## Study A156 - Clinical Report RRC92J1401

Multicentre double-blind study of the efficacy and safety of 5 mg cetirizine drops (10 mg/ml oral solution) or matching placebo, given with the evening meal over four weeks to children aged 2 to 6 years suffering from perennial allergic rhinitis.

(Protocols PCD89G251, PCE89G192 and PCF89G191)

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SUMMARY

Cetirizine drops, 5 mg once daily during 4 weeks, was compared to placebo in children aged 2-6 years suffering from perennial allergic rhinitis in a double-blind multicentre trial (18 centres). One hundred and thirty eight patients were entered in the study. One patient did not take the test-medication and was excluded from the Intention To Treat analysis. Of the remaining 137 patients (89 boys, 48 girls), 70 patients received placebo, 67 patients took cetirizine.

The primary efficacy variable was the percentage of days where the most severe of 5 rhinitis symptoms (sneezing, rhinorrhoea, blocked nose, nasal and ocular pruritus) was at most mild. This percentage had a median of 60% in the cetirizine group and of 52.1% in the placebo group. The difference was not significant (p = 0.29) (Wilcoxon Rank Sum Test). A power of 93% was reached for a minimal detectable difference between means of 20% (t-test). Safety was assessed by reporting any adverse events and by comparing haematological and biochemical tests before and after the trial. Adverse events (36 in placebo group, 41 in cetirizine group) were mainly trivial and no serious adverse events, possibly related to cetirizine, were reported.
RESUME

Cette étude multicentrique effectuée dans 18 centres en France, en Allemagne, en Italie et aux Pays-Bas, chez des enfants de 2 à 6 ans souffrant de rhinite allergique perannuelle, avait pour but d'évaluer l'efficacité et l'innocuité de la cétirizine, administrée pendant 4 semaines sous forme de gouttes, à la posologie de 5 mg (10 gouttes) une fois par jour.

L'essai, en double insu par rapport à un placebo d'apparence identique, avait obtenu l'approbation des comités d'éthique concernés.

Le diagnostic de rhinite allergique perannuelle devait avoir été établi au moins un an auparavant et l'allergie à un pneumallergène perannuel devait avoir été établie par un test cutané ou un RAST.

Étournements, rhinorrhée et obstruction nasale devaient être présents et la somme des scores d'évaluation par l'investigateur, sur une échelle de 0 (absent) à 3 (sévère, c.à.d. perturbant les activités diurnes et/ou le sommeil) devait atteindre au moins 5.
de produit testant dans les fractions tomées à chaque visite.
Le critère principal d'efficacité était le pourcentage de jours où le score le plus élevé des 5 symptômes était 0 ou 1 ; une différence de 20% entre les médianes des groupes était considérée cliniquement pertinente. Le test des rangs de WILCOXON a permis de comparer les distributions des deux groupes.
L'innocuité était évaluée par le relevé des événements indésirables et par les examens hématologiques et biochimiques, effectués avant et après traitement.
Les groupes sont comparables (tableaux 7 à 9, pages 24 à 25); 70 patients ont reçu le placebo et 67, la cétirizine.
Le pourcentage médian de jours où les symptômes étaient absents ou tout au plus légers est 52,1% dans le groupe placebo et 60% dans le groupe cétirizine. Cette différence de 7,9% n’entraîne pas de différence significative entre les distributions des deux groupes. Au cours de l’essai une puissance de 93% a été atteinte pour une différence de moyennes de 20%.
Des événements indésirables ont été rapportés par 20 patients dans chaque groupe (36 dans le groupe placebo et 41 dans le groupe cétilizine); leur incidence, sévérité et relation causale au produit testé peuvent être trouvées dans les tableaux 13 à 15 (pages 29 à 31).
Il apparaît que des événements liés à une infection des voies respiratoires (fièvre, syndrome grippal, infection, bronchite, toux, rhinite, otite moyenne) sont plus fréquents dans le groupe cétilizine (26 événements) que dans le groupe placebo (10 événements).
Deux événements graves ont été rapportés dans le groupe cétilizine (un syndrome de Henoch-Schönlein et une crise d’asthme ayant nécessité une hospitalisation) mais la relation causale avec le produit étudié est improbable.
Les analyses sanguines n'ont pas révélé de toxicité. Les anomalies les plus fréquentes concernaient la formule leucocytaire et en particulier l'éosinophilie, liée à la pathologie étudiée.
En conclusion, cette étude n'a pas pu démontrer l'efficacité de la cétilizine, administrée à raison de 5 mg une fois par jour pendant quatre semaines, chez des enfants de 2 à 6 ans souffrant de rhinite allergique perannuelle. La tolérance de la cétilizine a été excellente.

