rescue medications (ARMS⁴);
- number of symptom-free days;
- quality of life (RQLQ questionnaire⁵);
- global evaluation of treatment efficacy by the patient.

For all the efficacy endpoints, the results were analysed in the intention-to-treat population defined as patients receiving at least one dose of treatment and having had at least one measurement of the RTSS.

Results:
A total of 628 patients were randomised, of whom 569 were assigned to the ITT population (i.e. 142 patients in the 100 IR group, 136 in the 300 IR group, 143 in the 500 IR group and 148 in the placebo group) and 559 completed the study.
The mean retrospective RTSS score was 14.1 points in the ORALAIR group and 14.2 points in the placebo group.
Patients in whom allergic rhinoconjunctivitis was combined with asthma accounted for 10% of the total study population and were distributed uniformly among the groups.
Patients were sensitised to a single allergen in 45.3% of the cases and to more than one allergen in 54.7% of the cases.

On average, the analysis period lasted 30 days and the pollen peak 12 days.

- Primary efficacy endpoint:
During the analysis period, the mean RTSS score was lower in the 300 IR group than in the placebo group (3.58 ± 2.98 versus 4.93 ± 3.23, i.e. a difference of 1.39 points). An analysis of covariance (ANCOVA), taking into account as covariables the retrospective RTSS, asthma and sensitisation status, showed the difference between the groups to be statistically significant (p = 0.0001).

After adjustment for the use of rescue medications, the mean RTSS score (AAdSS) was 5.88 ± 3.82 in the 300 IR group and 4.17 ± 3.39 in the placebo group, i.e. a difference of 1.84 points. An analysis of covariance (ANCOVA), taking into account as covariables the asthma, sex, age and sensitisation status, showed that the difference between the treatments was statistically significant (p < 0.0001).

- Secondary endpoints:
The proportion of patients using at least one rescue medication did not differ: 64.7% in the 300 IR group and 73% in the placebo group.

³ Average Adjusted Symptoms Score: criterion validated by EMA for other ORALAIR studies in progress. Total of the scores for the 6 symptoms rated individually from 0 to 3.
⁴ Average Rescue Medication Score: mean of the daily scores for use of rescue medication, rated on a scale of from 0 to 3:
  0 = no rescue medication, 1 = antihistamine taken; 2 = nasal corticosteroid taken; 3 = oral corticosteroid taken (according to the opinion of the investigator). When a patient takes more than a single category of rescue medication, the one with the highest score is used.
⁵ Quality of life questionnaire specific for rhino-conjunctivitis in adults rated from 0 (not affected) to 6 (severely affected).
In both groups, patients used mainly oral antihistamines (53.7% in the 300 IR group and 60.8% in the placebo group), nasal corticosteroids (39.0% versus 50.0%) and antiallergic eye-drops (30.9% versus 45.3%). Systemic corticosteroids were used by 0.7% of the patients in the 300 IR group and 2.7% of those in the placebo group.

The ARMS score evaluating the consumption of rescue medications (0 to 3 points) was 0.31 ± 0.43 in the 300 IR group and 0.48 ± 0.53 with the placebo (p = 0.0047).

The proportion of days with rescue treatment was 19.72% in the 300 IR group and 27.85% in the placebo group (p = 0.0194).

The proportion of symptom-free and treatment-free days was 25.3% in the 300 IR group and 14.9% in the placebo group (p = 0.0006).

The proportion of days with monitored symptoms (RTSS ≤ 2) and without rescue medication was 43.5% in the 300 IR group and 28.7% with the placebo.

The mean quality of life score (RQLQ) increased by 0.20 (at randomisation) to 0.61 points (at the end of the pollen season) in the 300 IR group and by 0.23 to 0.74 points in the placebo group.5

Long-term study (VO53.06)
Randomised, double-blind study, after evaluating versus placebo the extent to which the efficacy of ORALAIR was maintained after 3 years according to 2 treatment regimens, with treatment starting 2 or 4 months before the pollen season and continuing until the end of the pollen season, in patients with allergic rhinoconjunctivitis caused by grass pollen.

It should be pointed out that the SPC currently recommends treatment being started 4 months before the start of the pollen season.

Patients were treated intermittently for 3 years, then followed up for a further 2 years.

Included patients had to be aged from 18 to 50 years and have been suffering with symptomatic allergic rhinoconjunctivitis caused by grass pollen for at least 2 pollen seasons, as confirmed by a skin-prick test (wheal ≥ 3 mm) and an allergen-specific IgE level > 0.70 kU/l. The RTSS retrospective symptom score had to be ≥ 12.

