

CLINICAL STUDY SUMMARY: A00420

Name of company: UCB Pharma	Individual study table referring to part of the dossier: Not applicable	<i>(For National Authority Use Only)</i>
Name of finished product: Xyzal®	Volume: Not applicable	
Name of active ingredient: Levocetirizine dihydrochloride	Page: Not applicable	
Clinical Trial Registry Identifier: NCT00453583		
Title of study: Evaluation of the treatment satisfaction in children suffering from an allergy and who received an antihistamine treatment		
Physician(s): In total, 424 Physicians participated in the study: 156 Physicians in Bulgaria, 101 in Spain, 45 in Romania, 39 in Russia, 33 in Portugal, 32 in India, and 18 in South-Korea.		
Study site(s): The study was conducted in 424 centers.		
Publication(s) (reference[s]): none		
Studied period: 1 day First patient enrolled: 21 Jun 2006 Last patient completed: 04 Mar 2008	Phase of development: Postmarketing non-interventional study	

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Objective(s):

Main objectives:

- To evaluate the parent’s satisfaction about the efficacy of the last prescribed antihistamine using an 11-point scale
- To evaluate the parent’s satisfaction about the tolerability of the last prescribed antihistamine using an 11-point scale
- To evaluate the parent’s overall satisfaction of the last prescribed antihistamine using an 11-point scale

Additional objectives:

- To evaluate the impact on the child’s ability to function at school (parent rating) after intake of the last antihistamine as assessed on a 7-point scale
- To evaluate the impact on the child’s quality of school activities (parent rating) after intake of the last antihistamine as assessed on a 7-point scale
- To evaluate the impact on the quality of the child’s sleep (parent rating) after intake of the last antihistamine as assessed on a 7-point scale
- The parent’s willingness to continue to use the same treatment in the future (yes/no)
- To evaluate the treating Physician’s satisfaction of the efficacy of the last prescribed antihistamine using an 11-point scale
- To evaluate the treating Physician’s satisfaction on the tolerability of the last prescribed antihistamine using an 11-point scale
- To evaluate the overall satisfaction by the treating Physician of the last taken antihistamine using an 11-point scale
- To evaluate the recommendation of the same treatment for identical patients (yes/no)
- To evaluate the safety profile through the investigation and comparison of the adverse events (AEs)

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<p>Methodology: This was a non-interventional, retrospective data collection study to evaluate the most commonly used H1-antihistamines for the treatment of different allergies in standard clinical pediatrics practice. The parent's and Physician's satisfaction with respect to efficacy, tolerability, and the overall satisfaction of the last antihistamine treatment was assessed. Safety assessments were based on the recording of AEs. No additional diagnostic and monitoring procedures were applied. The period that was evaluated depended on the duration of the last antihistamine treatment that was taken prior to the Consultation Visit. The questionnaire was provided and completed on the same day as the consultation. No further follow-up was performed.</p>		
<p>Number of patients (planned and analyzed): Planned: approximately 5000 patients, 2500 patients in the age group 2 to 6 years, inclusive and 2500 in the age group 7 to 12 years, inclusive.</p> <p>Enrolled: 4581 patients were enrolled, 2273 patients in the age group 2 to 6 years, inclusive and 1723 patients in the age group 7 to 12 years. The remaining patients evaluated were out of the pre-defined age range of 2 to 12 years, inclusive.</p>		
<p>Diagnosis and main criteria for inclusion:</p> <ul style="list-style-type: none"> • Male or female children aged between 2 and 12 years inclusive • Clinical history of an allergy leading to consultation • Latest treatment for allergy started within the last 2 months and lasted at least 2 weeks 		
<p>Test product, dose(s) and mode of administration, batch number(s): not applicable</p>		
<p>Duration of treatment: Fourteen to 60 days of treatment prior to the Consultation Visit of the study.</p>		
<p>Reference therapy, dose(s) and mode of administration, batch number(s): not applicable</p>		

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<p>Criteria for evaluation: Efficacy:</p> <p>Main efficacy variables:</p> <ul style="list-style-type: none"> • The parent’s efficacy satisfaction score • The parent’s tolerability satisfaction score • The parent’s overall satisfaction score <p>Additional efficacy variables:</p> <ul style="list-style-type: none"> • The ability to function at school score • The quality of school activity score • The quality of sleep score • The proportion of parents who answered positively to the question about re-use of the same treatment in the future • The Physician’s efficacy satisfaction score • The Physician’s tolerability satisfaction score • The Physician’s overall satisfaction score • The proportion of Physicians who answered positively to the question about re-use of the same treatment in the future <p>Pharmacokinetics/pharmacodynamics: not applicable</p> <p>Safety: recording of AEs</p>		