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I. **INTRODUCTION**

Cetirizine is a potent H1-antagonist of the piperazine group, used in the treatment of allergic rhinitis and chronic urticaria in adults at the dosage of 10mg once daily (1). In children 6-12 years old the plasma half life is about 7 hours (2), and 10mg given once daily or as 5mg twice daily was found to be efficacious and safe in the treatment of allergic rhinitis (3). A dosage of 5mg once daily was found to be efficacious and safe in a trial in seasonal allergic rhinitis (4). The objective of the present study was to evaluate the efficacy and safety of 5mg once daily administered over 4 weeks in children 2-6 years old and suffering from perennial allergic rhinitis.

II. **METHODS**

A. **Study design**

This phase III, randomised, double-blind, parallel group study was planned to enrol 120 evaluable patients, aged between 2 and 6 years, with a diagnosis of perennial allergic rhinitis. Fifteen investigators were to enrol between 6 and 12 patients each.

The enrolment of patients was suspended from May to October to avoid the pollen allergy season.
B. Patient Selection

Prior to inclusion in the study, the parent or legal guardian of the child was required to give informed consent (in France and Germany always in writing, in the Italy and Holland in writing or in front of a witness), having previously discussed the implications of the study with the investigator (patient information sheet).
Boys and girls aged between 2 and 6 years, attending out-patient clinics, with a diagnosis and at least one year history of perennial allergic rhinitis were eligible for enrolment into this study.

Diagnosis of sensivity to perennial allergens such as house dust mite and/or animal danders was confirmed by a positive skin test or a positive RAST (also CLA in Germany).

At the time of enrolment into the study, the patient was required to be experiencing an active phase of perennial allergic rhinitis, characterised by the following symptoms: sneezing, rhinorrhea and blocked nose. To be eligible for inclusion, the total score for these 3 symptoms at the time of screening had to be equal to or greater than 5, based on a 4-point scale: 0 = absence of the symptom, 1 = mild i.e. presence of the symptom which is not inconvenient, 2 = moderate i.e. the symptom is inconvenient but does not hamper the normal daily activities or disturb sleep, 3 = severe i.e. the symptom disturbs sleep and/or normal daily activities.

Those patients with any of the following symptoms or conditions were not eligible for enrolment in the study:

- a known allergy to a pollen which was present in the period preceding the study and/or was likely to appear during the study

- asthma likely to require a change of therapy during the course of the study, or needing corticosteroids either systematically or by inhalation in a dose greater than 200 μg daily

- atopic dermatitis needing a change of established treatments, or requiring systemic or topical corticosteroids either just prior or during the study period

- vasomotor or infectious rhinitis

- an upper respiratory tract infection in the three weeks preceding the screening for this study

- obstructive nasal polyps

- a history of hypersensitivity to piperazines

- a clinically relevant renal, hepatic or cardiovascular disease or a condition which would make participation in this study inadvisable

- clinically significant laboratory haematological or biochemical abnormalities not related to perennial allergic rhinitis

- the presence of any infection likely to necessitate a course of antibiotic treatment during the study period
- treatment with the following drugs during the pre-study periods specified:
  - astemizole in the previous 6 weeks
  - systemic steroids in the previous 4 weeks
  - ketotifen in the previous 2 weeks
  - topical steroids (nasal or ocular) in the previous week
  - disodium cromoglycate (nasal or ocular) in the previous week
  - nasal decongestants or oral antihistamines in the 2 days prior to inclusion
- a course of desensitization therapy in the ascending phase
- participation in a clinical trial in the previous 3 months
- recent or foreseeable changes in lifestyle, e.g. moving house, holidays, regular week-end trips, during the trial period
- the likelihood of poor compliance.