Patients could not be included if they were sensitive to an allergen other than grass pollen and had asthma requiring treatment other than with inhaled beta-2-agonists.

Patients were distributed into 3 groups:
- ORALAIR 300 IR starting 4 months before the pollen season;
- ORALAIR 300 IR starting 2 months before the pollen season;
- Placebo

The treatment of patients was continued until the end of the pollen season. These treatment regimens were repeated for 3 successive years.

Patients could use the following rescue medications: antihistamines, nasal corticosteroids and systemic corticosteroids.

Primary efficacy endpoint: Mean RTSS adjusted for the consumption of rescue medications (AAdSS) after 3 years of treatment.

Among the secondary endpoints:
- Mean RTSS, adjusted for the consumption of rescue medications (AAdSS) after 1 and 2 years of treatment and during the treatment-free follow-up period;
- use of rescue medications (ARMS);
- proportion of days with monitored symptoms and without taking symptomatic treatments.
Results:
Only the results up to the fourth year are available at the present time. A total of 633 patients were randomised, 207 of them in each of the ORALAIR groups and 219 in the placebo group. The percentage of patients with respect to the initial population who continued with the study during the second, third and fourth year of the study was:
- 76.8%, 71.5% and 68.1% in the ORALAIR 300 IR group (2 months)
- 80.7%, 72.9% and 70.0% in the ORALAIR 300 IR group (4 months)
- 83.1%, 75.8% and 71.2% in the placebo group.

Taking the groups as a whole, the percentage of patients with a compliance ≥ 80% was 96.9% in the first year, 97.5% in the second year and 97.8% in the third year.

Patients were sensitised to a single allergen in 40% of the cases and to more than one allergen in 60% of the cases. The mean retrospective score was 14.1 points in the ORALAIR group (4 months), 13.9 points in the ORALAIR group (2 months) and 14.1 points in the placebo group.

Primary efficacy endpoint:
During the course of the third year of treatment, the mean RTSS score adjusted for the consumption of rescue medications (AAdSS) was lower in each of the ORALAIR groups than in the placebo group (differences statistically significant, see Table 1).

Table 1: Mean RTSS score, adjusted for the consumption of rescue medications (AAdSS) during the third year (study V053-06)

<table>
<thead>
<tr>
<th></th>
<th>ORALAIR (4 months) n = 149</th>
<th>ORALAIR (2 months) n = 147</th>
<th>Placebo n = 165</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean adjusted RTSS ± SD</td>
<td>3.46 ± 3.63</td>
<td>3.38 ± 3.21</td>
<td>5.28 ± 3.94</td>
</tr>
<tr>
<td>Difference versus placebo p</td>
<td>-1.81 p &lt; 0.0001</td>
<td>-1.96 p &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[-2.61; -1.02]</td>
<td>[-2.76; -1.16]</td>
<td></td>
</tr>
</tbody>
</table>

Secondary endpoints:
- Treatment period:
  During the course of the first and second years of treatment, the mean RTSS score adjusted for the consumption of rescue medications (AAdSS) was lower in each of the ORALAIR groups than in the placebo group (see Table 2).
**Table 2:** Mean RTSS score, adjusted for the consumption of rescue medications (AAdSS) during the first and second years of treatment (study V053-06)

<table>
<thead>
<tr>
<th></th>
<th>ORALAIR (4 months)</th>
<th>ORALAIR (2 months)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>188</td>
<td>188</td>
<td>205</td>
</tr>
<tr>
<td>Mean adjusted RTSS ± SD</td>
<td>5.44 ± 3.99</td>
<td>5.27 ± 4.02</td>
<td>6.68 ± 4.24</td>
</tr>
<tr>
<td>Difference versus placebo</td>
<td>-1.25 p = 0.0008 [−1.97; -0.52]</td>
<td>-1.48 p &lt; 0.0001 [−2.20; -0.75]</td>
<td></td>
</tr>
<tr>
<td><strong>Year 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>160</td>
<td>155</td>
<td>172</td>
</tr>
<tr>
<td>Mean adjusted RTSS ± SD</td>
<td>4.32 ± 3.76</td>
<td>4.09 ± 3.51</td>
<td>6.18 ± 4.10</td>
</tr>
<tr>
<td>Difference versus placebo</td>
<td>-1.90 p &lt; 0.0001 [−2.69; -1.12]</td>
<td>-2.05 p &lt; 0.0001 [−2.84; -1.26]</td>
<td></td>
</tr>
</tbody>
</table>

During the 3 years of treatment:
- the mean score for use of rescue medications (ARMS, score from 0 to 3 points) was 0.28 (± 0.42) with ORALAIR (4 months) and 0.42 (± 0.49) with the placebo (p = 0.0011);
- the proportion of days with monitored symptoms and without taking rescue medication was 57.1% with ORALAIR (4 months) and 40.7% with the placebo (p < 0.0001).

