STUDY A175 - CLINICAL REPORT RRCE93F2302
Multicentre, double-blind, placebo controlled study of efficacy and safety of cetirizine 10 mg tablets (1/2, 1, or 1 & 1/2 tablet according to weight) given orally twice daily for 12 weeks to patients aged from 6 to 18 years and suffering from perennial atopic asthma.
(Protocols PCF90K111, RPCE91A1801, PCD90L301)

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09/11/1993
# TABLE OF CONTENTS

**SUMMARY** ......................................................... 1

I. INTRODUCTION .................................................. 3
   1. Rationale .................................................. 3
   2. Objectives of the study .................................... 5

II. METHODS .......................................................... 5
   1. Trial design ............................................... 5
   2. Selection of patients ....................................... 6
   3. Treatments .................................................. 7
   4. Conduct of the trial ....................................... 9
   5. Criteria of efficacy ....................................... 11
   6. Evaluation of safety ....................................... 11
   7. Evaluation of compliance .................................. 12
   8. Statistical analysis ..................................... 12

III. RESULTS ......................................................... 16
   1. Population ................................................ 16
   2. Inclusion rate ............................................ 16
   3. Demography ............................................... 16
   4. Description of asthma at baseline ....................... 16
   5. Treatment duration ....................................... 18
   6. Compliance ............................................... 19
   7. Reasons for terminating the study ....................... 19
   8. Protocol deviations ...................................... 19
   9. Analysis of efficacy ..................................... 20
  10. Analysis of safety ....................................... 23

IV. DISCUSSION ...................................................... 26

V. CONCLUSION ..................................................... 28

REFERENCES .......................................................... 29

TABLES I TO XXV ................................................... 32 to 61

Appendix I : List of patients completely excluded from the protocol selection 62
Appendix II : List of patients partially excluded from the protocol selection  65
Appendix III : List of investigators ............................ 66
Appendix IV : List of allergens with class ...................... 70
Appendix V  : Prior medications taken for asthma ............. 71
Appendix VI : Patient's outcome ................................ 75
Appendix VII : Protocol deviations .............................. 95

FIGURE 1 : Inclusion rate ........................................ 119

Final version CA/cz
09/11/1993
SUMMARY

The efficacy and safety of cetirizine (5, 10 or 15 mg twice daily, according to body weight) was compared to placebo in the treatment of mild perennial allergic asthma in children aged from 6 to 18 years.

Four hundred seventeen patients were selected. After an observation period of 2 weeks (= baseline) during which only inhaled $\beta_2$-agonists were allowed in case of an asthma attack, 174 patients received cetirizine and 177 patients received placebo. The treatment was to be taken for 12 weeks. FEV$_1$ and clinical symptoms were assessed regularly by the investigator (visits at 4-weeks intervals). The asthma symptoms and the consumption of inhaled $\beta_2$-agonists or other any asthma treatment was recorded daily by the patients on daily record cards (DRC).

Main efficacy criteria were:
- FAST = percentage of days and/or night with asthma recorded on DRC.
- Morning and evening peak flows.

The baseline was the 2 weeks observation period, and the end point was the total period of treatment.

Besides the main efficacy criteria, the frequency of asthma drug use (FMED), the severity index and the global evaluation of the study drug were also compared.

Although the results are in favour of cetirizine, differences between groups were globally not sufficient to show statistical and/or clinical significance:

- **FAST**: median improvement of 15.8% in the cetirizine group and 10.7% in the placebo group ($p = 0.190$).
- **Morning peak flow**: median improvement of 11.3 L/min in the cetirizine group and 3.8 L/min in the placebo group ($p = 0.028$).
- **Evening peak flow**: median improvement of 10.6 L/min in the cetirizine group and 3.5 L/min in the placebo group ($p = 0.067$).
- **FMED**: median improvement of 8.3% in the cetirizine group and 5.7% in the placebo group ($p = 0.339$).
- **Severity Index**: statu quo in both groups ($p = 0.296$).
- Global evaluation of treatment:
  investigator point of view:
  65% excellent or good results in the cetirizine group
  against 59% in the placebo group \( (p = 0.086) \).

  patient's point of view:
  75% excellent or good results in the cetirizine group
  against 61% in the placebo group \( (p = 0.022) \).

The analysis done on the so called "protocol selection" having excluded data recorded
after major protocol deviations, gave the same kind of results.

