1 SYNOPSIS

Name of Sponsor/Company McNeil Consumer & Specialty Pharmaceuticals ***Name of Finished Product:*** N/A ***Name of Active Ingredient:*** Ibuprofen 100 mg / 5 mL Pseudoephedrine HCl 15 mg / 5 mL	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: A Comparative Study of Coadministered Doses of Ibuprofen and Pseudoephedrine HCl and Each Drug Alone in the Treatment of Primary Nocturnal Enuresis in Children

Investigator(s): Multiple investigators, see Appendix 14.1.4

Study Center(s): Multiple centers, see Appendix 14.1.4

Publication (reference): None

Study period:
April 16, 2001 first enrolled
November 10, 2002 last completed

Phase of Development: Phase II or Therapeutic Exploratory

Objectives: The primary objective was to determine whether the efficacy of co-administered doses of ibuprofen and pseudoephedrine HCl in the treatment of primary nocturnal enuresis was greater than that for the respective dose of each drug alone. The secondary objective was to determine whether the individual drugs were each effective compared with placebo.

Methodology: This study was a double-blind, double-dummy, placebo-controlled, randomized, parallel-group, multiple-center study of 318 children, six through 11 years of age, with primary nocturnal enuresis. After a screening visit to verify that a subject met inclusion and exclusion criteria, eligible subjects then began the two-week baseline period. During this time, a parent or legally authorized representative recorded the number of wet and dry nights in a diary. They also completed a daily voiding history for four days. Subjects then returned to the study center, diaries were reviewed for completeness and clarity, and those who continued to meet the inclusion and exclusion criteria were stratified by age into two groups (six through eight years old and nine through 11 years old). Subjects in each group were then randomly assigned to one of four treatment regimens: (1) one dose level each of ibuprofen and pseudoephedrine HCl suspensions, (2) one dose level each of ibuprofen and placebo suspensions, (3) one dose level each of pseudoephedrine HCl and placebo suspensions, or (4) two doses of placebo suspension.

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The actual doses administered to a subject at bedtime were based on body weight, which was determined by study personnel at the randomization visit. Fluids were discouraged after dinner until morning; however, a subject may have had up to two ounces of fluid following the doses if necessary. During the two-week treatment period, parents or legally authorized representatives recorded information daily in the subject diaries, including date and time of medication dose and whether the subject was wet or dry during that night. All bottles of study medication were returned to the study center at the end of the two-week treatment period. The diary was reviewed by the study personnel for completeness and clarity, and was returned and submitted as part of the case report form. The subjects then began a two-week post-treatment period in which they recorded the number of dry and wet nights on a survey form that was forwarded by mail to the study center.

Number of Subjects (planned and analyzed): Approximately 300 subjects were planned to be enrolled to ensure that 256 completed. Three hundred eighteen (318) subjects were enrolled and 307 subjects completed.

Diagnosis and main criteria for Inclusion: Healthy male and female subjects, ages six through 11 years with primary nocturnal enuresis, were included in the study.

Test product, dose and mode of administration, batch number: The test products (1, 2, or 3) were administered orally at bedtime for two weeks. The appropriate volumes of each test product for each subject were based on body weight determined at the randomization visit.

1.) A dose of 12.5 mg/kg ibuprofen suspension, Batch #DPM034 and a dose of 15 or 30 mg pseudoephedrine HCl suspension, Batch #C-846-7.
2.) A dose of 12.5 mg/kg ibuprofen from a commercially available suspension, Batch #DPM034 and a dose of placebo suspension, Batch #C-846-9.
3.) A dose of 15 or 30 mg pseudoephedrine HCl suspension, Batch #C-846-7 and a dose of placebo suspension, Batch #C-846-9.

Duration of treatment: Subjects were administered medication nightly for two weeks during the treatment period.

Reference therapy, dose and mode of administration, batch number: The reference product (4) was administered orally at bedtime for two weeks. The appropriate volume for each subject was based on body weight determined at the randomization visit.

4.) Two doses of placebo suspension, Batch #C-846-9.

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Criteria for evaluation:

Efficacy: The primary efficacy endpoint was the mean reduction in wet nights from the 14-day baseline period to the 14-day treatment period. The secondary endpoints were the proportion of subjects with at least 50% reduction in wet nights from baseline, and the mean number of wet nights during the 14 days of treatment.

Safety: Safety assessments consisted of physical examinations with vital signs and the monitoring of adverse events.

Statistical Methods: Two study populations were defined for analyses. The safety population included subjects who took at least one dose of study medication and the per-protocol efficacy population was defined as all randomized subjects who 1) met all study inclusion and exclusion criteria, 2) complied with the protocol dosing requirements during the two-week treatment period (ie, dosed every night), 3) recorded a minimum of seven days of wetness outcomes, and 4) had no major protocol violations.

All protocol violations/deviations were reviewed by the medical monitor and the exclusion of subjects from the per-protocol population was determined before the study blind was broken. Minor protocol violations did not necessarily exclude a subject from the per-protocol population.

Demographic and baseline characteristics, including age, gender, race, height, weight, body mass index, voiding amount, and bladder capacity were summarized by treatment group for the safety and per-protocol populations.