**Follow-up period after treatments were stopped:**
Only the results of the first year of follow-up are available.

**Table 3:** Mean RTSS score, adjusted for the consumption of rescue medications during the fourth year (study V053-06)

<table>
<thead>
<tr>
<th></th>
<th>ORALAIR (4 months)</th>
<th>ORALAIR (2 months)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>143</td>
<td>137</td>
<td>155</td>
</tr>
<tr>
<td>Mean adjusted RTSS ± SD</td>
<td>4.28 ± 4.06</td>
<td>3.95 ± 3.64</td>
<td>5.34 ± 4.16</td>
</tr>
<tr>
<td>Difference versus placebo</td>
<td>-1.14 p = 0.0114 [−2.03; -0.26]</td>
<td>-1.43 p = 0.0019 [−2.32; -0.53]</td>
<td></td>
</tr>
</tbody>
</table>

During the first year of treatment-free follow-up (fourth year of the study), a minor difference was observed in favour of ORALAIR as regards:
- the mean RTSS score adjusted for the consumption of rescue medications (AAdSS) (see Table 3);
- use of rescue medications (ARMS): 0.35 (± 0.46) with ORALAIR (4 months) versus 0.45 (± 0.49) with the placebo (p = 0.0184);
- the proportion of days with monitored symptoms and without taking any rescue medication: 49.1% with ORALAIR (4 months) versus 40.2% with the placebo (p = 0.0220).
**Efficacy in children and adolescents (Study VO52.06)**

Randomised, double-blind study comparing the efficacy and tolerance of ORALAIR 300 IR to those of placebo in reducing allergy symptoms and the consumption of rescue medications in children suffering from allergic rhinoconjunctivitis caused by grass pollen. This multicentre study was conducted in 5 European countries, including France.

Patients had to be aged from 5 to 17 years and their allergic condition had to date back at least 2 years, with the diagnosis being confirmed by a positive prick-test and the presence of IgE specific for the grass pollens, and a retrospective RTSS symptom score ≥ 12 during the preceding pollen season.

Among the non-inclusion criteria:
- allergic rhinoconjunctivitis caused by an allergen other than grass pollen – patients having intermittent asthma not requiring treatment with nasal or systemic corticosteroids could be included;
- asthma requiring treatment other than with an inhaled beta-2-agonist;
- oral corticosteroids in the 12 weeks prior to the inclusion visit;
- desensitisation treatment to grass pollens or to other allergens during the past 5 years.

Patients were distributed into 2 groups:
- ORALAIR 300 IR/day (n = 139)
- Placebo (n = 139)

**Study design:**
After they were selected, patients received the treatment for about 4 months prior to the start of the pollen season and until its end. Patients were followed up for 2 weeks after the end of the treatment.

**Primary efficacy endpoint:** mean daily RTSS scores during the period of analysis.
An a posteriori analysis was performed on the RTSS endpoint, adjusted for the consumption of rescue medications (AADSS).

**Secondary endpoints:**
- use of rescue medications (ARMS);
- proportion of symptom-free days;
- global evaluation of treatment efficacy by the patient.

For all the efficacy endpoints, the results were analysed in the intention-to-treat population defined as patients receiving at least one dose of treatment and at least one measurement of the RTSS.

**Results:**
A total of 278 patients were randomised, of whom 266 were assigned to the ITT population (i.e. 131 patients in the 300 IR group, and 135 in the placebo group).
The mean retrospective RTSS score was 13.9 points in both groups.
Patients in whom allergic rhinoconjunctivitis was combined with asthma accounted for 16.8% of the patients in the 300 IR group and 17.3% of the total study population and these patients were distributed uniformly between the groups.
Patients were sensitised to a single allergen in 40% of the cases and to more than one allergen in 60% of the cases.
The peak pollen period lasted between 13 and 73 days, depending on the centre, 17 days in the case of France.
- **Primary efficacy endpoint:**
  During the course of the period of analysis, the mean RTSS score was lower in the 300 IR group than in the placebo group (3.25 ± 2.86 versus 4.51 ± 2.93, i.e. a difference of 1.13 points). An analysis of covariance (ANCOVA), taking into account as covariables the retrospective RTSS, age, sex, asthma and sensitisation status, showed that the difference between the groups was statistically significant (p = 0.0010).