The two products were well tolerated. Respiratory complaints (mainly infections) were
the most frequently reported adverse events.

The incidence of somnolence was 0.6% in both groups.

The laboratory changes were minimal, and without statistical or clinical relevance,
except for haemoglobin where a mean drop of 0.24 mg % was observed in the
cetirizine group and of 0.04 in the placebo group \( (\text{Wilcoxon test } p = 0.04) \).
This observation was neither sex, age nor dose related. No explanation has been
found.
1. **INTRODUCTION**

1. **Rationale**

Asthma affects more than 5 percent of the population in the industrial countries (1) and is the most frequent chronic disease in childhood (2).

The role of histamine in the bronchoconstriction has been suggested since 1949 (3). The moderate bronchodilator effect of many antihistamines such as intravenous or inhaled chlorpheniramine (4,5), and more recently astemizole (6) and terfenadine (7) and cetirizine (8) could be explained by a direct antihistamine effect on the H₁ receptors at the level of the smooth muscle of the bronchi.

However, oral antihistamines have long been considered of little value in the treatment of asthma, because sedation was reported, limiting their effectiveness, and also because it is now well recognised that histamine does not play the most important role in the pathogenesis of asthma.

It is now recognized that asthma is a special type of inflammation of the airways, involving allergic inflammatory cells like eosinophils and many mediators (e.g. PAF, prostaglandines, leukotrienes and histamines) (9,10).

Asthma is therefore much more than bronchoconstriction and treatment must be directed toward both reducing inflammation and promoting bronchodilation.

Inhaled corticosteroids are more and more used in the treatment of even mild asthma in adults, but not in children. One of the problem of topical use of corticosteroids, beside oral candidosis and hoarseness, is that these preparations are not effective on chronic sinusitis, allergic rhinitis and polyps (occurring very often in children) and that administration of aerosol is difficult below the age of 4-5 years. So inhaled steroids are mostly given to children with severe asthma, when DSG or ketotifen are not effective anymore (2).

Cetirizine is a powerful and selective antihistamine with a rapid and prolonged action (11, 12). It is commercialized in all EEC countries for the treatment of allergic rhinitis and urticaria at the dose of 10 mg od.

Clinical pharmacological studies of the skin and the lung were conducted with cetirizine (using doses between 10 and 30 mg per day) and showed:

- an inhibition of the histamine and PAF acether PGD₂, release and of the eosinophils, basophils and neutrophils migration in the reaction induced by an antigen in the skin (13, 14);

- an inhibition of bronchospasm induced by histamine and LTD₄ (15);
- an inhibition of the eosinophils accumulation in the bronchial lavage 24 hours after an allergenic provocation (16);

- an inhibition of the late asthmatic response induced in asthmatic subjects allergic to cat fur (17).
2. Objectives of the study

a) The objective of the trial was to compare the efficacy of cetirizine (dose depending on the patient's weight) : 5 - 10 - 15 mg and of a placebo administered twice daily for up to 12 weeks to patients aged 6 to 18 years suffering from perennial allergic asthma. Main efficacy criteria chosen for this study were:
   - the percentage of days and/or nights with asthma recorded on the patients' diaries
   - the evolution of the morning and evening peak flow measurements.

b) To compare the safety of the two treatments : adverse events, laboratory tests.

II. METHODS

1. Trial design

This was a double blind multicentre study, each centre randomizing its patients into two parallel groups : one cetirizine group (5, 10 or 15 mg bid according to body weight), one placebo group.

46 centers participating in the study : 19 in France, 14 in the United Kingdom, 7 in Germany, 5 in Belgium and one in the Netherlands.

The study was sized in order to detect a difference between groups of 10% of days and/or nights with asthma during the whole study period (= FAST) : 300 patients had to be included in the study, and the safety margin of an extra 100 patients was foreseen in the protocol to ensure sufficient suitable patients for the efficacy analysis. Each centre was asked to recruit between 8 and 16 patients.
2. Selection of patients

2.1 Inclusion criteria

- Outpatients who gave their written informed consent (or oral in front of a witness if allowed) to participate in the study, together with that of the parent(s) or legal guardian if < 18 years.

- Age: 6 to 18 years inclusive.

- Weight: 15 to 90 kg inclusive.

