2 SYNOPSIS

<table>
<thead>
<tr>
<th>NAME OF COMPANY</th>
<th>INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF THE DOSSIER:</th>
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<tbody>
<tr>
<td>UCB S.A. Pharma Sector</td>
<td>(FOR NATIONAL AUTHORITY USE ONLY)</td>
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<table>
<thead>
<tr>
<th>NAME OF FINISHED PRODUCT</th>
<th>National Authority Use Only</th>
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<tbody>
<tr>
<td>Zyrtec®</td>
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<table>
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<tr>
<th>NAME OF ACTIVE INGREDIENT</th>
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<tr>
<td>Cetirizine dihydrochloride</td>
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**Title of the study (combined report):**
THE EFFECTS OF A SINGLE DOSE OF CETIRIZINE (0.25 mg/kg b.w.) ON POLYGRAPHIC RECORDING DURING THE NIGHT IN HEALTHY AND ALLERGIC INFANTS: TWO PILOT, CROSSOVER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES

**Investigators:**
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- Dr. Y. Brusquet M.D., CHR Aix-en-Provence, Avenue des Tamaris, F-13616 Aix-en-Provence, France

**Publications:**

**Study Period:**
- Date of first enrolment: May 16, 1993
- Date of last patient completed: October 18, 1994

**Objectives:**
To assess the possible influence of a single dose of cetirizine (0.25 mg/kg b.w.) versus placebo both in healthy (study 9241) and allergic infants (study 9244) on the frequency and duration of sleep apnoea, as quantified by means of polysomnography.
Clinical Study Report for cetirizine/Studies 9241&9244

Methodology:
These were double-blind randomized, placebo-controlled crossover studies using similar protocols, one in non-allergic healthy infants (Study 9241), and one in infants with respiratory and allergic disorders (Study 9244). The night before inclusion in the trial, a blank polysomnographic recording was performed. Polygraphic sleep recordings lasted from 10.00 p.m. until 9.00 a.m. the following day. Study drug intake was to take place 20 minutes after the start of the recording. The first administration of a single dose of study medication occurred in the evening of the day the first blank recording was completed. After a 48.00 hr washout period the infant was crossed over to the other study medication and the polysomnographic test was repeated. The same type of equipment was used for polysomnography (ALICE, Healthdyne International) at both study sites.

Number of patients (planned and analyzed):
Planned: 12 healthy infants (study 9241, Investigator A. Kahn) and 20 allergic infants (study 9244, Investigator Y. Brusquet).
Analyzed:
Twenty-eight (28) subjects were enrolled in the study, five healthy infants at the center of Kahn/Brussels (Study 9241), and 23 allergic patients at the site of Brusquet/Aix (Study 9244).
Analyzed:
- For efficacy: not applicable;
- For safety: a) all 28 patients;
  b) infants < 13 months of age (N=20), who are at greater risk of SIDS

Diagnosis and main criteria for inclusion:
Study 9241: Healthy infants
Study 9244: Infants admitted to hospital for a check-up for chronic respiratory infections and allergic conditions
Other criteria for inclusion:
- infants of either gender, between 6 and 12 months of age (study 9241) and between 6 and 24 months of age (for study 9244; this was changed in amendment 2 to between 6 and 12 months of age after the inclusion of the 12th child),
- written informed consent given by the legal representative(s)
- weight at birth exceeding 2 kg, normal weight and height for their age (between the 3rd and 97th percentile).
Patients with a clinical history of apnoea were not allowed in either protocol.

Test product
Cetirizine 10 mg/ml oral solution
Dose: A single dose of 0.25 mg/kg b.w.
Administration Route: Oral
Batch #: 71

Reference therapy
Placebo
Dose: same volume/body weight as for cetirizine
Administration Route: Oral
Batch #: 70P

Treatment duration:
one single dose of each study medication in two-way crossover design

Criteria for Evaluation:
Efficacy: not applicable
Safety:
Overnight polysomnography, general physical observations, adverse events, urinalyses, compliance checks, and concomitant medications.