After adjustment for the use of rescue medications (AAdSS), the RTSS score was 4.30 ± 3.57 in the 300 IR group and 6.12 ± 3.85 in the placebo group, i.e. a difference of 1.64 points. An analysis of covariance (ANCOVA), taking into account as covariables the asthma, sex, age and sensitisation status, showed that the difference between the treatments was statistically significant (p = 0.0002).

- **Secondary endpoints:**
  The proportion of patients who have used at least one rescue medication was 81.7% in the 300 IR group and 85.2% in the placebo group, with no statistically significant difference. In both groups, patients used rescue medications in a similar way, principally oral antihistamines (> 63.4%). Systemic corticosteroids were used by fewer than 5.2% of patients.

The proportion of days on which rescue treatment was used was 35.36% in the 300 IR group and 46.4% in the placebo group (p = 0.0146).
The proportion of symptom-free days and days without use of rescue medication was 19.2% in the 300 IR group and 10.5% in the placebo group.
The proportion of days with monitored symptoms (RTSS ≤ 2) and without rescue medication was 33.8% in the 300 IR group and 23.7% with the placebo.

### 3.2. Tolerance
In the study in adults (VO34.04), 97/155 patients (63%) in the ORALAIR 300 IR group and 76/156 patients (49%) in the placebo group reported adverse events.
The most common adverse events were oral pruritus (26% versus 5% with placebo) and throat irritation (9% versus 3% with the placebo). The other common adverse effects (≥ 1/100, < 1/10) were: headache, paraesthesia, conjunctivitis, ear pruritus, sensation of a foreign body in the mouth, face oedema, face swelling, pruritus, urticaaria, rhinitis and asthenia.
The majority of adverse events were of mild to moderate intensity. Six out of 155 patients (4%) and none in the placebo group dropped out of the study early due to an adverse event.
In the long-term study (VO53.06), the most common adverse events were again itchy mouth and throat irritation.

In the study in children and adolescents (VO52.06), 118/139 patients (85%) reported an adverse event compared with 114/139 patients (82%) on placebo.
The most common adverse event was, as in the adults, oral pruritus (32% versus 1% with the placebo). The other common adverse events (≥ 1/100, < 1/10) were: eye pruritus, ear pruritus, nasal congestion, sneezing, throat irritation, swollen lips and tongue, oral mucosal blistering, stomatitis, vomiting, cheilitis, glossitis, atopic dermatitis, pruritus.
The majority of adverse events were of mild to moderate intensity. No patients died during the study. Six out of 139 patients (4%) and 1/139 patients (1.5%) in the placebo group dropped out of the study early due to an adverse event.

### 3.3. Conclusion
The efficacy and tolerance of ORALAIR were evaluated in two short-term, randomised, double-blind studies versus placebo, one carried out in adults (VO34.04), the other in children aged from 5 to 17 years (VO52.06) and suffering from allergic rhinoconjunctivitis for at least 2 years. These patients were treated with ORALAIR (100 IR, 300 IR and 500 IR in
adults and 300 IR in children and adolescents) or placebo from about 4 months before the pollen season until its end. The primary efficacy endpoint was the mean total RTSS score during the period of analysis (about 30 days including the pollen peak). This score represents the sum of the individual scores (from 0 to 3) for 6 symptoms, which could vary from 0 to 18.

Adults treated with a dose of 300 IR of ORALAIR (dose adopted by the marketing authorisation) had a lower mean RTSS score than with placebo (3.58 ± 2.97 versus 4.93 ± 3.23 with placebo, i.e. a difference of 1.39 points, p = 0.0001 according to an analysis of covariance taking into account the retrospective RTSS, the asthma and the sensitisation status), the same as after adjustment for consumption of rescue medications (AAdSS score: 4.17 ± 3.39 versus 5.88 ± 3.82 with the placebo, i.e. a difference of 1.84 points p < 0.0001).