C. The treatments

1. Study medications

The medications which were compared during the course of the trial were cetirizine drops (10 mg/ml oral solution, batches nrs 79, 81 and 83) and matching placebo (batches nrs 78P, 80P and 82P.).
2. Contra-indicated medications

During the course of the study, usage of the following drugs was prohibited: antihistamines (other than the study medication), decongestants, corticosteroids (other than 200μg daily by inhalation), sedatives and nasal or ocular medications.

3. Concomitant medications

Asthmatic patients maintained on treatments such as theophylline, β₂-mimetics, nedocromil, inhaled sodium cromoglycate or inhaled corticosteroids were eligible for the study provided the doses of such medications remained unaltered for the 4-week study period, and provided the corticosteroid dose did not exceed 200μg daily.

Patients with atopic dermatitis who were eligible for enrolment were permitted to continue on topical non-steroidal therapy during the course of the study.

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D. Conduct of the study

1. Clinical assessments

The study involved 3 clinical assessment visits. The initial evaluation was on day 1 (visit 1); eligible patients entered the study following this screening assessment. The intermediate clinical assessment was scheduled between days 12 and 18 (visit 2) and the final visit (visit 3) was between days 26 and 32.

2. Daily Record Cards

The parents were to complete a diary card each evening during the study, which recorded severity of the five selected rhinitis symptoms (itchy nose, sneezing, runny nose, blocked nose and itchy eyes).
E. Evaluation of Efficacy

1. Assessments made by the investigators

At each visit to the clinic the investigator evaluated the severity of the patient's symptoms of perennial allergic rhinitis, namely: sneezing, rhinorrhea, blocked nose, nasal and ocular pruritus on a 4-point scale, where 0 = symptom not present, 1 = mild, 2 = moderate, 3 = severe (same definitions as above). At the final visit the investigator made a global assessment of the response to the treatment on a 5-point scale where 0 = worsening, 1 = no change, 2 = slight improvement, 3 = good improvement, 4 = excellent improvement i.e. a complete resolution of the symptoms.

2. Assessments made by the parents

The parents made a daily evaluation of the perennial allergic rhinitis symptoms based upon a 4-point scale where 0 = not at all, 1 = slightly, 2 = a great deal, 3 = unbearable. The first diary entry referred to the symptoms of the day prior to enrolment completed in the presence of the investigator, and the second entry was based upon the symptoms on the enrolment day, prior to taking the medication.

F. Evaluation of Safety

The safety of the treatment regimens was assessed in part by comparisons of pre- and post-study laboratory measurements and in part by the occurrence of adverse events.

1. Laboratory Tests

The haematological safety evaluations included the following measures: erythrocytes, haemoglobin, haematocrit, total leucocytes, neutrophils, lymphocytes, monocytes, basophils and eosinophils. The biochemical parameters assessed consisted of total bilirubin, SGOT, SGPT, urea and creatinine.

2. Adverse Events

At clinic visits 2 and 3 the investigator elicited information on the tolerance of the medication by asking the standard question "Have you noticed anything in particular which concerns the health of your child?". In addition, the parent was asked to record in the diary card any events experienced by the child.

For all adverse events, irrespective of cause, the investigator had to complete a full record containing descriptive details of the event, its onset, pattern, severity, actions taken, outcome and relationship to treatment.
The severity of each adverse event was graded by the investigator on a 3-point scale where 1 = mild, 2 = moderate, 3 = severe. The relationship of the adverse event to the study drug was rated as none, unlikely, possible, probable or certain.

In the event of a serious adverse event, the investigator was to notify the study monitor immediately.

