
Safety and tolerability of fexofenadine hydrochloride, 15 and 30 mg, twice daily in children aged 6 months to 2 years with allergic rhinitis

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Background: Antihistamines are an established first-line treatment for allergic rhinitis and are widely prescribed in infants for allergic symptoms.

Objective: To establish the safety and tolerability of fexofenadine hydrochloride in children aged 6 months to 2 years in 2 studies (T/3001 and T/3002).

Methods: Both studies had a multicenter, randomized, placebo-controlled design. Mean treatment duration was 8 days. Subjects were randomized (T/3001, n = 174; and T/3002, n = 219) to twice-daily fexofenadine hydrochloride, 15 or 30 mg, or placebo mixed with a standard vehicle.

Results: In the combined population, the incidence of treatment-emergent adverse events (TEAEs) was comparable between groups (placebo, 48.2% [96/199]; fexofenadine hydrochloride, 15 mg, 40.0% [34/85]; and fexofenadine hydrochloride, 30 mg, 35.2% [38/108]). Vomiting was the most common TEAE (placebo, 13.6%; fexofenadine hydrochloride, 15 mg, 14.1%; and fexofenadine hydrochloride, 30 mg, 5.6%). Most TEAEs were unrelated to study medication, as evaluated by investigators; those possibly related to study medication were mild or moderate in intensity. No clinical differences were seen between fexofenadine and placebo for vital signs, electrocardiographic results, or physical examination results.

Conclusion: Fexofenadine hydrochloride, 15 or 30 mg, given for a mean duration of 8 days is well tolerated, with a good safety profile, in children aged 6 months to 2 years.

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INTRODUCTION

Allergic rhinitis (AR) is a common chronic condition and is estimated to affect up to 40% of children in some countries.^{1–3} The symptoms of AR include rhinorrhea, nasal congestion, sneezing, watery eyes, and itchy nose that, if poorly managed or untreated, may have a profound effect on quality of life and school performance.⁴ Allergic rhinitis may also exacerbate conditions such as asthma and otitis media.⁵

Oral antihistamines are well established as a first-line treatment for AR and are effective at treating the symptoms caused by allergen exposure. However, first-generation anti-

histamines, such as diphenhydramine and chlorpheniramine, have poor adverse effect profiles that are attributed to their lack of selectivity and their ability to cross the blood-brain barrier, which lead to psychomotor impairment and sedation. Newer-generation antihistamines, such as fexofenadine, are associated with fewer adverse effects and an increased H₁-receptor specificity compared with first-generation antihistamines.⁶

A number of clinical trials have established the safety and efficacy of fexofenadine in adults^{7–9} and school-aged children.^{10–13} However, to our knowledge, no study has examined the safety of fexofenadine in children younger than 2 years. Because antihistamines are widely prescribed in children younger than 2 years for the treatment of allergic symptoms, it is important to examine the safety and tolerability of fexofenadine in this age group. Therefore, the aim of the 2 studies reported herein was to establish the safety and tolerability of fexofenadine hydrochloride, 15 and 30 mg, twice daily in children aged 6 months to 2 years with AR.

METHODS

Study Designs

Both studies were multicenter, randomized, placebo-controlled, parallel-group safety studies in subjects aged 6 months to 2 years, with a treatment duration of at least 1 week with a single age- and/or weight-appropriate dose. The 2

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studies were designed so that when combined there would be a 1:2 ratio of subjects in the 6 months to 1 year age group and the 1 to 2 years age group, respectively; a total of 200 study completers were required. The study protocols and their amendments were approved by the relevant institutional review boards.