**Polysomnographic sleep and cardiorespiratory characteristics:**
- Total sleep time
- Time awake
- Percentage of time awake during recording
- Percentage non-REM sleep and REM sleep
- Central apnoeas (airflow and breathing movements stoppage ≥ 4.5 sec; number, maximum duration, average duration, total duration, percentage of recording time, number per hour of recording)
- Central apnoeas lasting at least 2 seconds (duration as a percentage of sleeping time, number per hour sleep, duration of periodic breathing as a percentage of sleep time)
- Obstructive apnoeas (airflow stoppage ≥ 3.0 sec with the persistence of breathing movements; number, maximum duration, number lasting ≥15 seconds, ≥10 and <15 seconds, ≥5 and <10 seconds, and ≥3 and <5 seconds, average duration, total duration, percentage of recording time, number per hour of recording)
- Mixed apnoeas (airflow stoppage ≥ 4.5 sec; number, maximum duration, number lasting ≥15 seconds, ≥10 and <15 seconds, ≥5 and <10 seconds, and ≥4.5 and <5 seconds, average duration, total duration, percentage of recording time, number per hour of recording)
- All obstructive events (obstructive and mixed apnoeas together): Number, maximum duration, total duration, percentage of recording time, number per hour of recording)
- All apnoeas (central, obstructive and mixed apnoeas together): Number, maximum duration, average duration, total duration, percentage of recording time, number per hour of recording)
- Heart rate during non-REM sleep, REM sleep and awakening: Average heart rate, number of low heart rate recordings, duration of bradycardia.

The primary variables for the evaluation of the polysomnographic sleep and cardiorespiratory characteristics are the number of obstructive apnoeas per hour of recording, the number of mixed apnoeas per hour of recording, and the number of all obstructive events per hour of recording. A secondary variable was the number of body movements, but insufficient data was available for this variable to perform an analysis. All other variables were considered as supportive in the framework of the protocols.
Statistical Methods:
Since the protocols of studies 9241 and 9244 are identical, except for one difference in inclusion criteria, (healthy children in study 9241 and children with respiratory and allergic disorders in study 9244), it was foreseen to perform a combined analysis, taking the center effect into account. However, in view of the unbalance of the number of children enrolled in the two studies (5 children in study 9241 and 23 children in study 9244), it was decided not to consider this factor. The statistical tests are performed two-tailed at the 5% level of significance.

No adjustment for multiple testing was considered. This approach is mainly justified by the fact that in a safety study a Type I error, the probability of which increases due to multiple testing, is to be considered as less important than a Type II error, the probability of which would increase if a multiple testing procedure were to be applied.

The statistical analysis is both descriptive and inferential.

The evaluation of the polysomnographic sleep and cardiorespiratory characteristics was performed both on the basis of the 28 patients enrolled in the study and on the basis of the data of the 20 children of at most 13 months of age, considering the observations during nights 2 and 41. The latter age group is more at risk for sleep apnoea. The comparison of each of the variables defined on the basis of the polygraphic recordings is performed using both the parametric and the nonparametric approach for the evaluation of two-period crossover trials described by Hills and Armitage (1979). The approach described by Hills and Armitage allows investigation into the effect of treatment (cetirizine and placebo), the effect of the period of administration (nights 2 and 4), and the interaction between these two factors (sequence effect).

The evaluation of adverse events is descriptive.

Conclusions:
Twenty-eight (28) subjects were enrolled in the two studies, 5 healthy infants (study 9241) and 23 allergic infants (study 9244).
The patients enrolled in both studies, 17 males (61%) and 11 females (39%), were on average 11.5 month old (st.dev. 4.0 months; range: from 3.7 to 22.8 months). Median gestational age was 39 weeks (range: between 29 and 41 weeks). Average birth weight was 3.0 kg (range: between 1.2 and 4.1 kg).

Patients belonging to the restricted ITT population (those aged <13 months), 14 males (70%) and 6 females (30%), were on average 9.6 month old (st.dev. 2.5 months; range: from 3.7 to 12.5 months). A majority of boys is consistent with a higher proportion of boys with childhood allergy. The median gestational age was 39.5 weeks (range: between 29 and 41 weeks). Birth weight was on average 3.0 kg and ranged between 1.2 and 3.8 kg.