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Statistical methods: All analyses were performed on the eligible population, defined as all patients included in the study. Summary statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation (SD), minimum, 25th and 75th percentiles, and maximum) were tabulated. All analyses were presented overall and by last antihistamine treatment. Subgroup analyses were performed by country, duration of last antihistamine treatment, type of disease combination, and by age category (2 to 6 years, inclusive and 7 to 12 years, inclusive).

The main and additional efficacy variables were analyzed descriptively. Levocetirizine was descriptively compared with each of the other antihistamine treatments on the main efficacy variables using an analysis of covariance with type of disease combination, country, and last antihistamine treatment as factors and age and duration of last antihistamine treatment as covariates. The difference between the treatments was estimated by the difference between the least square (LS) means together with their 95% confidence interval (CI). An exploratory analysis for the comparison of levocetirizine with the other antihistamines was performed. P-values for the difference of the adjusted mean were based on the estimated LS means. The p-values for the proportion difference were provided by a Fisher exact test.

The percentage of patients presenting at least 1 AE was evaluated. The AEs were described by MedDRA[®] Primary Organ Class and by Preferred Term.

Summary and conclusions:

Patient disposition: In total, 4581 patients were enrolled of which the majority had received levocetirizine as last antihistamine treatment in each country, except for India where most of the patients had received cetirizine (37.5%). The mean (SD) age was 6.81 (3.30) and there were more male patients (57.8%) than female patients (42.2%). The majority of patients suffered from allergic rhinitis (AR) (66.5%). The incidence of AR in the surveyed population was the highest in Portugal (90.6%), Spain (84.4%), and South-Korea (82.4%), whereas the incidence of urticaria was the highest in Eastern Europe (Romania, 33.1% and Bulgaria, 20.4%) and India (23.2%). The most common allergens, for which patients were sensitized, were house dust mites (38.6%) and grass pollen (22.5%).

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Efficacy results:

Main efficacy variable:

The overall mean (SD) parent’s satisfaction score for efficacy on a scale from 0=not satisfied to 10=very satisfied, was 8.24 (1.82), with the highest scores for levocetirizine (8.73 [1.52]) and fexofenadine (8.43 [1.02]). The mean (SD) parents-rated efficacy satisfaction scores for the other main antihistamines were 7.90 (1.97) for desloratadine, 7.84 (1.64) for hydroxyzine, 7.82 (1.82) for cetirizine, and 7.48 (2.23) for loratadine. The responses of the levocetirizine group for the parent’s efficacy satisfaction were significantly higher compared to those of the first generation antihistamines, except for hydroxyzine (adjusted mean [95% CI]=0.56 [-0.19; 1.31]; p=0.145). Levocetirizine also scored significantly better compared to the second generation antihistamines analyzed, except for fexofenadine (adjusted mean [95% CI]=-0.52 [-1.34; 0.30]; p=0.216).

The mean (SD) satisfaction score with respect to tolerability was 8.75 (1.64), with the highest score in the levocetirizine group of 9.14 (1.32). The mean (SD) parents-rated tolerability satisfaction scores for the other main antihistamines were 8.81 (1.57) for desloratadine, 8.71 (1.07) for fexofenadine, 8.37 (1.75) for cetirizine, 8.27 (1.83) for loratadine, and 7.50 (1.97) for hydroxyzine. The responses of levocetirizine with regard to satisfaction of treatment tolerability were significantly higher compared to those of the first and second generation antihistamines analyzed, except for fexofenadine (adjusted mean [95% CI]=-0.33 [-1.03; 0.38]; p=0.362).

Regarding the global satisfaction, the parent’s overall mean (SD) score was 8.38 (1.79). The global satisfaction scores were higher for levocetirizine 8.85 (1.48), and fexofenadine 8.57 (1.25). The mean (SD) parents-rated global satisfaction scores for the other main antihistamines were 8.17 (1.92) for desloratadine, 7.95 (1.81) for cetirizine, 7.69 (1.60) for hydroxyzine, and 7.64 (2.13) for loratadine. The global satisfaction for levocetirizine was significantly higher compared to those of all other antihistamine treatments analyzed, except for fexofenadine (adjusted mean [95% CI]=-0.62 [-1.42; 0.18]; p=0.127). Results should be interpreted with caution as no adjustment on the alpha level was performed for the multiple comparisons (levocetirizine versus other antihistamines). When comparing the efficacy, tolerability and overall satisfaction of the last antihistamine treatment as rated by the parents per country, the scores were higher in European countries compared to Asian countries.