Patients

Pediatric subjects aged 6 months to 1 year weighing 10.5 kg or less (study T/3001) and those aged 1 to 2 years weighing more than 10.5 kg (study T/3002) with AR diagnosed by medical history, pattern, or physical findings were enrolled. All subjects were either current candidates for antihistamine therapy or had tolerated antihistamine therapy in the past. Additional subjects could be enrolled in the respective study if they met the weight criterion but were aged 1 to 2 years (study T/3001) or aged 6 months to 1 year (study T/3002). Exclusion criteria included moderate or severe asthma; short-term episodes of upper respiratory tract infection, bronchiolitis, wheezing, and acute otitis media at study enrollment; and cardiac or hepatic symptoms or any condition that may have interfered with swallowing or gastrointestinal absorption of oral medication. Excluded drugs included other H₁-receptor antagonists, nasal corticosteroids, nasal cromolyn sodium, or oral decongestants; however, the use of these drugs could be discontinued at visit 1 and the subject could be rescreened for enrollment. In addition, the parent or guardian of the subject

was required to demonstrate the ability to prepare a dose of oral placebo granulation powder mixed with an approved vehicle. Parents or guardians provided written informed consent for all subjects before enrollment in the studies.

Dose Determination

The dose was to be based on a pharmacokinetic study in the same age group. The data from the pharmacokinetic study, and data from other pharmacokinetic studies in pediatric subjects and adults, indicated that a 30-mg dose of fexofenadine hydrochloride administered to subjects aged 1 to 12 years and weighing greater than 10.5 kg and a 15-mg dose administered to subjects aged 6 months and older and weighing 10.5 kg or less produce exposures similar to those seen with the 60-mg dose in adults. Therefore, 2 studies were conducted to take into account the results from the population pharmacokinetic analysis, based on the 2 age groups: 6 months to 1 year and 1 to 2 years.

Study Protocol

Subjects were randomized to receive fexofenadine hydrochloride, 15 mg (study T/3001) or 30 mg (study T/3002), or placebo granulation powder (capsule content) twice daily, mixed with a standard vehicle (applesauce or rice cereal mixed with an infant formula), for a minimum of 7 days (14 doses). Both studies consisted of 2 visits: enrollment and randomization at visit 1 (day 1) and final or early withdrawal

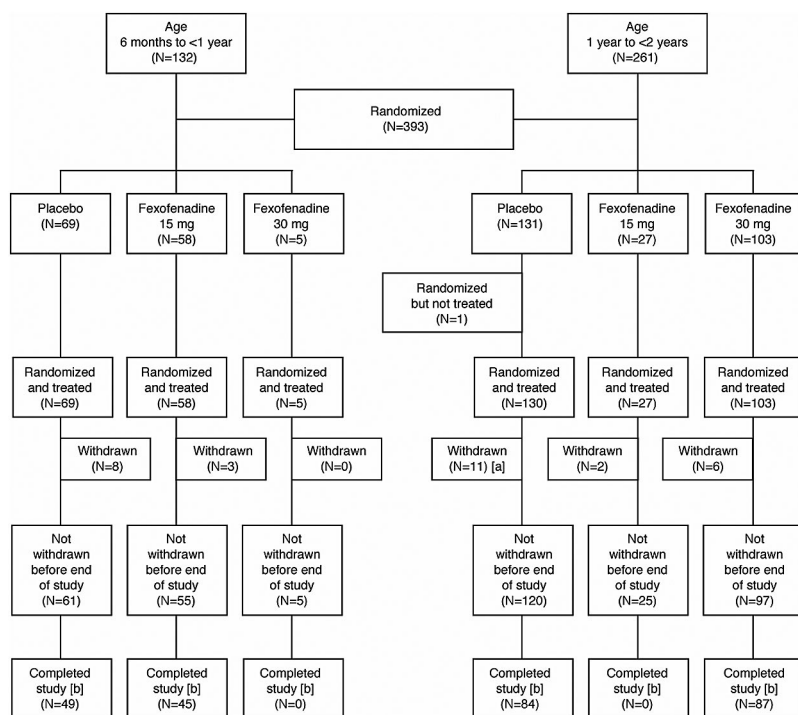


Figure 1. Study flow diagram. The number of subjects withdrawn includes 10 treated subjects plus 1 subject randomized but not treated (a); subject completion status was determined by age and weight, exposure to study medication, and safety assessments, including vital signs, electrocardiography, and a physical examination (b).

