Opinion
8 January 2014

WYSTAMM 1 mg/ml, oral solution
120 ml vial with syringe for oral administration (CIP: 34009 222 560 2 3)

Applicant: BOUCHARA-RECORDATI

<table>
<thead>
<tr>
<th>INN</th>
<th>rupatadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2013):</td>
<td>R06AX28 (antihistamines for systemic use)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
</tbody>
</table>
| Lists concerned | National Health Insurance (French Social Security Code L.162-17)  
<p>|                 | Hospital use (French Public Health Code L.5123-2) |
| Indication concerned | &quot;Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11&quot; |</p>
<table>
<thead>
<tr>
<th>Actual Benefit</th>
<th>Moderate AB pending re-assessment of oral antihistamines.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in Actual Benefit</td>
<td>No improvement in actual benefit (IAB V) compared with other oral H1 antihistamines available in oral form.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>First-line treatment.</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)  
06/08/2012 (decentralised procedure)

Prescribing and dispensing conditions / special status  
List II

ATC Classification  
2013 
  R    Respiratory system 
  R06   Antihistamines for systemic use 
  R06A  Antihistamines for systemic use 
  R06AX Other antihistamines for systemic use 
  R06AX28 Rupatadine

02 BACKGROUND

WYSTAMM 1 mg/ml, oral solution, is a children's version of the proprietary medicinal product WYSTAMM already available in tablet form at a dose of 10 mg indicated in adults and adolescents (aged 12 and above). This proprietary medicinal product is restricted to children aged 6 to 11.

03 THERAPEUTIC INDICATIONS

"Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11."

04 DOSAGE

"Children aged 6 to 11 whose body weight is greater than or equal to 25 kg. 
5 ml (5 mg of rupatadine) of oral solution once a day, to be taken with or without food. 
The safety of use and efficacy of rupatadine have not been established in children of 2 to 5 years of age below 25 kg (see also section 4.4\(^1\)). 
Use of rupatadine is not recommended in children under 2 years of age as there are no data in this population (see section 4.4\(^1\)). 
The 10 mg tablet form of rupatadine is better adapted to adults and adolescents (aged 12 and above). 

Patients with renal or hepatic failure:
Use of rupatadine is not recommended in patients with renal or hepatic failure as there are no data in these populations."

\(^1\) Of the SPC
**Therapeutic Need**

According to guidelines from the European Academy of Allergy and Clinical Immunology (2000), the therapeutic strategy is based on the classifying of allergic rhinitis into seasonal allergic rhinitis primarily caused by pollen and perennial allergic rhinitis primarily caused by dust mites and animal dander.

The proposed therapeutic strategy in these guidelines is as follows:

- **In adults:**
  - In the case of seasonal allergic rhinitis:
    - *mild or occasional symptoms*: H1 antihistamines; cromones may be an alternative;
    - *moderate or frequent symptoms*: nasal corticosteroids; add an H1 antihistamine if the symptoms cannot be controlled;
    - *severe symptoms*: intranasal corticosteroid/H1 antihistamine combination; when the combination does not allow for the symptoms to be controlled, a short-term oral corticosteroid or an alternative symptomatic treatment will be added; otherwise immunotherapy may be considered.
  - In the case of perennial allergic rhinitis:
    - *allergen avoidance* where possible;
    - *mild or occasional symptoms*: H1 antihistamines;
    - *moderate or frequent symptoms*: nasal corticosteroids; add an H1 antihistamine if the symptoms cannot be controlled;
    - *severe symptoms*: intranasal corticosteroid/H1 antihistamine combination; when the combination does not allow for the symptoms to be controlled, the choice of treatment will be made based on the symptoms which persist;
    - *persistent nasal obstruction*: short-term local or oral decongestant or short-term oral corticosteroid treatment; in the event of failure, a turbinectomy may be considered;
    - *persistent rhinorrhea*: intranasal ipratropium; immunotherapy may be considered.

- **In children:**
  - Allergen avoidance and environment control are more important in children than in adults so as to avoid new sensitivities or involvement of other tissues. H1 antihistamines are a first-line drug treatment. If there is not enough control of the symptoms, the treatment is continued with a nasal corticosteroid by adjusting the dosage depending on age and the existence of joint treatment of the asthma with local corticosteroids. In the event of failure, a local corticosteroid/antihistamine combination can be tried. Immunotherapy may be considered as a last resort.