- Documented history of perennial allergic asthma:
  - diagnosis dating back at least one year
  - positive skin test or RAST to at least one perennial allergen, either at the time of inclusion in the study or within the preceding year
  - morning-evening peak flow variability of at least 10%
  - presence of asthma symptoms during baseline (i.e. between the first and second visits)
  - use of \( \beta_2 \)-agonists (under regular dosage or PRN) since at least 2 months before the first visit
  - \( \text{FEV}_1 \) \( \geq \) 80% of predicted value or reversible to \( \beta_2 \)-agonists (increase being sufficient to reach 80% of predicted value).

2.2 Exclusion criteria

- Female of child-bearing potential, not using reliable methods of contraception (pregnancy test if requested): pregnancy or breast-feeding.

- Positive prick test or RAST for pollens (trees, plants) that are in season at the time of their inclusion in the study or during the 14 weeks following the inclusion.

- Desensitization course in ascending phase (maintenance courses allowed).

- Previous hospitalization for status asthmaticus.

- Use of systemic or inhaled steroids (the latter at a dose greater than 400 \( \mu \)g/day) for a period longer than 7 consecutive days at any time during the 6 months preceding Visit 1.

- Use of systemic or inhaled corticosteroids (the latter at a dose greater than 400 \( \mu \)g/day) for any period up to 7 consecutive days during 2 weeks preceding Visit 1.

- Aspirin sensitive asthma.

- Renal, hepatic or cardiac disease.
- Severe lung infection or progressive pulmonary tuberculosis.

- Abnormal chest X-ray (e.g. thoracic malformation, compressed trachea, emphysema, bronchectasis).

- Mucoviscidosis.

- Asthma caused by gastro-oesophageal reflux.

- Swallowing difficulty.

- Chronic urticaria or any skin ailment treated with anti-histamines, unless this treatment was stopped at the time of the pre-selection visit ($V_1$).

- Atopic dermatitis requiring local corticosteroid treatment.

- Allergic rhinitis requiring systemic treatment or local corticosteroids.

- Hypersensitivity to diphenylpiperazine derivatives (for example, cetirizine, hydroxyzine, meclizine, buclizine).

- Alcohol or drug-addiction problems, mental unstability, risk of not complying with the conditions imposed by the trial, foreseeable future environment change (moving home, treatment of house dust mite or other chemical treatments).

- Patients smoking more than 10 cigarettes per day.

- Patients who have participated in a clinical trial during the past 3 months.

- Patients who wished to donate blood during the trial period.

3. **Treatments**
3.2 **Washout periods**

No washout required at the first visit.

3.3 **Concomitant treatments**

3.3.1 *Allowed for the treatment of asthma*

- during baseline: only inhaled β₂-agonists
  - on demand
  - preventively for exercise induced asthma

- from the second visit on: additionally to the inhaled β₂-agonists, following treatments were allowed, when control of asthma was unsatisfactory, and for 4 days at the most per month
  - theophylline and derivatives
  - oral β₂-agonists.

3.3.2 *Allowed for the treatment of rhinoconjunctivitis and atopic dermatitis*

Any topical treatment without corticosteroids.

3.3.3 *Prohibited during the whole study*

- cromoglycate by inhalation
- nedocromil
- anticholinergics
- systemic antihistamines
- corticosteroids
- salmeterol or formoterol.
4.5 Evaluation by the patient

Patients were requested to fill in a daily record card, in which the following items were recorded in the morning and in the evening, when getting up and at bedtime:

- peak flow measurements (if β₂-agonists were needed, morning or evening measurements had to be done before their intake).
  The best of 3 measurements was recorded.
- day-time and nocturnal asthma symptoms on a 4-point scale:
  0 = no asthma
  1 = light asthma
  2 = moderate asthma
  3 = severe asthma
- any adverse events
- the number of puffs of inhaled β₂-agonists taken to control an asthma episode
- the number of puffs of inhaled β₂-agonists taken preventively for exercise induced asthma
- any other concomitant medication used.
- overall assessment of efficacy and safety (see section 4.4).
5. **Criteria of efficacy**

5.1 **Main criteria for assessment of efficacy**

- Percentage of days with either day-time or nocturnal asthma (or both), i.e. the percentage of days with at least one asthma score above treatment on the daily record card, calculated over the whole treatment period: FAST.

- **Morning** and **evening peak flows** (median) recorded on the daily record card.