Table 1. Baseline Demographic Data for Subjects in Study T/3001

Variable	Subjects aged 6 mo-1 y		Subjects aged 1-2 y		P value ^a
	Placebo group (n = 64)	Fexofenadine hydrochloride, 15 mg, twice-daily group (n = 58)	Placebo group (n = 25)	Fexofenadine hydrochloride, 15 mg, twice-daily group (n = 27)	
Sex, No. (%)					
Female	29 (45.3)	25 (43.1)	14 (56.0)	13 (48.1)	.66
Male	35 (54.7)	33 (56.9)	11 (44.0)	14 (51.9)	
Age, mean $\pm$ SD, mo	8.4 $\pm$ 1.9	8.8 $\pm$ 1.6	15.7 $\pm$ 3.3	16.1 $\pm$ 32.1	.29
Weight, kg					
Mean $\pm$ SD	8.6 $\pm$ 0.9	8.7 $\pm$ 1.0	9.7 $\pm$ 0.7	9.8 $\pm$ 0.5	.32
Range	6.4-10.4	6.4-10.4	8.1-10.5	8.6-10.4	
Height, cm					
Mean $\pm$ SD	68.5 $\pm$ 7.3	68.9 $\pm$ 6.8	76.4 $\pm$ 4.7	78.5 $\pm$ 3.5 ^b	.35
Range	43.2-83.8	40.6-80.0	63.0-88.1	67.0-85.1 ^b	

^a Values for sex were calculated using the Fisher exact test; other values were calculated using the Wilcoxon rank sum test.

^b n = 26.

Table 2. Baseline Demographic Data for Subjects in Study T/3002

Variable	Subjects aged 6 mo-1 y		Subjects aged 1-2 y		P value ^a
	Placebo group (n = 5)	Fexofenadine hydrochloride, 30 mg, twice-daily group (n = 5)	Placebo group (n = 105)	Fexofenadine hydrochloride, 30 mg, twice-daily group (n = 103)	
Sex, No. (%)					
Female	3 (60.0)	2 (40.0)	36 (34.3)	41 (39.8)	.58
Male	2 (40.0)	3 (60.0)	69 (65.7)	62 (60.2)	
Age, mean $\pm$ SD, mo	10.6 $\pm$ 0.6	10.4 $\pm$ 0.6	18.7 $\pm$ 3.2	17.9 $\pm$ 3.2	.07
Weight, kg					
Mean $\pm$ SD	11.3 $\pm$ 0.9	11.2 $\pm$ 0.5	12.1 $\pm$ 1.2	12.2 $\pm$ 1.2	.91
Range	10.6-12.8	10.6-12.0	10.5-16.1	10.6-17.0	
Height, cm					
Mean $\pm$ SD	78.0 $\pm$ 2.8	77.0 $\pm$ 3.8	82.2 $\pm$ 5.3 ^b	81.9 $\pm$ 4.4	.24
Range	73.7-81.3	72.9-82.2	61.0-91.6 ^b	66.0-92.7	

^a Values for sex were calculated using the Fisher exact test; other values were calculated using the Wilcoxon rank sum test.

^b n = 104.

at visit 2 (day 8 or 9). At both visits, a physical examination, including AR symptoms, vital signs (body temperature, heart rate, and blood pressure), body weight, and 12-lead electrocardiography (ECG), was performed. Body areas (such as the spine, chest and lungs, heart, abdomen, skin, throat, and extremities) were rated as normal or abnormal during the physical examinations. The ECG at visit 2 was to be performed at approximately 2.5 $\pm$ 0.5 hours after the morning dose. If this was not possible, an interim visit was scheduled within 1 to 2 days (days 6 or 7) of visit 2 at approximately 2.5 $\pm$ 0.5 hours after the morning dose.

Safety Analysis

The evaluation of safety was based on adverse events (AEs), ECG recordings, physical examination results, and vital sign measurements, which were collected at visits 1 and 2.