Appropriate treatment of the patient was the investigator's responsibility. If deemed absolutely necessary, the investigator could open a sealed envelope and discover the treatment allocated to the patient, who was then withdrawn from the study.
H. Statistical Methods

1. General

An Intention To Treat analysis, including all patients who were randomised and received treatment, was conducted on all variables. All the tests which were applied were two-tailed and the level of significance was 5%. The statistical analysis was conducted using the SAS software version 6.07, under licence from SAS Institute Inc.

2. Demographic data

Only summary statistics were presented.

3. Assessment of rhinitis by the parents - Primary efficacy variable

- The maximum score for any of the five symptoms (or the four symptoms) recorded on day 1 or the preceding day was taken as baseline.
- The primary efficacy variable was defined as the cumulative relative frequency of days with no or only mild symptoms, i.e. the percentage of days with a maximum score ≤1 (PDS≤1) for the total treatment period from day 2 on. The distributions of PDS≤1 of both groups were compared using the Wilcoxon rank sum test. A 20% difference between medians was considered as
clinically relevant. The power function was calculated for a two-sided test for equality of two means, with a first kind error of 5%.

- Secondary efficacy variables were the cumulative relative frequencies for days without symptoms (PDS=0) and for days with a maximum score ≤2 (PDS≤2), for the five symptoms and for only four symptoms, after exclusion of nasal obstruction. Treatment effect on days 2 and 3 was evaluated by comparing at each of these two days both groups on the maximal score calculated with the 5 symptoms, and the 4 symptoms. This operation was performed by using the Cochran-Mantel-Haenszel test, stratified by the baseline.

- Descriptive statistics were computed for the daily mean score of each symptom and for the daily maximum score of the 5 symptoms (and after exclusion of nasal obstruction), and represented graphically up to day 29.

4. Assessments of efficacy by the investigator

- Symptom scores at visit 1 are baseline symptoms.
- An estimation of missing data was made if the patient was a "treatment failure" i.e. withdrawn for inefficacy and/or adverse events: the scores at visit 3 were estimated by the scores at visit 2.
- Disease severity was again defined by the highest score of any of the 5 symptoms. The score difference between the first and the second visit, and that between the first and the third one were computed for every symptom and for the highest score. Comparison of both groups at visits 2 and 3 was made on the basis of this maximal score, by the Cochran-Mantel-Haenszel test, stratified for the maximal score at visit 1. The same comparisons were made after exclusion of the scores for nasal obstruction.
- The global evaluation of treatments, rated on a 5-point scale, was compared in terms of frequency distribution using the Cochran-Mantel-Haenszel test.

5. Adverse Events

- Adverse events were classified according to COSTART.
- For each treatment, a frequency distribution of number (and percentage) of patients with at least one adverse event was constructed per body-system and COSTART term. If the same COSTART term was reported several times for the same patient, only one was retained, unless it was the same COSTART term reported under different body-systems.
- For each treatment, a frequency distribution was constructed per body-system, COSTART term, and severity of the adverse events. If the same COSTART term was reported several times for the same patient, the maximum severity was retained.
- For each treatment group, the number of patients, by COSTART term and by relationship — in the opinion of the investigator — of the adverse event to the drug, was computed. If the same COSTART term was reported several times for the same patient, the maximum relationship was retained.
6. Laboratory tests

The laboratory results were standardised by converting them in SI units, with the exception of SGPT and SGOT, expressed in U/l. Neutrophils, lymphocytes, monocytes, basophils and eosinophils percentages were converted in absolute numbers.

In view of statistical analyses, the values of the laboratory results of the first and second blood samples were characterised by their status as: below the lower normal limit, within the normal limits, or above the upper normal limit;

They were subjected to the following analyses:
- for each patient for each parameter, the measured values at the initial visit and at the last visit were listed, if at least one was abnormal
- for each parameter the following was calculated:
  * a frequency distribution of the patient’s status by visit and treatment;
  * a frequency distribution of the patient’s status at laboratory 2 by treatment, controlling for status at laboratory 1. The Cochran-Mantel-Haenszel test, computed on the ranks and stratified by the baseline, was applied on this table.

