Rupafin® (Rupatadine) Paediatric Oral Solution
1 mg/mL

1. Pharmacokinetics in Children

Specific pharmacokinetic data about Rupafin® paediatric oral solution 1 mg/mL in children aged 6–11 years with allergic rhinitis are available from a phase II, proof-of-concept trial.

In this open-label trial, 5 boys and 6 girls of mean age 10.2 years and mean bodyweight 38.5 kg received once-daily Rupafin® 2.5 or 5 mL for 4 weeks. Rupafin® was rapidly absorbed, as evident from a median T$_{\text{max}}$ value of 0.50 h, which was similar to the value previously reported in adults (0.75–1 h). In children, the active metabolites of Rupafin® (i.e. BCP and hydroxy-BCP) had T$_{\text{max}}$ values of 2 h and 4 h, respectively, which were also similar to corresponding values in adults. In children, mean peak plasma concentration (C$_{\text{max}}$) values were similar for Rupafin® (2.50 µg/L) and BCP (2.51 µg/L), although the value for hydroxy-BCP was markedly lower (0.57 µg/L) [Figure 1]. The mean value for Rupafin® C$_{\text{max}}$ in children (2.50 µg/L) was similar to that previously reported in adults (2.60 µg/L), and the same was true for area under the plasma Rupafin® concentration vs time curve (AUC$_{0-\infty}$: 8.86 µg•h/L [children]; 9.20 µg•h/L [adults]).
Figure 1. Mean plasma concentration vs time profiles for Rupafin® and its metabolites.

The elimination half-life of Rupafin® was faster in children (3.12 h) than adults (5.80 h), whereas the clearance value in children (514 L/h) was similar to that previously documented in adults (467 L/h).

Overall, pharmacokinetic findings from this phase II study support the recommendation that the Rupafin® dosage in children aged 6–11 years (and with bodyweight <25 kg) should be half that in adults and adolescents aged ≥12 years.

No specific drug interaction studies of Rupafin® have been conducted in children. The reader is therefore referred to detailed reviews containing information about potential Rupafin® drug interactions in non paediatric populations.
1.1. **POPULATION PHARMACOKINETICS**

Based on the data of the abovementioned pharmacokinetic trial, a population pharmacokinetic model was also developed with the aim of characterizing the pharmacokinetic profile of children aged between 6-11 years; that is, to obtain the population parameters that describe the pharmacokinetics of Rupafin® and the inter-individual variability.

The model was developed using specific software which simulates a thousand individual concentration-time profiles generated using the fixed and random population estimated by the model, assuming different body weights. Different parameters (statistically known as covariates) were tested in the model, but only bodyweight was found to influence the pharmacokinetics of Rupafin®, as expected from results previously reported for other drugs with similar characteristics.

Results from simulations for populations with a bodyweight of 10 kg, 15 kg, 20 kg and 24 kg are shown in Figure 2 (after the administration of a single oral dose of 2.5 mg) and Figure 3 (after the administration of a single oral dose of 5 mg):
Figure 2. Results from simulations (one thousand virtual individual pharmacokinetic profiles for Rupafin® were simulated) after the administration of a single oral dose of 2.5mg in children using the model estimates. Solid thin lines cover the area including 98% of the simulated concentrations, and the thick line represents the mean of the simulated profiles. Upper left panel data simulated for a population weighing 10kg. Upper right panel, data simulated for a population weighing 15kg. Lower left panel data simulated for a population weighing 20kg. Lower right panel, data simulated for a population weighing 24kg.
Figure 3. Results from simulations (one thousand virtual individual PK profiles for Rupafin® were simulated) after the administration of a single oral dose of 5mg in children using the model estimates. Solid thin lines cover the area including 98% of the simulated concentrations, and the thick line represents the mean of the simulated profiles. Upper left panel data simulated for a population weighing 10kg. Upper right panel, data simulated for a population weighing 15kg. Lower left panel data simulated for a population weighing 20kg. Lower right panel, data simulated for a population weighing 24kg.

Overall, this population pharmacokinetic study confirmed that the pharmacokinetics of Rupafin® depend on the bodyweight of children. A 2.5 mg dose of Rupafin® oral solution in children with a bodyweight in the range 10 to 25 kg and a dose of 5 mg in children with a bodyweight > 25 kg showed similar exposure to that obtained in adults and adolescents with a dose of 10 mg in tablets.
2. Clinical Efficacy of Rupafin® in Children with Allergic Rhinitis

2.1. Phase IIa and Phase III Clinical Trials

2.1.1. PHASE IIa – EFFICACY ASSESSMENT

A phase IIa study of Rupafin® was conducted in Australia: the planned sample size was 18 patients, but the final study population comprised 11 children (5 boys, 6 girls) with seasonal allergic rhinitis; mean age was 10.2 years, mean height 1.4 m, and mean body mass index (BMI) 18.8 kg/m². Part one of this open-label trial involved single-dose pharmacokinetic sampling over 48 h and part two involved 4 weeks’ administration of Rupafin® paediatric oral solution 1 mg/mL once daily (Figure 4). Children with bodyweight <25 kg received 2.5 mL (2.5 mg) once daily; and children with bodyweight ≥25 kg received 5 mL (5 mg) once daily.