Statistical Analysis

Demographic and baseline characteristics were compared between groups using the Wilcoxon rank sum test for continu-

ous variables and the Fisher exact test for categorical variables. All other data were presented using summary descriptive statistics.

RESULTS

Patient Demographics

Both studies were performed at the same sites in the United States (study T/3001 was performed at 43 sites and study T/3002 was performed at 44 sites). The study flow is shown in Figure 1. A total of 393 subjects were randomized (174 in study T/3001 and 219 in study T/3002). One subject in study T/3002 withdrew before receiving the study medication; therefore, 392 subjects received treatment (fexofenadine hydrochloride, 15 mg, n = 85; fexofenadine hydrochloride, 30 mg, n = 108; and placebo, n = 199). Data from all subjects exposed to double-blind study medication were included in the safety analysis. For a subject to be considered to have completed the study per protocol, the following criteria had to

Table 3. Treatment-Emergent Adverse Events Occurring in 3.0% or More of Subjects in Any Treatment Group^a

Adverse event	Subjects aged 6 mo-<1 y			Subjects aged 1 y-<2 y		
	Placebo group (n = 69)	Fexofenadine twice-daily groups		Placebo group (n = 130)	Fexofenadine twice-daily groups	
		15 mg (n = 58)	30 mg (n = 5)		15 mg (n = 27)	30 mg (n = 103)
Any TEAE	28 (40.6)	23 (39.7)	2 (40.0)	68 (52.3)	11 (40.7)	36 (35.0)
Digestive system	11 (15.9)	15 (25.9)	1 (20.0)	27 (20.8)	5 (18.5)	16 (15.5)
Vomiting	10 (14.5)	9 (15.5)	1 (20.0)	17 (13.1)	3 (11.1)	5 (4.9)
Diarrhea	1 (1.4)	3 (5.2)	0	3 (2.3)	1 (3.7)	6 (5.8)
Gastroenteritis	0	2 (3.4)	0	2 (1.5)	1 (3.7)	1 (1.0)
Flatulence	0	0	0	4 (3.1)	0	1 (1.0)
Respiratory system	7 (10.1)	7 (12.1)	1 (20.0)	24 (18.5)	2 (7.4)	12 (11.7)
Cough increased	0	1 (1.7)	0	8 (6.2)	1 (3.7)	4 (3.9)
Upper respiratory tract infection	4 (5.8)	1 (1.7)	1 (20.0)	8 (6.2)	1 (3.7)	4 (3.9)
Rhinitis	0	2 (3.4)	0	8 (6.2)	0	3 (2.9)
Body as a whole	8 (11.6)	5 (8.6)	0	22 (16.9)	2 (7.4)	8 (7.8)
Fever	4 (5.8)	1 (1.7)	0	14 (10.8)	1 (3.7)	5 (4.9)
Unintentional injury	1 (1.4)	0	0	0	1 (3.7)	1 (1.0)
Infection	2 (2.9)	2 (3.4)	0	8 (6.2)	0	2 (1.9)
Special senses	6 (8.7)	2 (3.4)	0	9 (6.9)	3 (11.1)	9 (8.7)
Otitis media	5 (7.2)	1 (1.7)	0	6 (4.6)	2 (7.4)	7 (6.8)
Ophthalmitis	0	0	0	0	1 (3.7)	0
Ear disorder	0	0	0	3 (2.3)	1 (3.7)	0
Skin and appendages	1 (1.4)	4 (6.9)	0	7 (5.4)	1 (3.7)	4 (3.9)
Rash	1 (1.4)	4 (6.9)	0	6 (4.6)	1 (3.7)	2 (1.9)

Abbreviation: TEAE, treatment-emergent adverse event.

^a Data are given as number (percentage) of each group.

be met: appropriate age and weight for the study in which the subject had been enrolled, number of successful doses (minimum, 14 doses), and complete safety assessments. A total of 265 subjects completed the study per protocol (fexofenadine hydrochloride, 15 mg, n = 45; fexofenadine hydrochloride, 30 mg, n = 87; and placebo, n = 133).