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Additional efficacy variables:

The Physician's satisfaction score on the efficacy, tolerability, and global satisfaction of the last antihistamine treatment was similar to the scores provided by the parents.

Overall, the mean (SD) ability to function at school score on a scale from 1=marked worsening to 7=marked improvement was 5.31 (1.23), which implies a slight improvement, with the highest scores for patients who have been treated with levocetirizine (5.59 [1.20]) and fexofenadine (5.43 [0.84]). The ability to function at school after levocetirizine treatment was significantly more improved compared to all other second generation antihistamines, except for fexofenadine (p=0.223). The ability to function at school after levocetirizine treatment was not significantly different from hydroxyzine treatment (p=0.186).

Overall, the mean (SD) quality of school activity score was 5.32 (1.23), which implies a slight improvement. The highest mean (SD) scores were observed for patients who received levocetirizine (5.59 [1.21]) and fexofenadine (5.58 [1.01]) as last antihistamine treatment. The quality of school activities was significantly more improved after levocetirizine treatment when compared to all second generation antihistamines, except for fexofenadine (p=0.076). Levocetirizine showed no significant difference with hydroxyzine on the quality of school activity (p=0.424).

Overall, the mean (SD) quality of sleep score was 5.45 (1.26), which implies a slight improvement. The impact on the mean (SD) child's quality of sleep score was the highest for patients who received levocetirizine (5.72 [1.23]). The quality of sleep was significantly more improved after levocetirizine treatment when compared to the second generation antihistamines, except for fexofenadine (p=0.322). The quality of sleep after levocetirizine treatment did not significantly differ from hydroxyzine (p=0.546).

Nearly all Physicians (97.4%) who prescribed levocetirizine reported they would recommend the same treatment to other patients with the same symptoms. The proportion of Physicians who would recommend the other antihistamine treatments analyzed ranged from 95.5% for hydroxyzine to 50.0% for clemastine.

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In addition, according to the parents, more patients receiving levocetirizine (97.2%) were willing to continue the treatment. Note that 55.6% of the parents were not willing to continue clemastine treatment in the future.

Pharmacokinetics/pharmacodynamics results: not applicable

Safety results: No deaths or serious AEs (SAEs) were reported. Adverse events were reported rarely, by only 3.5% of patients overall. Patients treated with the second generation antihistamines reported less AEs compared to first generation antihistamines. In the second generation antihistamine group, the proportion of patients with AEs was the highest after cetirizine treatment (4.7%), which was significantly higher compared to levocetirizine ($p < 0.001$). The proportion of patients with AEs was similar after treatment with levocetirizine (2.0%), desloratadine (1.8%), loratadine (2.5%), and fexofenadine (2.4%).

The proportion of patients that reported AEs was the highest in India (11.2%) and after an antihistamine treatment of less than 15 days (8.0%). Adverse events were reported by 4.0% of patients who suffered from urticaria, 3.6% of patients with another allergic disease, and 3.0% of patients with AR. No difference was noted between both age categories.

Overall, the most commonly reported AEs were nervous system disorders, reported by 125 patients (2.7%). Somnolence was the most commonly reported AEs by Preferred Term (2.5% of patients). Nervous system disorders and psychiatric disorders were considered as significant AEs. Only 4 patients (0.1%) reported psychiatric disorders as AEs.

Conclusions: In conclusion, this observational study shows that in terms of treatment efficacy and overall satisfaction, all second generation antihistamines scored better compared to first generation antihistamines, except for hydroxyzine. The tolerability satisfaction was better for all second generation antihistamines, which was also reflected in the lower number of AEs reported. Levocetirizine showed a superior efficacy and tolerability compared to most of the antihistamines in the same class. The safety profile for all second generation antihistamines was similar, except for cetirizine with a significantly higher proportion of patients with AEs compared to levocetirizine, and better compared to the first generation antihistamines. No new findings related to the safety of cetirizine, hydroxyzine, and levocetirizine were reported.