5.2 **Secondary criteria for assessment of efficacy**

- Percentage of days when at least one puff of inhaled $\beta_2$-agonists has been taken (either during the night, during the day or preventively taken for exercise) calculated over the whole treatment period: **FMED**. The use of other asthmatic drugs were put into the same category as the $\beta_2$-agonists.

- Percentage of **treatment failures**, i.e. percentage of study withdrawals for inefficacy or adverse event with a possible, probable or certain relationship with the trial drug.

6. **Evaluation of safety**

- Adverse event reported at visits or on the daily record cards. Patients were asked the following question: have you observed anything unusual regarding your health since your last visit?
8. **Statistical analysis**

8.1 **Population definition**

Two populations were defined for the analysis:

- intention-to-treat population (ITT). All randomized patients who received at least one dose of study medication (thus all patients with a treatment number).

- Protocol population (PROT). Subset of ITT population from which some non evaluable patients (ineligible, major protocol deviations) were removed, upon decision of the Study Review Committee, before breaking the code.

The ITT population was used for all analyses. The protocol population was used for the primary efficacy criteria only.

8.2 **Descriptive analyses**

Descriptive analyses, by visit or by period and for the total period of treatment was performed on all variables (see chapter II.4).

8.3 **Efficacy variables**

8.3.1 **DRC variables**

a) Using the daily record cards, 3 derivative variables were calculated:
- per period between the visits
- for the total period of treatment.

• **FAST**: one of the main efficacy criteria (see also section II 5.1). FAST was obtained by dividing the number of days with a score > 0 for day-time and/or nocturnal asthma by the number of days of each period and by the total number of days between the second and last visit (result in percent).
• **FMED**: one of the secondary efficacy criteria (see also section II 5.2). FMED was obtained by dividing the number of days when at least one puff of inhaled $\beta_2$-agonist or another asthma drug was taken, by the number of days between the second and last visit (result in percent).

• **Severity index**: not foreseen by the protocol. According to the formula

$$\frac{\text{ASD} + \text{ASN}}{2} + \text{MED}$$

where

- **ASD**: mean day-time asthma score of the days with asthma (thus days without asthma are not taken into account) (theoretical range for ASD = 1-3).
- **ASN**: mean nocturnal asthma score of the nights with asthma (thus nights without asthma are not taken into account) (theoretical range for ASN = 1-3).
- **MED**: mean score of $\beta_2$-agonists consumption or other asthma drugs use, calculated as:
  - score = 1 1 puff/day
  - 2 from 2 to 6 puffs/day
  - 3 more than 6 puffs/day or other asthma drug use.

The days without medication are not taken into account.

The severity index is therefore scored between 1 and 6.

b) mean morning and evening peak flows (MPF and EPF).

### 8.3.2 Variables measured at visits

- symptoms of asthma at visits
- FEV$_1$
- global evaluation of treatment
- treatment failures.

### 8.3.3 Statistical methods

- When a baseline was available, it was taken into account:
  - visit 2 status was chosen for the symptoms of asthma FEV$_1$
  - period between visit 1 and 2 was chosen for all variables of the DRC:
    - FAST
    - FMED
    - severity index.
    - peak flows

Final version CA/cz
09/11/1993
- Wilcoxon rank sum test was used to compare the distribution of FAST, FMED and peak flows (MPF/EPF) between the two groups. Tests were carried out on the differences between the values for a considered period and the baseline.

- The evolution of the symptoms at the visits were summarized as "worsening", "no change", and "improvement" by comparison to the situation at visit 2. The score distributions of the two groups, stratified according to the baseline score, were compared by means of the Cochran-Mantel-Haenszel test.

- The evolution of FEV₁ of the two treatments (difference with baseline) were compared by means of the Wilcoxon rank sum test.

- The global evaluations of the two treatments were compared with the Cochran-Mantel-Haenszel test.

- The proportion of treatment failures in the two groups were compared using the Fisher's exact test.

All the tests were two tailed, and the significance level was 5%.

8.4 Safety analyses

8.4.1 Adverse events
All adverse events were recorded and classified according to COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms, Department of Health and Human Services, Rockville, Maryland, 1989, 3rd edition). The comparison of occurrence of adverse events between treatment groups was performed by using the Fisher's exact test.