Efficacy: not applicable

1 This study has been reported in the statistical report MRCE 94A2601/5 dated 13 December 1994. In a second step, it was decided to write an ICH report based on the previous report. So recording of the data and statistical analysis were based on scientific knowledge in the period 1993-1994, however clinical interpretation is based on knowledge in the year 2000.
Conclusions (cont.):

Safety:

Infants (N=28, 11 girls and 17 boys) aged 11.5 months ± 4.0 St. dev., 23 were allergic, mainly asthmatic, and 5 were considered non allergic. Judging from the blank polysomnographic recording, they showed no abnormally frequent or prolonged apnoeas. They received a single dose of 0.25 mg/kg b.w. cetirizine and matching placebo in a balanced two-way cross-over design. Study medications were administered at night, at the beginning of night-time sleep polygraphy. The objective was to assess the effect of cetirizine on sleep characteristics, in particular obstructive and mixed apnoeas.

All 28 infants took study medication as scheduled, and were therefore analyzed regarding safety parameters.

The frequency of adverse events was similar in both treatment periods. Four (4) of the 5 events reported were typical intercurrent infections frequently observed in early infancy. One (1) was apnoea and bradycardia after placebo. Only two adverse events were reported after cetirizine or in the follow-up period after cetirizine. None were considered by the investigators to be related to cetirizine.

There were no serious adverse events or deaths reported.

All infants included in the studies were eligible for the ITT analysis of the polysomnographic recordings.

On the basis of the data concerning obstructive, mixed apnoeas, and their sum (denoted as 'All Obstructive Events') no significant differences were found between the two treatments. In order to quantify the magnitude of the difference between cetirizine and placebo, the 90% nonparametric confidence interval on the median difference between cetirizine and placebo in obstructive apnoeas per hour was calculated. These confidence intervals were (0,0) for the ITT population and (-0.10, 0.10) for the restricted ITT population with a point estimate of 0 in both cases which indicates no difference between the treatments. In addition, the upper limit of these confidence intervals is clearly less than the clinically relevant difference of 0.18. Thus cetirizine is considered not to be different from placebo with respect to the induction of obstructive apnoeas during sleep time.
Safety (continued)

Regarding the secondary parameters of sleep polygraphy, the total sleep duration was slightly longer with cetirizine (471.8 min versus 473.7 min, p=0.023) in the ITT population. This difference was not confirmed in the restricted ITT population (471.5 versus 468.1 min, p=0.23), and was considered as clinically non relevant (representing an increase of 2% over the total sleep duration with placebo in the ITT population and 0.4% in the Restricted ITT). Moreover, the time awake in the 2 treatment groups does not differ significantly in the ITT (22.8 min versus 29.6 minutes, p=0.16) or in the Restricted ITT (28.4 min versus 28.3 min, p=0.41) populations.

The percentage of Non-REM sleep was higher with cetirizine (52.6% versus 48.2%, p=0.010), whereas the percentage of REM sleep was slightly less (p=0.010). This was observed in the ITT population as well as in the restricted ITT population (50.5% versus 47.0%, p=0.047 for Non-REM) and p=0.047 for REM sleep. This variation between treatments is below the variation between nights reported in the literature. Nevertheless this observation could be related to an increased sleep tendency, if associated with a reduced arousability. At the time of the study, such observations could not be considered as primary or secondary objectives for the study, based on the current literature. At present time, however such factors would be considered as risk condition for SIDS even if the methodology for studying arousability is not yet standardized. (Kahn 1997)

There was a trend for fewer central apnoeas and central apnoeas were of less duration after cetirizine in the ITT population, but not in the restricted ITT population.

The treatments were not different with respect to any other sleep and cardiorespiratory parameters measured during polysomnographic recording. Oximetry and movements, however, were not done for most recordings.

General physical observations of the infants were unremarkable.

Compliance checks on returned study medications showed that study medication had been aspirated in appropriate amounts from the bottles of study medication. Urine samples were accidentally unfrozen and destroyed. No measurements of cetirizine in urine were possible.

Concomitant medications were unremarkable.

It is concluded that a single dose of 0.25 mg/kg b.w. of cetirizine has no effect on the major safety parameters of night-time polysomnographic recordings, i.e. obstructive and mixed sleep apnoeas, or any other supportive parameters related to the cardiorespiratory system of infants with no prior apparent life-threatening event during their sleep. However increased total sleep time and increased proportion of quiet sleep could be indicative of sedative effect if associated with a decreased arousability.

Date of this report: 24 August 2000