# Clinical Report CE90C075 - Study A111

**Multicentre Comparative Study of Cetirizine and Terfenadine in Children Aged 6 to 12 Years Suffering from an Allergic Condition**

(Protocol PCF87J241)

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SUMMARY

A multicentre study comparing cetirizine with terfenadine was performed by general medical practitioners on a pediatric population suffering from conditions which normally require antihistamine treatment.

207 patients aged between six and twelve years, recruited by 34 general practitioners, received either 2 x 5 mg per day of cetirizine or 2 x 30 mg per day of terfenadine, for an average period of seven days.

The clinical results were based on an evaluation of efficacy: an evaluation of the severity of the complaint in terms of an analog visual scale, and overall evaluation of the efficacy of the treatment on a five-point scale (from 0 for worsening to 4 for substantial improvement); and on an evaluation of tolerance of the treatment: recording of undesirable effects and overall evaluation of tolerance of the treatment.

No statistically significant difference was found between the two treatment groups in terms of efficacy or of tolerance.
I. INTRODUCTION

Studies of animal and human pharmacology have demonstrated that cetirizine 2 HCl possesses a powerful and lasting antihistamine $H_1$ effect, without any anticholinergic effects at therapeutic doses.

Cutaneous measurements have shown cetirizine to have an inhibiting effect on reactions to histamine, 48/80 and methacholine (1, 2, 3).

Préliminary studies in human clinical pharmacology have shown that cetirizine inhibits eosinophil migration induced by an antigen-antibody conflict (4, 5).

Clinical trials performed on adults have shown that cetirizine has a positive action in cases of rhinitis and urticaria, which are classic indications for antihistamines $H_1$ (6, 7, 8, 9, 10).

Preliminary research suggests that in addition to the usual antihistamine $H_1$ indications, cetirizine has an effect on both seasonal and perennial atopica asthma in adults (11, 12).

Cetirizine has little sedative effect on the central nervous system as compared with the classic antihistamines (13, 14). These encouraging results have led us to suggest that research work be performed to define the role of cetirizine in the treatment of allergic conditions in children of school age.
II. MATERIALS AND METHODS

1. General description of the study

A minimum of 200 patients, aged from six to twelve years, was required for this comparison of cetirizine and terfenadine. Children with a condition warranting one to ten days of anti-allergic treatment were required. The drugs were to be administered twice per day: either 2 x 5 mg of cetirizine in the form of a drinkable solute, or 2 x 30 mg of terfenadine, in the form of suspension. The difference in presentation of the drugs to be compared did not allow double-blind arrangements, but the bottles with which the patients were supplied carried an anonymous label and were identical in their outward appearance.
2. **Ethics**

The protocol was approved by the Ethics Committee of the Braine-l'Alleud-Waterloo Hospital. The study was performed in accordance with the Helsinki Declaration, as amended at Tokyo (1975) and Venice (1983). Investigators were required to obtain the informed consent of their patients.

3. **Patient selection**

The patients, both boys and girls, were to be selected from among those who consulted the doctor regarding an allergic condition requiring the use of an antihistamine as primary or secondary treatment. They were to be aged between six and twelve years, and to weigh between twenty and fifty kg. Children exhibiting clinically significant renal, hepatic, cardiac or haematological pathologies, a known allergy to piperazines, or a condition requiring the use of corticosteroids during the study period, were not eligible. Any treatment administered during the month preceding admission to the study and including corticosteroids in depot form, or in the week preceding admission and including oral, inhaled, parenteral or topical administration of corticosteroids or an antihistamine, was also grounds for exclusion. If the antihistamine was ketotifene or astemizole the intervening period was extended to two or four weeks respectively. Children who had taken part in another clinical trial during the previous three months were also ineligible.
6. **Evaluation of efficacy**

a) The evaluation of efficacy was based on improvements observed in the analog visual scale (post- versus pre-treatment).

b) During Consultation 2 the investigator made an overall evaluation of the efficacy of treatment, using a five-point scale:

0  worsening
1  no change
2  slight improvement
3  moderate improvement
4  substantial improvement (disappearance of all symptoms).
8. **Discontinuance of treatment**

Patients who discontinued their participation for reasons of side-effects or inefficacy were not replaced, but were included in the analysis. Patients who consumed a prohibited drug were dropped and replaced. Patients who could not attend for consultation on the scheduled date, for legitimate reasons, could continue the treatment and attend for consultation as soon as possible. Interruption of the treatment for more than one day (two administrations), however, constituted grounds for dropping and replacing the patient.