Figure 4. Design of a phase IIa study of Rupafin® paediatric oral solution 1 mg/mL in children aged 6–11 years with seasonal allergic rhinitis.

h, hours; PD, pharmacodynamic; PK, pharmacokinetic; V, visit.
Besides pharmacokinetic assessments, this open-label trial involved evaluations of: the peripheral H₁-antihistaminic activity of Rupafin®; the effects of Rupafin® on allergic symptom control; and Rupafin® tolerability. That is, flare testing was conducted at 5 sites on each child’s back at pre-study screening and at visit 3: intradermal provocation injections comprised control (0.05 mL saline); and histamine 0.1, 0.2, 0.4 and 0.8 µg, each in 0.05 mL saline. Flare areas were recorded every 2 minutes after injection, for 10 minutes, by placing an appropriately labelled acetate sheet over each flare and tracing around the flare. The diameter of each flare was measured from acetate sheets using a Visitrack image analyser. At pre-study screening, to enter the trial, each child had to have a negative response (flare diameter <20 mm) to the saline control, and a positive response (flare diameter >20 mm) to each histamine concentration.

Allergic symptom control was assessed by total five-symptom score (5TSS) from patient diary cards. The symptoms assessed were: nasal congestion; sneezing; rhinorrhea; itchy nose, mouth, throat and/or ears; and itchy, watery and red eyes. Each symptom was scored on a scale from 0–4: 0, no symptoms; 1, mild; 2, moderate; 3, severe; and 4, very severe.

Tolerability evaluations comprised: a physical examination, including BMI measurement; a 12-lead ECG at pre-study screening and visit 3; biochemical and haematological laboratory tests in the screening period and at visits 2 and 3; and the incidence of adverse events.

2.1.2. Results

Rupafin® paediatric oral solution 1 mg/mL provided significant peripheral antihistaminic activity after 4 weeks in children aged 6–11 years with allergic rhinitis (Figure 5); this marked efficacy was attained at levels of Rupafin® exposure similar to those previously reported in adults. A significant (p<0.001)
increase in flare size was evident in line with increasing histamine concentrations, but at 4 weeks, analysis of variance revealed a statistically significant (p=0.026) effect for Rupafin® in reducing mean flare size.

**Figure 5.** Rupafin® paediatric oral solution 1 mg/mL has significant peripheral antihistaminic activity in children with allergic rhinitis: data show the reduction in histamine-induced mean flare size over 4 weeks.

Significantly improved symptoms of allergic rhinitis were also noted after 4 weeks’ Rupafin® administration. Overall, Rupafin® significantly reduced 5TSS by 67% from baseline (p=0.041), and total nasal symptoms score (4TSS) by 63% from baseline (p=0.021) [Figure 6].
Figure 6. Rupafin® paediatric oral solution 1 mg/mL significantly reduces clinical symptoms of allergic rhinitis in children.

5TSS, total symptom score for nasal congestion; sneezing; rhinorrhoea; itchy nose, mouth, throat and/or ears; and itchy, watery and red eyes.

4TSS, total symptom score for the 4 nasal symptoms.

Statistical significance: *p=0.041, **p=0.021 for Rupafin® (4 weeks) vs baseline.
2.1.3. **PHASE III – PIVOTAL EFFICACY AND SAFETY ASSESSMENT**

A multicentre, phase III study was conducted to demonstrate the efficacy of Rupafin® paediatric oral solution 1 mg/mL in improving nasal symptom control over 4–6 weeks in children aged 6–11 years with ARIA-defined persistent allergic rhinitis (i.e. symptoms on >4 days/week and for >4 weeks). This randomised, double-blind, placebo-controlled trial was performed at 34 sites in Argentina (n=12), Hungary (8), South Africa (10) and Spain (4). Among a total of 445 patients screened, 360 were randomised to receive Rupafin® (as per the dosage schedule in the phase II trial; n=180) or placebo (180) for 6 weeks. That is, Rupafin®-treated patients received 2.5 mg (2.5 mL) once daily (bodyweight <25 kg) or 5 mg (5 mL) once daily (bodyweight ≥25 kg) [Figure 7].