8.4.2 Laboratory data
In order to take the existence of several normal ranges of laboratory parameters into account, all parameters were standardised. Two standardisation methods were used: three category ordinal scales (below, within, above the norms) and standardised value (relative distance between the measured value and the middle point of the normal range divided by the half length of the normal range). The following formula was used to calculate the standardised values:

\[
\text{standardized value} = \frac{X-M}{1/2(U-L)}
\]
when \( X \) = measured value, \( M \) = mid point of normal range, \( U \) = upper limit of normal range and \( L \) = lower limit of normal range. The standardised value is expressed in arbitrary units. The normal range for standardised value goes from \(-1 \) (\( X = L \)) to \(+1 \) (\( X = U \)).

For the first standardisation method (below, within, above the norms), the score distributions of the two groups, stratified according to the baseline score, were compared by means of the Cochran-Mantel-Haenszel test. For the second standardisation method (standardized values), the evolution of standardized values (difference between the two labs) of the two treatments were compared by the Wilcoxon's test.
III. RESULTS

1. Population
Patients of the two groups are totally comparable for age, height, weight and sex.

4. **Description of asthma at baseline (Table II)**

4.1 **Asthma duration**

The median duration of asthma at the time of visit 1 was 4.2 years in the cetirizine group and 4.1 years in the placebo group.

4.2 **Allergy documentation**

4.2.1 **Perennial**

One hundred seventy one patients in the cetirizine group and 170 patients in the placebo group had a positive skin test or RAST for at least one perennial allergen, and no evidence of perennial allergy could be demonstrated in 3 patients in both groups; a doubtful result was found in 4 patients in the placebo group. The most frequent allergen was house dust mite (42% and 44% respectively in
cetirizine and placebo group). All allergens were well balanced in both groups.

4.2.2 *Seasonal*
Although there was an obvious interference of the pollen season for 7 patients in each group, it is interesting to note that about 50% of the patients had a positive test for at least one seasonal allergen.

The most frequent one was grass pollen (35% and 34% respectively in the cetirizine and placebo group) followed by trees (9% and 8% respectively).

All seasonal allergens were well balanced in both groups.

The complete list of all allergens can be found in Appendix IV.

As the inclusion rate and the allergic profile were similar in both groups, one can assume that the results study were not biased by pollen interference.
4.4 Symptoms of asthma at visit 2 (assessed by investigator)

Approximately 50% of the patients did present at visit 2 without either cough, dyspnea or wheezing. When these symptoms were present, they were mild in about 30-40% of the cases. The two groups were relatively well balanced for the 3 symptoms, the "moderate" or "severe" symptoms being somewhat more frequent in the placebo group (18% for cough, 10% for dyspnea, 12% for wheezing) than in the cetirizine group (13%, 6% and 9% respectively).

4.5 Lung function tests at visit 2

Median FEV₁(\% of predicted value) at baseline was 87.4% in the cetirizine group and 88.2% in the placebo group, which was expected from the protocol inclusion criterion.

Final version CA/cz
09/11/1993
4.6 Symptoms of asthma on the DRC assessed by the patient (period 1)

Symptoms of asthma (FAST) were somewhat less frequent in the cetirizine group (mean = 53.1%, median = 51.2%) than in the placebo group (mean = 59.0%, median = 64.3%) but the difference between groups was not statistically significant (p = 0.132).

Mean diurnal and nocturnal asthma score was respectively 0.57 and 0.48 in the cetirizine group, 0.63 and 0.58 in the placebo group.

4.7 Peak flows on the DRC (period 1)

Medians of the morning peak flows were equal to 303.8 L/min and 298.7 L/min, whereas the medians for the evening peak flows were equal to 322.6 L/min and 317.5 L/min respectively in the cetirizine and placebo group. The differences between groups were not statistically significant (p = 0.497 and 0.389 respectively).

4.8 Asthma baseline of the protocol population

Generally speaking, no major differences between the ITT and protocol populations were seen.

The tendency of the placebo group to be more affected than the cetirizine group is also seen here, and more specifically for the FAST with mean and median values equal to 54.8% and 55.6% in the cetirizine group and 60.8% and 64.3% in the placebo group.

Although that difference was not statistically significant (p = 0.186), it must be underlined that the difference between medians is just below the 10%. The baselines of the asthma in the protocol population are also described in Table II.