In the therapeutic strategy from ARIA guidelines (updated in 2008³ and 2010⁴), an alternative classification of allergic rhinitis was defined depending on the duration and intensity of symptoms. Thus, depending on how long the condition lasts, we distinguish intermittent allergic rhinitis (symptoms lasting less than 4 days a week and less than 4 weeks a year) and persistent allergic rhinitis (symptoms lasting more than 4 days a week and more than 4 weeks a year). Two stages of severity are identified: with mild symptoms and with moderate to severe symptoms. About 1/3 of seasonal allergic rhinitis and perennial allergic rhinitis cases are cases of persistent allergic rhinitis. According to these guidelines, H1 antihistamines form part of a first-line treatment strategy for mild and moderate-severe intermittent allergic rhinitis and mild persistent forms. H1 antihistamines are

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also recommended as a second-line treatment in severe persistent forms in combination with a nasal corticosteroid after nasal corticosteroids alone have failed. The 2010 update of these guidelines specifies the benefit of these second-generation oral antihistamines compared with first generation oral antihistamines and the benefit of second generation oral antihistamines compared with intranasal antihistamines. Intranasal corticosteroids are to be preferred over second-generation oral antihistamines as they are more effective (lower efficacy profile in children), whilst second-generation oral antihistamines may be used as a first-line treatment if the oral route is preferred over the nasal one. These guidelines do not take into account the level of severity of the symptoms.

In children, the treatment principles are the same with the necessary precautions put in place to avoid the side effects that are typical in this age range, particularly with corticosteroids.

## 06 CLINICALLY RELEVANT COMPARATORS

### 06.1 Medicinal products

<table>
<thead>
<tr>
<th>INN</th>
<th>Proprietary medicinal product</th>
<th>Indication</th>
<th>Date of TC opinion</th>
<th>AB</th>
<th>Reimbursed</th>
<th>INN</th>
<th>Proprietary medicinal product</th>
<th>Indication</th>
<th>Date of TC opinion</th>
<th>AB</th>
<th>Reimbursed</th>
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<tbody>
<tr>
<td><strong>Second-generation antihistamines (non-anticholinergics)</strong></td>
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<tr>
<td>cetirizine</td>
<td>VIRLIX Sanofi Aventis France</td>
<td>In adults and children aged 2 and above:</td>
<td>7 September 2011</td>
<td>Allergic rhinitis Moderate AB</td>
<td>Yes</td>
<td>desloratadine</td>
<td>AERIUS MSD France</td>
<td>Symptomatic treatment of allergic rhinitis</td>
<td>15 February 2012</td>
<td>Symptomatic treatment of allergic rhinitis Moderate AB</td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
<td>· treatment of nose and eye symptoms in seasonal and perennial allergic rhinitis.</td>
<td></td>
<td>Chronic idiopathic urticaria Moderate AB</td>
<td></td>
<td>loratadine</td>
<td>CLARITYNE Schering-Plough</td>
<td>Symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.</td>
<td>16 November 2011</td>
<td>Symptomatic treatment of allergic rhinitis Moderate AB</td>
<td>Yes</td>
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<td>· treatment of symptoms of chronic idiopathic urticaria.</td>
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<td><strong>First-generation antihistamines (anticholinergics)</strong></td>
<td></td>
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<td>alimemazine</td>
<td>THERALENE UCB Pharma SA</td>
<td>Occasional insomnia. Temporary insomnia. Pre-medication before general anaesthesia in children. Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria.</td>
<td>14 December 2011</td>
<td>Occasional insomnia, temporary insomnia: Provisionally low AB, pending conclusions from its re-assessment by the AFSSAPS [French Agency for the Safety of Health Products] currently under way. Symptomatic treatment of various allergic manifestations: rhinitis (seasonal or perennial), conjunctivitis, urticaria.</td>
<td>Yes</td>
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<tr>
<td>INN</td>
<td>Proprietary medicinal product</td>
<td>Indication</td>
<td>Date of TC opinion</td>
<td>AB</td>
<td>Reimbursed Yes/No</td>
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| mequitazine | PRIMALAN Pierre Fabre Médicament | Symptomatic treatment of allergic manifestations:  
· allergic rhinitis (seasonal or perennial),  
· conjunctivitis,  
· urticaria. | 9 September 2009 | Yes | The actual benefit of these proprietary medicinal products remains insufficient.  
- moderate in allergic rhinitis (seasonal or perennial) and urticaria.  
- low in allergic conjunctivitis. | Yes |