9. **Statistical methodology**
   
a) **Analog Visual Scale**

   The improvements (pre- versus post-treatment) had to be analysed by means of an independent sample test. The analysis was to be supplemented by a calculation of the confidence limits of the average improvement between treatments.

b) **Overall evaluation**

   Chi-square test to compare distributions for both treatment.
III. RESULTS

The data gathered was subjected to statistical analysis\(^1\). The study took place between 23.10.1987 and 14.7.1988.

1. **Patient selection**

A total of 213 patients were treated by 34 general practitioners (see list in Appendix 1). Six patients were eliminated from the analysis of efficacy for violation of the protocol, because the interval between the two consultations exceeded the length of treatment possible with the contents of the bottles (Table I). The remaining 207 patients were analysed despite the following discrepancies:
- one patient aged five years only (229/04);
- six patients weighing less than twenty kg (Table II).

2. **Pre-treatment comparison of groups**

a) 104 patients were treated with cetirizine
   103 with terfenadine.

b) The average duration of treatment in both groups was seven days.

c) The average age of the cetirizine group, which consisted of 46 girls and 58 boys, was 8.7 ± 1.9 years; the average weight was
   30.8 ± 8.3 kg, and the average height 133.1 ± 14.2 cm.
   The average age of the terfenadine group, which consisted of 55 girls and 48 boys, was 8.5 ± 2.2 years; the average weight was
   29.5 ± 8.6 kg, and the average height 130.4 ± 13.6 cm.
   The groups are comparable (Table III).

d) The diagnosis distribution is illustrated in Table IV. Patients could exhibit more than one condition.

e) The average pre-treatment severity grade of the symptoms or condition diagnosed using the analog visual scale was 63.6 for
   the cetirizine group and 65.5 for the terfenadine group (Table V).

\(^1\) Comparison of cetirizine and tafenadine in allergic schoolchildren, A. Boukaert, Professor of Mathematics Applied to Medicine, Catholic University of Louvain (1988).
3. **Combined treatment**

Other forms of treatment were combined with the trial drugs in twenty-five cetirizine group patients and twenty-five terfenadine group patients. The drugs taken by these patients concurrently with the trial drugs were β₂-mimetics, theophylline, cromoglycate, local or general antibiotics, local antiseptics, mucolytics and aspirin.

4. **Evaluation of efficacy**
The efficacy evaluation performed using the analog visual scale shows an average difference of 48.6 in the cetirizine group and 50.2 in the terfenadine group, an improvement of 76% and 77% respectively (Table VI). The same evaluation made using the five-point scale and aggregating results to negative development (no change or worsening) and positive development (slight, moderate or substantial improvement), showed that 97 patients out of 103 improved after taking cetirizine and 99 patients out of 102 improved after taking terfenadine (Table VII). There is therefore no statistically significant difference between the two treatment groups. Comparison of the groups by type of allergic condition was possible only in the pathologies that occurred most frequently during the study, i.e. acute allergic rhinitis, urticaria, pruritus and asthma. There is no statistically significant difference between the two groups on this parameter either (Table VIII and IX).

5. **Evaluation of tolerance**

Undesirable effects were observed in 7.8% of cetirizine patients and 15% of terfenadine patients. The difference is not statistically significant (p=0.17 (Table X).

A description of the undesirable effects is furnished in Table XI. Overall tolerance to the treatment was judged to be excellent in 8.35% of cetirizine patients and 78.4% of terfenadine patients. The difference is not statistically significant (p=0.7) (Table XII).
In the terfenadine group (Population 3), the investigators therefore considered that patient compliance was satisfactory for 98% of cetirizine patients and 97% of terfenadine patients. Detection of the drug in urine samples collected during Consultation 2 was performed in UCB's Metabolism and Pharmacokinetics Laboratory. A separate report has been drawn up on this work (15). Compliance as estimated on the basis of these measurements is in the neighbourhood of 90%.
IV. DISCUSSION

The study conducted by the general practitioners on the pediatric population was an overall success, since it would appear that a majority of the patients followed the prescribed treatment properly. The selected indications for the prescription of antihistamines were relatively well represented, but the proportion of atopical dermatitis and allergic conjunctivities was low, probably because local treatment was preferred. Chronic allergic rhinitis did not occur frequently either, no doubt because of the late start of the study (late October). Combined treatment was relatively frequent, in spite of the recommendation in the protocol, but with an even distribution between the two groups.

V. CONCLUSION

No statistically significant differences were found between the two groups of children aged between six and twelve years after treatment for an allergic condition by means of either 2 x 5 mg per day of cetirizine or 2 x 30 mg per day of terfenadine. Both drugs were equally effective, and equally well tolerated.