5. Treatment duration (Table III)

The mean number of days between the second and last visits (= theoretical treatment duration) was 80 in the cetirizine group (range 7-126) and 78 in the placebo group (range 7-126).
6. **Compliance (Table IV)**

Compliance for the total period (mean = 95.7% and 93.9% respectively in the cetirizine and placebo group) as well as for each period taken individually was well balanced in both group.

7. **Reasons for terminating the study (Table V)**

One hundred forty seven patients in the cetirizine group (84.5%) and 137 patients in the placebo group (77.4%) completed all phases of the study. Twenty seven patients in the cetirizine group and 40 patients in the placebo group terminated the study prematurely or were withdrawn for multiple reasons (foreseen by protocol) and listed in Table V.

The withdrawals for inefficacy or adverse event, as decided by the investigator or the patient, were the following : 13 in the cetirizine group and 23 in the placebo group (p = 0.113). Details are given in Appendix VI.
9. Analysis of efficacy

9.1 Daily record cards

9.1.1 Main efficacy criterion: frequency of day-time and/or nocturnal asthma (FAST) (Table VII)
FAST improved in both groups as compared to baseline. In the ITT selection median improvement (total period - baseline) was 16% in the cetirizine group and 11% in the placebo group.
Comparison between the improvements of both groups (approximately 5% difference) is not statistically significant (p = 0.190) and clinically not relevant.

9.1.2 Main efficacy criterion: morning peak flows (MPF) (Table VIII)
MPF improved in the cetirizine group (median improvement for the total period = 11.3 L/min) and remained almost exchanged in the placebo group (median improvement for the total period = 3.8 L/min).
This difference between the improvements of both groups is statistically significant (p = 0.028), but is of limited clinical relevance.
To be noticed also that the same kind of borderline differences were observed at all periods, and that these differences were also statistically significant except at period 4 (p = 0.008 at period 2, 0.024 at period 3).

9.1.3 Main efficacy criterion: evening peak flows (EPF) (Table IX)
The evolution of the EPF was superimposable to that of MPF.
For the total period, median improvement from baseline was 10.6 L/min in the cetirizine group and 3.5 L/min in the placebo group (p = 0.067).
Statistically significant differences were seen after the second and third period (p = 0.021 and 0.040 respectively), but again the clinical relevance was negligible.

9.1.4 FMED (Table X)
The frequency of use of β₂-agonists or other asthma drugs decreased slightly in the two groups as compared to baseline.
The median improvements (total period - baseline) were 8.3% of days in the cetirizine group and 5.7% of days in the placebo group (difference not significant).

9.1.5 Severity index (Table XI)
The severity index was rather low from baseline on (3.00 in both groups), and remained unchanged during the study. The differences between groups were not significant.
9.2 Evaluations during visits

9.2.1 Symptoms evaluated by the investigator (Tables XII-XIII)
At baseline, symptoms were present in nearly 50% of the patients in the cetirizine and placebo group (55% and 56% for cough, 41% in each group for dyspnea, 43% and 50% for wheezing).

Mean scores were similar in both groups and rather low (about 0.8) for all symptoms. Thus, the room for improvement was quite small. The evolution of the three symptoms is presented in Table XIII and show similar and small improvements of the 3 symptoms in both groups.

To be noticed that the differences between groups at Visit 4 (Visit 4 - baseline) is significant in favour of cetirizine for cough and dyspnea, but this is of little clinical relevance.

9.2.2 Lung function test (Table XIV)
FEV₁ (6 hours after any β₂ use) was about 89% of predicted in both groups at baseline, and improved slightly at the final visit (median increase of 1.7% in the cetirizine group and 1.1% in the placebo group). These differences were neither clinically nor statistically significant (p = 0.897).

To be reminded that the room for improvement was negligible due to the requirements of the inclusion criteria concerning lung function (FEV₁ > 80% or reversible to inhaled β₂-agonist with a value > 80% after β₂ use).

9.2.3 Global evaluation of treatment (Table XV)
Global evaluation of treatment performed at the end of the study by the investigator and the patients gave following results.

Sixty five % of the patients in the cetirizine group and 59% in the placebo group were rated as excellent or good by the investigator (a bad or very bad evaluation being given for 10% of patients in the cetirizine group and 16% in the placebo group). The difference between groups was not statistically significant (p = 0.086). Seventy five % of the patients in the cetirizine group and 61% of the patients in the placebo group evaluated the efficacy of their treatment as excellent or good, a bad or very bad evaluation being given by 8% of the patients in the cetirizine group and 17% in the placebo group (p = 0.022).