In view of a standardised evaluation of the relevance of the laboratory abnormalities, they were described as clinically relevant when:
- value < 0.8 times the lower normal limit or > 1.3 times the upper normal limit for haemoglobin, haematocrit and erythrocytes;
- value < normal lower limit or > upper normal limit for leucocytes, neutrophils, lymphocytes and eosinophils;
- value > upper normal limit for monocytes and basophils;
- value > 1.2 times the upper normal limit for total bilirubin, blood urea and creatinine.
- value > 2 times the upper normal limit for SGOT and SGPT.

III. RESULTS

The results presented are contained in the statistical report RRCE92A0301.

A. Time-frame / Enrolment

One hundred and thirty eight patients were enrolled into this study by 18 investigators in Germany (5), France (5), Italy (5)
C. Demography

The demographic variables, sex, age, height and weight are summarized for both treatment groups in Table 7. The distributions of the patients in the treatment groups by age and weight ranges are presented in Tables 8 and 9. The two treatment groups in terms of the main demographic variables were well balanced. There were almost twice more boys than girls in both treatment groups. In the whole sample, the mean age was 4.7 years and the mean weight 19.1 kg. Only 2 cetirizine patients were outside the age limits set by the protocol.

D. Medical History and Physical Examination.
The two groups were well balanced in terms of the duration and severity of their perennial rhinitis (Table 10). Two patients in the cetirizine group and 3 in the placebo group had their perennial allergic rhinitis diagnosed for less than one year. One placebo patient and 3 cetirizine patients were included without any positive allergy test. In 12 patients (5 cetirizine, 7 placebo), these tests had not been performed within the year as required by the protocol, 10 of these in centre 445.

The clinical examinations conducted at inclusion revealed that almost all patients had nasal and sinus symptomatology (cetirizine: 64, placebo: 69). A full listing of the patient’s physical examination findings can be found in Appendix I.6 of the statistical report.

Although the sum of the main 3 symptoms (sneezing, rhinorrhea and blocked nose) was ≥5 in all patients, sneezing was not present in 1 patient, and nasal obstruction in 3 others, all cetirizine patients.

E. Analysis of efficacy

1. Daily evaluation of symptoms of rhinitis by the parents

Full details and summary statistics for each of the five rhinitis symptoms, together with the maximum score for 5 or 4 (excluding blocked nose) recordings in the diary card between day 0, i.e. the day before commencing treatment, to the last day of treatment are presented in Appendix II.2 of the statistical report.

The number of patients (parents) completing the diary cards declined over time; after 4 weeks, by day 29, approximately 25 patients in each treatment group were still completing the diaries.
The primary efficacy variable for this trial was the PDS<sub>1</sub> computed on the 5 symptoms. Its median has a value of 52.1% for placebo and 60.0% for cetirizine. The difference of 7.9% between both medians is in favour of cetirizine treatment, but the Wilcoxon Rank Sum test revealed no significant difference between both groups (p = 0.29). The mean relative to cetirizine (56.3 %) is also higher than that corresponding to placebo (49.9 %). The 95 % confidence limits of the difference of means (6.4 %) are −4.9 % and 17.8 %. A power of 93 % is achieved for a difference of means of 20 %.

The distributions of the highest scores for any of the 5 (or 4) symptoms during the initial period (days 2 and 3), when compared by the stratified Cochran-Mantel-Haenszel test, were not different.

2. Evaluation of the rhinitis symptoms by the investigators at the visits.

The mean score of each symptom as well as the maximal score decreased from visit 1 to visit 2, and further, though less markedly from visit 2 to visit 3 (Table 12). The evolution is not different between the two treatment groups.

3. Global evaluation of treatment by the investigator.

Figure 9 gives the global evaluation of the response to treatment made by the investigator at the final visit, based on a 5-point scale defined above. No significant difference is found between placebo and cetirizine distributions.
F. Analysis of safety

1. Adverse events

There were 20 patients in each treatment group who reported one or more adverse events: 36 in the placebo group, 41 in the cetirizine group. Tables 13, 14 and 15 list respectively, per treatment, body system and Costart term, the incidence of adverse events, their severity and relationship to study medication as judged by the investigator.