![Phase III study design](image)

**Figure 7.** Design of a phase III study of Rupafin® paediatric oral solution 1 mg/mL in children aged 6–11 years with persistent allergic rhinitis. od, once daily
Principal inclusion criteria comprised: persistent allergic rhinitis for ≥12 months; a total nasal symptom score (4TSS; nasal congestion, itching, sneezing, rhinorrhoea) of ≥24 over 4 days during the 2-week screening period; a positive skin-prick test (>3 mm more than a negative control) to house dust mites, fungal spores and/or grass pollens; and bodyweight ≥16 kg. Demographic data for the 360 patients randomised are shown in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rupafin® (n=180)</th>
<th>Placebo (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>8.7 (1.7)</td>
<td>8.8 (1.7)</td>
</tr>
<tr>
<td>Sex; no. (%) male</td>
<td>106 (58.9)</td>
<td>111 (61.7)</td>
</tr>
<tr>
<td>Race; no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>20 (11.1)</td>
<td>19 (10.6)</td>
</tr>
<tr>
<td>Black</td>
<td>31 (17.2)</td>
<td>32 (17.8)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>84 (46.7)</td>
<td>88 (48.9)</td>
</tr>
<tr>
<td>Other</td>
<td>45 (25.0)</td>
<td>41 (22.8)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.33 (0.1)</td>
<td>1.34 (0.1)</td>
</tr>
<tr>
<td>Bodyweight, kg</td>
<td>31.0 (9.3)</td>
<td>31.8 (9.8)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>17.1 (2.8)</td>
<td>17.4 (3.0)</td>
</tr>
</tbody>
</table>

* Mean (± SD), unless otherwise stipulated.

The main population for efficacy analyses was the intent-to-treat population (n=360). The primary study endpoint was allergic rhinitis symptom severity, assessed by mean change from baseline in 4TSS over 4 weeks. Key secondary study endpoints comprised: mean changes from baseline in 4TSS over 6 weeks, and mean changes in 5TSS over 4 and 6 weeks; mean daily 5TSS; and assessment of QoL.
from the Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)\textsuperscript{10} (see section 4.2). Safety evaluations, in all study participants who received ≥1 dose of study medication, involved ECG and blood testing at baseline and the final study visit, and adverse event recording throughout the trial (see section 5).\textsuperscript{40}

2.1.4. Nasal and total symptoms

This phase III study is the first to provide definitive clinical evidence of efficacy for an oral H\textsubscript{1}-receptor antagonist in children with persistent allergic rhinitis. Despite a marked placebo effect, Rupafin\textsuperscript{®} paediatric oral solution 1 mg/mL reduced 4TSS over 4 and 6 weeks (Figure 8), and 5TSS over 4 weeks (Figure 18), to a significantly greater extent than placebo. The mean baseline 4TSS value was 7.2 in both groups, but mean reductions in this parameter over 4 weeks were 3.1 (−43.1% from baseline) in the Rupafin\textsuperscript{®} group compared with 2.5 (−34.7%) in the placebo group (analysis of covariance [ANCOVA]; p=0.018 for difference). Corresponding decreases at 6 weeks were 3.3 (−45.8%) and 2.7 (−37.5%) [p=0.048; ANCOVA].
Figure 8. Rupafin® paediatric oral solution 1 mg/mL is significantly more effective than placebo in reducing nasal symptoms over 4–6 weeks in children with persistent allergic rhinitis.

4TSS, total symptom score for 4 nasal symptoms: congestion; sneezing; rhinorrhea; itchy nose, mouth, throat and/or ears.

Statistical significance (ANCOVA): *p=0.048, **p=0.018 for Rupafin® vs placebo.

Regarding 5TSS, mean values at baseline were 8.5 in the Rupafin® group and 8.4 in the placebo group. Respective mean decreases at week 4 were 3.5 (−41.2% from baseline) and 2.8 (−33.3%) [p=0.03 for difference; ANCOVA]. Decreases at week 6 revealed no statistically significant difference between groups: 3.8 (−44.7%) in the Rupafin® group, compared with 3.1 (−36.9%) in the placebo group (p=0.08 for difference; Figure 18); however, at 6 weeks in the per-protocol population (Rupafin®, n=138; placebo, n=137), Rupafin® was significantly more effective than placebo regarding patient-assessed and
investigator-assessed reductions from baseline in instantaneous 5TSS values (p=0.005 and p=0.034, respectively).