9.2.4 Treatment failures
The proportion of patients who withdrew from the study due to inefficacy or to an adverse event with a relation to study drug rated as possible or probable was superimposable to the drop outs for inefficacy, since all adverse events leading to an early withdrawal were found not to be related to study drug.
For that reason, treatment failures comparison was restricted to the comparison of dropouts because of inefficacy: 11 patients (6.3%) in the cetirizine group and 19 patients in the placebo group (10.7%) fall into this category ($p = 0.181$).

9.3 Protocol selection: analysis of the three primary efficacy criteria

9.3.1 FAST (Table XVI)
The results of the protocol selection are quite similar to those of the ITT selection: median improvement (total period - baseline) was 17% in the cetirizine group and 12% in the placebo group (comparison between groups is not significant: $p = 0.152$).

At the 4th period, however, there was a substantial difference between cetirizine (improvement of 24%) and placebo (improvement of 13%). The comparison between groups was statistically significant ($p = 0.035$).

9.3.2 Morning peak flows (MPF) and evening peak flows (EPF) (Tables XVII - XVIII)
Like in the ITT selections, MPF and EPF improved somewhat in both groups, the improvements being greater in the cetirizine than in the placebo group.

The median improvements between the total period and the baseline are the following:

- MPF:
  + 13.0 L/min in the cetirizine group and 5.7 L/min in the placebo group.
  The comparison between group (total period - baseline) is not statistically significant ($p = 0.104$).

- EPF:
  + 11.1 L/min in the cetirizine group and 4.3 L/min in the placebo group. The comparison between group (total period - baseline) is not statistically significant ($p = 0.073$).
10. **Analysis of safety**

10.1 **Adverse events (Tables XIX - XX)**

Ninety one patients in the cetirizine group (52.3%) and 88 patients in the placebo group (49.7%) reported at least one adverse event during the study (p = 0.670).

The most frequent adverse events were those affecting the respiratory system: pharyngitis (12.6%), bronchitis (10.9%), asthma (9.8%) in the cetirizine group and rhinitis (12.4%), bronchitis (10.2%), pharyngitis and asthma (6.8% each) in the placebo group.

Sedation was reported only once in each group (0.6%).

Fifteen adverse events were reported as severe in the cetirizine group and 8 in the placebo group.
10.2 **Serious adverse events**

Four adverse events in the cetirizine group and three in the placebo group were considered as serious as they required hospitalisation of the patient.
10.3 Laboratory data (Tables XXI - XXII)
When studied by status (below, normal, above normal) and by shift (i.e. change from status, either increasing or decreasing shift), the number of patients with an out of range status was small, and the number of increasing or decreasing shifts was well balanced in the two groups, indicating the absence of deleterious effect of cetirizine on laboratory parameters.

However, a nearly significant difference between groups was observed for haemoglobin, where more decreasing shifts were seen in the cetirizine group (12%) than in the placebo group (5%) (p = 0.085).

The results in standardised values may be found in Table XXII, and confirm the results obtained in the shift values.

- A decrease of haemoglobin (reduction of a median decrease of 0.11 unit between the two labs on the standardized scale) in cetirizine group while this median is zero (no change between the two labs) in placebo group (p = 0.026).

In order to quantify these variations, haemoglobin values were expressed in mg % (and converted if needed into mg % if expressed in another unit system).

The results in converted units (mg %) may be found in Table XXIII and show a mean decrease of 0.24 mg % in the cetirizine group and of 0.04 mg % in the placebo group. Although these differences were of very little clinical relevance, they were statistically significant (p = 0.043).

In order to try to define the problem, more detailed analyses were done focused on the sub-population with a decrease in haemoglobin at the end of the trial as compared to baseline (Table XXIV - XXV).