Noteworthy is the high incidence of events related to respiratory tract infections (fever, flu syndrome, infection, bronchitis, increased cough, rhinitis, otitis media) which is higher in the cetirizine group (26) than in the placebo group (10).
2. Laboratory Tests

Blood samples were obtained at both visits in 66 of the 67 cetirizine treated patients and in 68 of the 70 placebo treated patients.

No laboratory abnormality required withdrawal from the trial.

Few laboratory results were considered as clinically relevant by the investigators with the exception of increased eosinophil counts. This is however most probably related to the atopic disease and treatment does not seem to modify this: at start 50 patients had hypereosinophilia (23 placebo, 27 cetirizine patients) and after treatment 47 patients had hypereosinophilia (25 placebo, 22 cetirizine).

Total and differential white blood cell counts were indeed the most frequent laboratory abnormalities in this study. Inversion of the neutrophil/lymphocyte ratio was frequently observed in both groups: this abnormality is often seen in children below 6 years. High total leucocyte counts were observed in 8 placebo patients and 10 cetirizine patients before starting the trial; at the end of the trial there were 9 placebo patients and 13 cetirizine patients who had leucocytosis.

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Other clinically relevant abnormalities were:
- in both groups there were a few cases of low haematocrit or low haemoglobin at start and completion of the trial without clear worsening;
- in the placebo group two patients had elevated transaminases at start of the trial, which normalized at the end in one patient, the control value was missing in the other; in another patient the serum creatinine was abnormal at the start and at the end but improved.
- in one cetirizine patient (446/011) a normal creatinine at start, was found to be 1.28 times above upper normal limit at the end and was not controlled again.
IV. DISCUSSION

The two treatment groups were well balanced at inclusion in terms of demographic parameters, medical history, duration and severity of perennial rhinitis.
As expected, blocked nose was the most severe symptom at inclusion (mean score of 2.49 for placebo, 2.33 for cetirizine) and ocular pruritus the least severe (0.49 and 0.72 respectively).

All individual symptoms improved over time, especially during the first week of treatment, and even if there appears to be a slightly better response in the cetirizine group for the primary efficacy variable (a difference in medians of 7.9 %), no meaningful differences were observed between the groups.

An analysis of the primary efficacy variable was made after exclusion of 23 patients with major protocol deviations and also in whom the total score was ≥ 3 on Day 0 or Day 1. 59 placebo patients and 55 cetirizine patients were retained for this analysis: the median PDS≤1 was 46.2% in the placebo group and 52.2% in the cetirizine group; the difference of 6.0% is in favour of cetirizine. As in the Intention To Treat analysis, no significant difference was found between both groups.

It is generally accepted that perennial rhinitis is less responsive to H1-antagonists than seasonal rhinitis, but the good to excellent improvement in 42% of the placebo patients reported at the last visit, is surprising.

It is not always possible to exclude concomitant infectious rhinitis in this patient population over a 4-week period. The hypothesis is made that several of these allergic children had superimposed infectious rhinitis which was not always diagnosed. Indeed, many children, especially in the cetirizine group, reported fever, flu-like syndromes and infections; there were also more cases of increased coughing and otitis media in the cetirizine patients. The increased leucocyte counts in these patients also seem to indicate that infections may have confounded the clinical picture or blunted the effect of anti-allergic treatment.

It is also possible that a treatment would have had better chances of success in this patient population where the cetirizine plasma half life is about 5 hours (5), had it been given as a twice daily regimen. In children, there is pharmacological evidence suggesting that a twice daily administration might yield better therapeutic results (6).

As far as safety is concerned, the number of patients reporting adverse events was identical in both groups.
No adverse events were thought to be possibly treatment-related in the cetirizine group. In particular, no cases of somnolence were reported in this group. Apart from more cases of increased total white blood cell counts in the cetirizine patients, no trends in laboratory abnormalities were observed.

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V. CONCLUSIONS

In this study involving 137 children aged between 2 and 6 years suffering from perennial allergic rhinitis, there were no clinically or statistically significant differences between cetirizine 5 mg daily and placebo over a 4-week period.

Cetirizine was very well tolerated in this study.
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