There were no statistically significant differences in baseline characteristics between the 2 treatment groups within the individual studies or within either of the 2 age ranges in the combined study population (Table 1 and Table 2). In the safety population, there was a similar duration of treatment across the 2 age ranges and across the fexofenadine and placebo groups. In subjects aged 6 months to younger than 1 year, the mean $\pm$ SD number of treatment days was 8.30 ± 1.23 days in the fexofenadine hydrochloride, 15 mg, group; 8.40 ± 0.55 days in the fexofenadine hydrochloride, 30 mg, group; and 8.00 ± 1.35 days in the placebo group. For subjects aged 1 year to younger than 2 years, the mean $\pm$ SD number of treatment days in the placebo, fexofenadine hydrochloride, 15 mg, and fexofenadine hydrochloride, 30 mg, groups was 8.00 ± 1.57 , 8.10 ± 1.20 , and 8.00 ± 1.66 days, respectively. Thirty patients withdrew before completion of the study, with the most common reason being the occurrence of an AE (n = 17 [7 in the fexofenadine group and 10 in the placebo group]).

Safety Analysis

The number of subjects with treatment-emergent AEs (TEAEs) was comparable between the 2 treatment groups in study T/3001 (fexofenadine, 40.0%; and placebo, 42.7%), whereas in study T/3002, more subjects receiving placebo than those receiving fexofenadine (52.7% vs 35.2%) reported an AE. Overall, TEAEs were reported in 37.3% of the subjects in the combined fexofenadine treatment groups and in 48.2% of the subjects in the placebo group. Most TEAEs were mild to moderate in intensity. The TEAEs most frequently affected the digestive system, the respiratory system, and the body as a whole in the individual studies and overall. The TEAEs that occurred in 3.0% or more of the subjects in any treatment group are shown by age category in Table 3, and the TEAEs that occurred in 3.0% or more of the subjects in the overall combined study population are shown in Table 4. The most frequent TEAE was vomiting, particularly in the younger age group.

Most reported TEAEs were evaluated by the investigators as being unrelated to study medication. Overall, TEAEs considered to be possibly related to study medication were reported in only 17 fexofenadine-treated subjects (8.8%) and 19 placebo-treated subjects (9.5%). All TEAEs possibly related to study medication were rated as mild or moderate in inten-

Table 4. Treatment-Emergent Adverse Events Occurring in 3.0% or More of Subjects in the Combined Study Population^a

Adverse event	Placebo group (n = 199)	Fexofenadine, 15 mg, twice-daily group (n = 85)	Fexofenadine, 30 mg, twice-daily group (n = 108)
Any TEAE	96 (48.2)	34 (40.0)	38 (35.2)
Digestive system	38 (19.1)	20 (23.5)	17 (15.7)
Vomiting	27 (13.6)	12 (14.1)	6 (5.6)
Diarrhea	4 (2.0)	4 (4.7)	6 (5.6)
Gastroenteritis	2 (1.0)	3 (3.5)	1 (0.9)
Flatulence	4 (2.0)	0	1 (0.9)
Respiratory system	31 (15.6)	9 (10.6)	13 (12.0)
Cough increased	8 (4.0)	2 (2.4)	4 (3.7)
Upper respiratory tract infection	12 (6.0)	2 (2.4)	5 (4.6)
Rhinitis	8 (4.0)	2 (2.4)	3 (2.8)
Body as a whole	30 (15.1)	7 (8.2)	8 (7.4)
Fever	18 (9.0)	2 (2.4)	5 (4.6)
Unintentional injury	1 (0.5)	1 (1.2)	1 (0.9)
Infection	10 (5.0)	2 (2.4)	2 (1.9)
Special senses	15 (7.5)	5 (5.9)	9 (8.3)
Otitis media	11 (5.5)	3 (3.5)	7 (6.5)
Ophthalmitis	0	1 (1.2)	0
Ear disorder	3 (1.5)	1 (1.2)	0
Skin and appendages	8 (4.0)	5 (5.9)	4 (3.7)
Rash	7 (3.5)	5 (5.9)	2 (1.9)

Abbreviation: TEAE, treatment-emergent adverse event.