Figure 9. Rupafin® paediatric oral solution 1 mg/mL is significantly more effective than placebo in reducing total symptom score over 4 weeks in children with persistent allergic rhinitis. 5TSS, total symptom score for: nasal congestion; sneezing; rhinorrhea; itchy nose, mouth, throat and/or ears; and itchy, watery and red eyes.

Statistical significance (ANCOVA): *p=0.03 for Rupafin® vs placebo.

2.1.5. Onset of action

Throughout the trial, mean daily 5TSS values were markedly lower in Rupafin® than placebo recipients. Moreover, a rapid onset of action was evident for Rupafin® (Figure 10): 12 h after the first
ingestion of study medication, the mean daily 5TSS value was 6.1 in the Rupafin® group compared with 6.8 in the placebo group (p=0.032 for difference; ANOVA).

Figure 10. Rupafin® paediatric oral solution 1 mg/mL has a rapid and sustained effect in reducing nasal and ocular symptoms in children with persistent allergic rhinitis. 40

5TSS, total symptom score for: nasal congestion; sneezing; rhinorrhea; itchy nose, mouth, throat and/or ears; and itchy, watery and red eyes.

Statistical significance: p=0.032 (ANOVA) for Rupafin®–placebo difference 12 h after first dose of study medication.

2.1.6. Reductions in individual symptoms
Mean reductions in daily scores for individual symptoms were markedly greater with Rupafin® compared with placebo from baseline to week 6 (Figure 20). After 6 weeks of treatment, statistically significant differences between Rupafin® and placebo recipients were seen for `runny nose’ (p=0.023) and `itchy nose, mouth, throat and/or ears’ (p=0.04).

**Figure 11.** Mean reductions from baseline in daily symptom score for individual symptoms over the 6-week study period with Rupafin® paediatric oral solution 1 mg/mL or placebo in children with persistent allergic rhinitis.

DSS, daily symptom scores (i.e. reflective scores for individual symptoms from patient diary cards).

Statistical significance (Rupafin® vs placebo): *p=0.04; **p=0.023.
2.1.7. **Effect on Quality of Life**

A secondary endpoint in the phase III study of Rupafin® paediatric oral solution 1 mg/mL in children with persistent allergic rhinitis was QoL, assessed by PRQLQ responses at weeks 4 and 6.

Validated in children, the PRQLQ consists of 23 items in five domains (nose symptoms, eye symptoms, practical problems, activity limitation and other symptoms). Responses are given on a seven-point scale (0 = not bothered/none of the time, 6 = extremely bothered/all of the time), and children are asked to score their experiences during the previous 7 days. 'Practical problems' and 'activity limitation' domains contain questions that are not directly symptom-related (practical problems: rub nose and eyes, blow nose, carry tissues, take medications, feel embarrassed; activity limitation: playing outdoors, hard to get to sleep at night; hard to pay attention; wake up during the night.

Rupafin® versus placebo produced significantly better mean total PRQLQ scores at week 4 (1.4 vs 1.7; p=0.009 [ANOVA]) and week 6 (1.2 vs 1.5; p=0.023 [ANOVA]). Furthermore, Rupafin® versus placebo was associated with significantly better domain scores for nose symptoms at weeks 4 and 6, and for eye symptoms, practical problems and activity limitations at week 4.
4.3 Therapeutic Indications

Rupafin® paediatric oral solution 1 mg/mL is indicated for the symptomatic treatment of allergic rhinitis (intermittent or persistent; mild, moderate or severe) in children aged 6–11 years, administered at a dosage of 5 mL once daily in children with bodyweight ≥25 kg.

4.4 Dosage and Administration

Rupafin® paediatric oral solution 1 mg/mL is administered at a dosage of 5 mL once daily in children with bodyweight ≥25 kg.

Rupafin® can be administered without regard to concurrent food ingestion; however, Rupafin® should not be administered with grapefruit juice.

Rupafin® is not recommended for patients with renal or hepatic impairment. In addition, Rupafin® should be used with caution in patients with known prolongation of the QT interval, patients with uncontrolled hypokalaemia, or patients with ongoing proarrhythmic conditions (e.g. clinically significant bradycardia, acute myocardial ischaemia).

Rupafin® should be administered with caution in patients taking concurrent drugs that inhibit or are metabolised by cytochrome P450 isozyme 3A4 (CYP3A4).

Patients with the rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take Rupafin®.
5. Safety Profile of Rupafin® in Children

The incidence of adverse events in children aged 6–11 years treated with Rupafin® paediatric oral solution 1 mg/mL is lower than that reported in Rupafin® recipients aged ≥12 years, and Rupafin® paediatric oral solution is generally well tolerated (table 2).