06.2 Other health technologies
Not applicable.

Conclusion
The most relevant comparators are second-generation (non anticholinergics) antihistamines.
### INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

<table>
<thead>
<tr>
<th>Country</th>
<th>Reimbursement</th>
<th>Scope (indications) and condition(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Yes (18/10/2012)</td>
<td>Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11. Reimbursement rate: 100%.</td>
</tr>
<tr>
<td>Belgium</td>
<td>No</td>
<td>Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11. Marketed without application for reimbursement since 01/10/2012.</td>
</tr>
<tr>
<td>Spain</td>
<td>Yes (15/03/2013)</td>
<td>Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11. Reimbursement rate: 40-60% depending on the patient's income.</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes (01/05/2012)</td>
<td>Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11. Reimbursement rate: 100%.</td>
</tr>
<tr>
<td>Poland</td>
<td>No</td>
<td>Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11. Marketed without application for reimbursement since 23/10/2012.</td>
</tr>
<tr>
<td>Portugal</td>
<td>No</td>
<td>Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11. Marketed without application for reimbursement since 04/01/2013.</td>
</tr>
</tbody>
</table>
08  ANALYSIS OF AVAILABLE DATA

The evaluation of the efficacy and safety of rupatadine in children aged 6 to 11 in the treatment of allergic rhinitis is based on a randomised, double-blind versus placebo study (DC04/RUP/3/08).

08.1 Efficacy

<table>
<thead>
<tr>
<th>DC04/RUP/3/08 study</th>
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<tr>
<td><strong>Principal study objective</strong></td>
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<tr>
<td><strong>Method</strong></td>
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</tbody>
</table>
| **Inclusion criteria** | - Children aged 6 to 11 inclusive  
- Weight \( \geq 16 \) kg  
- A history of persistent allergic rhinitis (symptoms lasting more than 4 days a week) for at least 12 months prior to selection  
- Positive prick test of 3 mm or more than the negative control test with at least one of the following allergens: fungal spores (Alternaria, Aspergillus, Cladosporium), grass pollen (bermuda and rye)  
- Symptoms lasting more than 4 weeks due to the allergen for which the skin test was positive (ARIA guideline). |
| **Treatment groups** | - Rupatadine: 2.5 mg (2.5 ml of 1 mg/ml rupatadine solution) in children with a weight lower than 25 Kg and 5 mg (5 ml of 1 mg/ml rupatadine solution) in children with a weight greater than 25 Kg  
- Placebo. |
| **Associated treatments** | Use of rescue medicines because of the severity of one of the evaluated symptoms was considered as a treatment failure and the patient was excluded from the study. |
| **Primary efficacy endpoint:** | Change in total score of 4 symptoms (T4SS): nasal congestion, sneezing, rhinorrhea, itching of the neck/mouth/throat/ears at 28 days compared with what it was at baseline.  
The total average score of 4 symptoms (T4SS) was evaluated daily by the patients using a scale of 4 levels: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. |
| **Secondary included endpoints** | Change of the T4SS after 42 days of treatment compared with what it was at baseline. |
| **Statistical analysis** | The main population for the efficacy and safety analysis was the ITT population.  
An analysis of covariance test was used to analysis the primary endpoint (T4SS) with the treatment as primary factor, the centre as factor and the baseline score as covariable. |

**Results:**
A total of 360 patients were randomised: 180 patients in the placebo group and 180 patients in the rupatadine oral solution group.  
The characteristics of patients were the same between the two groups.  
The patients were on average 8.8 years of age and were primarily boys (60%). Their average weight was 31.4 kg with an average BMI of 17.3 kg/m^2. The T4SS score at baseline was 7.2 (± 1.1).  