- the haemoglobin decrease in this sub-population was equal to 0.76 mg % in the cetirizine group and 0.62 mg % in the placebo group (p = 0.345), but more patients had a haemoglobin decrease in the cetirizine group (95 patients), than in the placebo group (74 patients);

- there were relatively more girls and less boys in the cetirizine group than in the placebo group (43.2% and 56.8% for cetirizine, 36.5% and 63.5% for placebo);

- most of the patients were in the class of age between 9-11 years (43% in the cetirizine group and 37% in the placebo group), which excludes a possible effect of menarche for the haemoglobin drop;

- the drop in haemoglobin was not dose related (dose expressed in mg/kg) (p = 0.521).
IV. DISCUSSION

In this study, cetirizine administered orally at the dose of 5, 10 or 15 mg bid was systematically better than placebo on all efficacy variables, but the differences observed between groups were globally not important enough to reach statistical and clinical relevance.

Power of the study calculated for the main efficacy criteria was sufficient to show differences of 10%, if they exist.

The principal criteria of efficacy for the study were the percentages of days (and/or nights with asthma (FAST) on one hand, a ("subjective" parameter) and the peak flows on the other hand ("objective" parameters), calculated for the ITT selection for the total period of treatment.

FAST improved more in the cetirizine group than in the placebo group, and the difference between groups was more important after the 3rd and 4th period of treatment, but was smaller than 10% for the total period of treatment. On the contrary, cetirizine did not seem to reduce the severity of an asthma attack when it was present.

Morning and evening peak flows improved slightly in the cetirizine group and did not change much in the placebo group. Although the differences between groups were statistically significant for the total period of treatment for the morning peak flow and almost significant for the evening peak flow, one cannot claim that this difference is clinically relevant, but it reflects however the fact that cetirizine is not devoid of beneficial effects on the lung function of mild asthmatic patients.

These mitigated results are also supported by the global evaluation of the treatments made at the end of the study. There is a clear and statistically significant difference in favour of cetirizine for the global evaluation made by the patients, but the differences are smoothed for the global evaluation made by the physician, who has perhaps a more objective view than the patients.

The analysis of FAST and peak flows for the protocol selection totally confirm the results of the ITT selection: better effect of cetirizine on FAST (substantial and significant improvement after the 4th period) and on peak flows measurements (differences not statistically significant).
The results of this study (reduction of the frequency of asthma and of β₂-agonist use, no change in the severity of the asthma episodes) are in the same line but are certainly less clear cut than those observed in a previous study (21), where a clear and significant effect was seen:

- for FAST:
  mean improvement was 18% of days in the cetirizine group and 7% of days in the placebo group, p = 0.006
- for the morning peak flows:
  improvement of 15.4 L/min in the cetirizine group and 10.7 L/min in the placebo group (p = 0.06)
- for the evening peak flows:
  improvement of 16.3 L/min and 7.1 L/min respectively in the cetirizine and placebo group (p = 0.008).

The safety profile of cetirizine in this study is excellent.

There was no statistically significant differences between the two groups, and adverse events were mainly mild or moderate; relationship to the test drug was exceptionally rated as probable.

The majority of adverse events are those affecting the "respiratory system" (COSTART terms: bronchitis, pharyngitis, rhinitis and asthma).

An explanation is that the study took place mainly in winter (to avoid pollen influence) when respiratory tract infections are frequent, especially in asthmatic patients (vicious circle infection, hyperreactivity, asthma).

It is important to notice that central effects were almost absent in this study, sedation being reported only once in each group. These results are in line with those observed in the previous study (21), where 1.7% of patients reported somnolence in the cetirizine group and 0.8% in the placebo group.

No valuable explanation could be found concerning the haemoglobin drop, but it must be reminded that the difference between groups observed after treatment compared to baseline was not clinically relevant. The difference between groups was due to the fact that the haemoglobin drop was more frequent in the cetirizine than the placebo group, the amplitude of the drop being comparable in both groups. The effect was not dose related and was mostly observed in patients between 9 and 11 years (thus before menarche).
VI. CONCLUSION

In this double blind study, cetirizine (5 mg, 10 mg or 15 mg bid, according to weight) reduced the frequency of asthma, but not the severity of an attack when it occurred, and improved the peak flows. Differences between the improvements observed in the cetirizine and placebo groups were globally not statistically significant. Cetirizine and placebo were well tolerated.

Although going in the same way, the results of this study do not totally confirm the good and statistically significant results of a previous study performed according to the same protocol.

Thus, taking everything into account from the efficacy point of view and considering the good tolerance of cetirizine, it can be claimed that cetirizine is safe in asthmatic children, and that it appears even to have slight beneficial effects on mild perennial asthma symptoms.
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Final version CA/cz
09/11/1993
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