Overall, 191 children aged 6–11 years have been exposed to Rupafin® paediatric oral solution in clinical trials. That is, 51 patients with allergic rhinitis were treated with Rupafin® 2.5 mg once daily, and 140 were treated with 5 mg once daily, for 1–8 weeks. A total 54.9% of patients in the 2.5 mg group and 35.7% in the 5 mg group, compared with 30.0% of placebo recipients, experienced at least one adverse event (i.e. irrespective of the causal relationship to study medication). Headache was the most common adverse event, noted in 14.7% of Rupafin®-treated children compared with 6% of placebo recipients, but this event was generally mild and usually resolved on the same day that it occurred; headache has also been reported as the most common adverse event during administration of other second-generation antihistamines (e.g. fexofenadine 30 mg twice daily; levocetirizine 5 mg once daily) to children aged 6–11 years with allergic rhinitis. Less-frequent Rupafin®-induced adverse events comprised cough, abdominal pain, nausea, eczema and influenza.

In clinical trials, the incidence of adverse reactions considered possibly, probably or definitely related to Rupafin® was low, and no major differences were noted between the 2 Rupafin® groups and placebo: for instance, headache was documented in 3.9% of patients in the lower-dose Rupafin® group, in 2.1% of children in the higher-dose Rupafin® group, and in 1.7% of placebo recipients. The incidence of treatment-related somnolence, an important consideration from the viewpoint of reduced academic performance in schoolchildren, was also very low: 1.4% in the Rupafin® 5 mg group. This finding is
consistent with the low incidence of sedation generally reported for second-generation antihistamines in the paediatric population.

Rupafin® paediatric oral solution was not associated with any serious adverse events or laboratory abnormalities in children. In particular, no ECG abnormalities occurred, and no cases of raised creatine phosphokinase, alanine aminotransferase or aspartate aminotransferase levels manifested.

Figure 12. Total adverse events (irrespective of the causal relationship to study medication) and adverse reactions (possibly, probably or definitely related to study medication) reported in clinical trials with Rupafin® paediatric oral solution 1 mg/mL in children 6-11 years. Data are obtained from pooled placebo and Rupafin® doses in the clinical trial database.
<table>
<thead>
<tr>
<th>Common adverse events (incidence ≥0.1% to &lt;1%); no. (%) of patients:</th>
<th>Rupafin® 2.5 mg (n=51)</th>
<th>Rupafin® 5 mg (n=140)</th>
<th>Placebo (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8 (15.7)</td>
<td>20 (14.3)</td>
<td>10 (5.6)</td>
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<tr>
<td>Cough</td>
<td>-</td>
<td>7 (5.0)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>-</td>
<td>4 (2.8)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>4 (2.8)</td>
<td>-</td>
</tr>
<tr>
<td>Eczema</td>
<td>-</td>
<td>4 (2.8)</td>
<td>-</td>
</tr>
<tr>
<td>Influenza</td>
<td>2 (3.9)</td>
<td>4 (2.8)</td>
<td>2 (1.0)</td>
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</table>

**ADVERSE REACTIONS**

Common adverse reactions (incidence ≥0.1% to <1%); no. (%) of patients:

<table>
<thead>
<tr>
<th>Common adverse reactions (incidence ≥0.1% to &lt;1%); no. (%) of patients:</th>
<th>Rupafin® 2.5 mg (n=51)</th>
<th>Rupafin® 5 mg (n=140)</th>
<th>Placebo (n=180)</th>
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</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2 (3.9)</td>
<td>3 (2.1)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>-</td>
<td>2 (1.4)</td>
<td>-</td>
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<tr>
<td>Upper respiratory tract infection</td>
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<td>-</td>
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Uncommon adverse reactions (incidence ≥0.1% to <1%); no. (%) of patients:

<table>
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<th>Uncommon adverse reactions (incidence ≥0.1% to &lt;1%); no. (%) of patients:</th>
<th>Rupafin® 2.5 mg (n=51)</th>
<th>Rupafin® 5 mg (n=140)</th>
<th>Placebo (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>-</td>
<td>1 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td>Influenza</td>
<td>-</td>
<td>1 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>-</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Eczema</td>
<td>-</td>
<td>1 (0.7)</td>
<td>-</td>
</tr>
</tbody>
</table>

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*a* Irrespective of causal relationship to study medication.

*b* Possibly, probably or definitely related to study medication.
Bibliography


Izquierdo I, Cranswick N, Karrasch J, et al. Rupatadine in children aged 6-11 years with allergic rhinitis: a proof of concept evaluation by a 4 weeks treatment follow-up study. *European Academy of Allergy and Clinical Immunology (EAACI).* Venice, Italy; 2009.