^a Data are given as number (percentage) of each group.

sity, with the most common being vomiting and diarrhea. Overall, no meaningful differences in incidence, pattern, or intensity of the TEAEs were found across treatment groups.

Overall, 10 (5.0%) of the subjects in the placebo group and 6 (3.1%) of the subjects in the combined fexofenadine group experienced TEAEs that led to discontinuation of study medication use. Of these subjects, 5 (3 in the placebo group and 2 in the fexofenadine group) were in the 6 months to 1 year age group and the remaining 11 (7 in the placebo group and 4 in the fexofenadine group) were in the 1 to 2 years age group. The most common TEAEs causing discontinuation (in >1 subject) were otitis media, increased cough, viral infection, and gastroenteritis. Two subjects in the placebo group experienced TEAEs rated as severe in intensity by the investigator; 1 of these events was also reported as a serious AE (a respiratory syncytial viral infection that was treated with nebulized albuterol and antibiotics). The subject fully recovered, and the investigator judged the event to be related to a concomitant or underlying illness and not to treatment medication.

Vital Signs, Electrocardiographic Measurements, and Physical Examination Results

No clinical differences were observed between the fexofenadine treatment groups and placebo for any vital sign or any ECG variable. No clinically meaningful differences were observed between the fexofenadine treatment groups and placebo for any of the physical examination results.

DISCUSSION

The results of this analysis reveal that the second-generation antihistamine fexofenadine was well tolerated, with a good safety profile, in pediatric subjects aged 6 months to 2 years with AR. Overall, the incidence of TEAEs was similar in fexofenadine- and placebo-treated subjects aged 6 months to 1 year, with vomiting being the most frequent TEAE in both treatment groups. In subjects aged 1 to 2 years, the overall incidence of TEAEs was higher in placebo-treated subjects than in fexofenadine-treated subjects because of more reports of vomiting, fever, and other TEAEs related to the respiratory tract in the placebo group. Most subjects in both groups experienced TEAEs that were mild to moderate in nature.

The AEs described herein are in agreement with previous studies^{7,9–11,13} confirming the safety and tolerability of fexofenadine in adult subjects and older children (≥6 years) and in children aged 2 to 5 years.¹⁴ A study¹⁰ of the safety and efficacy of fexofenadine hydrochloride, 30 mg, twice daily in 935 children aged 6 to 11 years also found that the AE rate in the fexofenadine group was not significantly different from that seen in the placebo group (18.3% for fexofenadine hydrochloride, 30 mg, vs 18.7% for placebo).

The final ECG recordings in the present studies were similar to baseline measures, suggesting the absence of potential cardiovascular effects. Previous reports^{15,16} have confirmed that, at therapeutic doses, second-generation antihistamines have a high degree of cardiac safety. In addition, no

clinically relevant differences in vital signs and physical examination findings were observed in the present study. Because a previous study in pediatric subjects aged 2 to 5 years did not reveal any effect on laboratory variables,¹⁴ laboratory tests were not required by the US Food and Drug Administration as a safety variable in the present study.

Millions of children have AR worldwide, and they may also experience long-term complications that affect their quality of life, including learning difficulties and emotional problems.^{4,17} In addition, AR is associated with the development of comorbidities, such as asthma and otitis media.¹⁸ Ideally, treatment of AR should be with an agent that has proven efficacy and a good safety and tolerability profile; this is especially important in young children who are developmentally vulnerable to any potentially deleterious adverse effects of a therapy.

The results of the 2 studies reported herein suggest that fexofenadine hydrochloride at 15 or 30 mg twice daily is well tolerated in children aged 6 months to 2 years. To our knowledge, this is the first report to establish the safety and tolerability of fexofenadine at clinically relevant doses in children aged between 6 months and 2 years.

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