**Primary efficacy endpoint (ITT):**
The decrease in the T4SS score at 28 days compared with what it was at baseline was more significant in the rupatadine group (-3.1) than in the placebo group (-2.5, \( p = 0.018 \)).
Secondary endpoints (ITT):
After 42 days of treatment, the difference in favour of rupatadine in terms of a change in the T4SS score compared with what it was at baseline was: -3.3 with rupatadine versus -2.7 with placebo (p = 0.048).

08.2 Safety/Adverse effects

DC04/RUP/3/08 study
Adverse events were observed in 37.2% of patients in the rupatadine group and in 30.0% of patients in the placebo group.
The adverse events most commonly reported with rupatadine were headaches (12.8%). In the placebo group, the most common adverse events were headaches (5.6%) and a cough (3.9%).
There was no serious adverse event during the study.

Summary of product characteristics
Infections of the upper respiratory tract, headaches and drowsiness also figured among the common adverse effects (≥1/100 to < 1/10).

08.3 Summary & discussion
The efficacy and safety of rupatadine oral solution in the treatment of allergic rhinitis in children aged 6 to 11 were evaluated in a randomised, double-blind versus placebo study, lasting 42 days.
The patients included had to have had persistent allergic rhinitis for at least 1 year, confirmed by a prick test and symptoms caused by the allergen for which the skin test was positive lasting at least 4 weeks prior to baseline.
A total of 360 patients were randomised to receive either rupatadine (2.5 mg in children with a weight lower than 25 kg and 5 mg in children with a weight greater than 25 kg) or a placebo.
At baseline, the patients had an average T4SS score of 7.2 in the two groups (scale of 12 points).
The decrease in the T4SS score at 28 days compared with what it was at baseline (primary efficacy endpoint) was more significant in the rupatadine group than in the placebo group: -3.1 with rupatadine versus -2.5 with placebo (p = 0.018).
After 42 days of treatment, the difference in favour of rupatadine in terms of a change in the T4SS score compared with what it was at baseline was: -3.3 with rupatadine versus -2.7 with placebo (p = 0.048).
The differences observed between rupatadine and placebo, although statistically significant, are small (0.6 points at 28 and 42 days) and not very clinically relevant. Rupatadine oral solution has not been compared with any other H1 antihistamine available as an oral solution.
Headaches were the adverse event most commonly reported in the rupatadine group (12.8%).
09 THERAPEUTIC USE

In children, WYSTAMM oral solution is a first-line treatment in allergic rhinitis (including its persistent form).

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

▶️ Allergic rhinitis is not a serious condition. However, in its chronic form, it can gradually deteriorate a patient's quality of life.

▶️ This medicinal product is part of a symptomatic treatment.

▶️ The efficacy/adverse effects ratio for this medicinal product is modest.

▶️ There are treatment alternatives.

▶️ This medicinal product is a first-line therapy.

Taking account of these points, the Committee considers that the actual benefit of WYSTAMM 1 mg/ml oral solution is moderate in the indication of the Marketing Authorisation pending the reassessment of the class of oral antihistamines.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) in children aged 6 to 11" and at the dosages in the Marketing Authorisation.

▶️ Proposed reimbursement rate: 30%

010.2 Improvement in actual benefit (IAB)

WYSTAMM 1 mg/ml oral solution does not provide an improvement in actual benefit (IAB V) compared with other oral antihistamines in oral form.
010.3 Target population

In an epidemiology study carried out in Western Europe in 2004,\textsuperscript{5} the prevalence of allergic rhinitis confirmed by a clinical examination in adults over 18 years of age was estimated to be 24.5\%. If we extrapolate these results to children, according to INED [National Institute for Demographic Studies] data (2012), amongst the French population, allergic rhinitis affects approximately 1,180,000 children of 6 to 11 years of.

According to this same study, the prevalence of allergic rhinitis treated with medicines in adults aged 18 and over was estimated to be 11\%, i.e. extrapolating it to children, a population of 530,000 children aged 6 to 11 suffering from allergic rhinitis and treated by medicine.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- **Packaging**

  The 120 ml packaging is not suitable for a month's treatment.

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\textsuperscript{5} Bauchau V and Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy*, 2005; 60: 350-53.