Children and adolescents treated with a dose of 300 IR of ORALAIR (dose adopted by the marketing authorisation) had a lower mean RTSS score than with the placebo (3.25 ± 2.86 versus 4.51 ± 2.93 with the placebo, i.e. a difference of 1.13 points, p = 0.0010 according to an analysis of covariance taking into account the retrospective RTSS, asthma and sensitisation status), the same as after adjustment for consumption of rescue medications (AAdSS score: 4.30 ± 3.57 versus 6.12 ± 3.85 with the placebo, i.e. a difference of 1.64 points, p = 0.0002).

The most common adverse events with ORALAIR 300 IR than with the placebo were itchy mouth: 26% versus 5% in adults and 32% versus 1% in children and adolescents.

The long-term efficacy and tolerance were evaluated over 3 years in a randomised double-blind study versus placebo in adults. ORALAIR was administered intermittently from 4 months before the start of the pollen season until its end, with a repeat of the treatment in the following year in accordance with the same regimen. After 3 years, the patients were followed up for a fourth year without treatment.

During the third year of treatment, the mean RTSS score adjusted for the consumption of rescue medications (AAdSS) was lower in each of the ORALAIR 300 IR groups than in the placebo group: 3.46 ± 0.03 versus 5.28 ± 3.94, i.e. a difference of 1.81 (p < 0.0001). This difference was 1.25 in the first year, 1.90 in the second year and 1.14 during the fourth year of follow-up without treatment. As in the short-term study, the most frequent adverse events compared with the placebo were an itchy mouth (25.8% versus 1.8%) and throat irritation (14.6% versus 4.2%).

No comparative studies were carried out versus GRAZAX (timothy pollen oral lyophilisate).

The data for GRAZAX, its closest comparator medicine, are recalled. GRAZAX was compared with the placebo in a study lasting 3 years and conducted in 634 adults aged from 18 to 65 years suffering from allergic rhinoconjunctivitis caused by timothy pollen, as confirmed by a prick-test, for at least 2 years. GRAZAX was administered 4 months before the start of the first pollen season and until the end of the year. The difference between GRAZAX and the placebo (administered under the same conditions as GRAZAX) in terms of the mean total RTSS score measured during the pollen period was 1.29 points (95% CI = [0.90; 1.68], p < 0.001) in favour of GRAZAX (see the Transparency Committee’s opinions of 7 November 2007, 22 July 2009 and 16 February 2011).

During the 2-year study extension phase, the treatment was continued and administered continuously but with a smaller study population than at the start. A statistically significant difference was observed in favour of GRAZAX with respect to the placebo in the RTSS score of 1.36 points (95% CI = [0.86; 1.86], p < 0.001) in the second year and of 1.04 points (95% CI = [0.52; 1.56], p ≤ 0.0001) in the third year.

After 3 years of treatment, patients were followed up without treatment for a further 2 years, during which the statistically significant difference between these two groups was maintained: 0.95 points (95% CI = [0.40; 1.50], p = 0.0007) in the fourth year of the study, and 0.84 points (95% CI = [0.28; 1.40], p = 0.0037) in the fifth year.
In addition, the consumption of rescue medications was reduced in a statistically significant manner in the GRAZAX group in comparison with the placebo group during the first 4 years; no statistically significant difference in this criterion was observed in the fifth year.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Allergic rhinitis and allergic conjunctivitis are common conditions that can impair quality of life because of the inconvenience they cause.

This proprietary medicinal product provides preventive treatment.

Public-health benefit:

- Allergic rhinitis represents a low public health burden. Improving its management is not a need which is part of an established public health priority.
- The clinical data available for the proprietary medicinal product ORALAIR does not allow the anticipated impact of ORALAIR in terms of morbidity and quality of life to be estimated as compared with current therapeutic management of allergic rhinitis.
- Consequently, ORALAIR is not expected to benefit public health in this indication.

The efficacy/tolerance ratio is modest.

It is a second-line therapy.

There are treatment alternatives.

The actual benefit of the proprietary medicinal product ORALAIR is low.

4.2. Improvement in actual benefit (IAB)

The Transparency Committee took account of the small quantitative effect which ORALAIR has been shown to have on the treatment of rhinitis and conjunctivitis triggered by grass pollens. The APSIs (allergens prepared for a single individual), used in these same indications, because they are not proprietary medicinal products, have not undergone clinical assessment, nor do they have marketing authorisation.

Consequently, the Committee is of the opinion that ORALAIR, like GRAZAX, offers a minor improvement in actual benefit (IAB IV) in the management of allergic rhinitis and conjunctivitis triggered by grass pollens in patients who do not respond adequately to treatments that address the symptoms, i.e. antihistamines and/or corticosteroids administered by any route.

4.3. Therapeutic use

Allergic rhinitis and allergic conjunctivitis are common conditions which can impair quality of life because of the inconvenience they cause.

4.3.1. Therapeutic strategy

Treatment is based on three approaches: removing the allergen where possible, symptomatic treatment, and desensitisation.

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Symptomatic treatment relies on oral antihistamines, local or oral corticosteroids, sometimes cromones, and decongestants.

Treatment by allergen immunotherapy requires that:
- the patient is motivated, the discomfort experienced is sufficiently severe, and the result of symptomatic treatment is inadequate;
- the allergen is identified by interviewing the patient and performing skin and/or blood tests.

Desensitisation has proved to be effective for mites, *Alternaria* fungus and pollens (grass and pellitory pollens).

The sublingual route is currently preferred to the subcutaneous route.

4.3.2. Role of the proprietary medicinal product

ORALAIR can be offered as a second-line treatment when symptomatic treatment by antihistamines and/or corticosteroids has proved inadequate. If no significant improvement in symptoms is seen, treatment should not be continued the following year.

4.4. Target population

ORALAIR is indicated for the “treatment of allergic rhinitis, with or without conjunctivitis, caused by grass pollens, 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 pollens.”

The target population of ORALAIR is patients with a confirmed diagnosis of allergic rhinitis caused by grass pollen and inadequately controlled by symptomatic treatments.

The prevalence of allergic rhinitis in the general adult population in France is estimated at 24.5% (21.0%-28.0%)\(^7\), i.e. between 5 and 7 million people in the population of 18 to 45-year-olds in France.\(^8\) The ISAAC Study\(^9\) in children and adolescents carried out in Western European countries estimated the prevalence of allergic rhinitis at 8.5% among children aged 6 to 7 years and 14.4% among children aged 13 to 14 years. Extrapolating this data to the French population of children aged between 5 and 12 and between 13 and 17, gives a figure of around one million children and adolescents suffering from allergic rhinitis in France.

The study conducted by Bauchau et al.\(^7\) found grass pollen allergy (presence of specific IgEs) in 52% of patients diagnosed with allergic rhinitis. 54% of these patients had been diagnosed prior to the study and 79% were receiving treatment. On this basis, the population receiving treatment for allergic rhinitis caused by grass pollen is estimated at between 1 and 1.5 million adults and around 250,000 children and adolescents.

Of the patients treated, almost 30%\(^11\) reported a lack of efficacy in relation to the treatment with antihistamines and/or corticosteroids, i.e. a total of between 300,000 and 450,000 adults and around 70,000 children and adolescents.

The target population for ORALAIR is estimated at between 300,000 and 450,000 adults and around 70,000 children and adolescents.

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\(^8\) Population of 18-45 year olds in France on 1 January 2010: 23 661 798 (Source: http://www.insee.fr)

\(^9\) Aït-Khaled N. et al., Global map of the prevalence of symptoms of rhinoconjunctivitis in children: the international study of asthma and allergies childhood (ISAAC) phase three 2009, Allergy, 64, 123-148

\(^10\) Population of 5-12-year-olds in France on 1 January 2010: 6,359,968; population of 12-17-year-olds in France as of 1 January 2010: 3,906,288 (Source: http://www.insee.fr)

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosages given in the Marketing Authorisation.

Treatment with ORALAIR should be initiated exclusively by doctors experienced in the treatment of allergic conditions.

The Committee considers that a study should be set up to examine the following aspects under actual conditions of use:
- the characteristics of patients being treated with ORALAIR: sociodemographic data, antecedents, comorbidities, diagnosis and confirmation of diagnosis, history and severity of the disease, past treatments, etc.;
- the characteristics of prescribing physicians (discipline, practice type, etc.);
- the details of prescription (indication, dosage, concomitant treatments including antihistamines, local corticosteroids, cromones, decongestants, how long before the grass pollen season did treatment start, etc.) and the therapeutic use;
- the compliance rate for the treatment;
- the frequency of discontinuations and the reasons for them;
- the frequency of adverse effects;

The duration of the study, to be decided by an independent scientific committee, must be justified and must be long enough to meet the Committee's request, and in particular must take account of the seasonal nature of allergic rhinoconjunctivitis triggered by grass pollen.

Packaging: appropriate for the prescription conditions.

Reimbursement rate: 15%