A one-way analysis of variance was used to test for differences among treatment groups in the means of continuous baseline measures. The chi-square test was used to compare the distribution of categorical demographic variables among treatment groups.

The following outcome measures were analyzed and specified in the statistical analysis plan: 1) change from baseline in the number of wet nights during the 14-day treatment period, 2) proportion of subjects with at least 50% reduction in wet nights from baseline, and 3) mean number of wet nights during the 14 days of treatment.

An analysis of covariance (ANCOVA) was used to test for differences in treatment group means during the study for the change from baseline in the number of wet nights during the

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14-day treatment period. The model included treatment, investigator, and age group as factors, and baseline number of wet nights as a covariate.

A logistic regression model was used to compare treatment groups for the proportion of subjects with at least 50% reduction in wet nights from baseline. The model included treatment and age group as factors. Logistic regression models were also used to compare treatment groups for the proportion of subjects with at least 40%, 30%, and 25% reductions in wet nights from baseline. For subjects who prematurely discontinued from the study, the proportion of wet nights was calculated as 14 times (the number of wet nights before discontinuation divided by the number of days on the study).

Pair-wise comparisons were made as follows: For the primary endpoint, the combined treatment was compared to each of its components and to placebo. In addition, each component treatment was compared to placebo. For the secondary endpoints, all treatment groups were compared with placebo. The comparisons of individual treatments to placebo were evaluated at an alpha of 0.05, two-tailed. The comparisons of co-administered doses to each component were evaluated at an alpha of 0.05, one-tailed.

Two additional secondary analyses of bladder capacity by treatment group and responder status were conducted. Bladder capacity was evaluated in two ways: in milliliters and as a percentage of a predicted bladder capacity based on age. Responder status was defined as a percent reduction in the number of wet nights comparing the 14-day treatment period to the baseline period; reductions of at least 50%, 40%, and 30% were evaluated.

Adverse events were classified according to the COSTART IV dictionary. The incidence of adverse events was tabulated by treatment group, COSTART body system, and preferred terms. The incidence of discontinuation due to adverse events was also summarized by treatment group. Comparisons among treatment groups were made by using Fisher's exact test.

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Efficacy Results:

The primary efficacy endpoint in this study was the mean reduction in wet nights from the 14-day baseline period to the 14-day treatment period. The mean reduction in wet nights from baseline was 2.9 days for both the combined ibuprofen and pseudoephedrine group and the ibuprofen alone group, compared with 1.8 days for pseudoephedrine and 1.4 days for placebo. The difference between the combined treatment and pseudoephedrine alone was statistically significant ($p = 0.0512$); however, the difference between the combined treatment and ibuprofen alone was not statistically significant ($p = 0.9141$). In addition, the differences between the combined treatment vs placebo and ibuprofen alone vs placebo were both significant ($p = 0.0049$ and $p = 0.0040$, respectively). The difference between pseudoephedrine alone and placebo was not statistically significant ($p = 0.4649$).

Results for the secondary endpoints demonstrated that the combined ibuprofen and pseudoephedrine treatment was significantly superior to placebo for reductions in wet nights of at least 50%, 40%, 30% and 25%. Twenty-seven percent (27.0%) of subjects who received the combined treatment compared with 13.9% of those who received placebo had at least a 50% reduction in the number of wet nights during the treatment period compared with the baseline period ($p = 0.0332$). While ibuprofen alone was significantly superior to placebo for reductions in wet nights of at least 30% and 25%, there were no significant differences between pseudoephedrine and placebo in the percent reductions in wet nights.

The mean number of wet nights during the 14-day treatment period was similar for the placebo and pseudoephedrine groups, 10.2 and 10.4, respectively, and significantly lower for the combined treatment and ibuprofen groups, 8.6 and 9.3, respectively, compared with placebo.

Responders (ie, those with at least a 50% reduction in the number of wet nights compared with baseline) had a larger mean bladder capacity than did non-responders within each treatment group. This was also true when reductions of at least 40% and at least 30% were evaluated.

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Safety Results:

All study treatments were well tolerated and no safety issues were identified in this study. Overall, 21.1% of subjects reported adverse events; there was no significant difference among treatment groups. However, drug-related adverse events were reported more frequently by subjects treated with ibuprofen and pseudoephedrine combined (6.1%) or ibuprofen alone (9.0%) than by those treated with pseudoephedrine alone (3.9%) or placebo (3.7%). The most commonly reported adverse events were headache (4.7%), infection (2.5%), abdominal pain (2.2%), fever (1.9%), cough increased (1.6%), and taste perversion (1.3%); there were no statistically significant differences among treatment groups in the incidence of these adverse events. No deaths or other serious adverse events were reported. Digestive system adverse events were cause for withdrawal of treatment for two subjects in the combined ibuprofen and pseudoephedrine group, one in the ibuprofen group, two in the pseudoephedrine group, and none in the placebo group. There were no statistically significant differences among treatment groups in the change from baseline to the end of treatment for vital signs.

Conclusions:

- Combined treatment with ibuprofen (12.5 mg/kg) and pseudoephedrine (15 mg or 30 mg) was significantly superior to placebo and pseudoephedrine alone, but was not significantly superior to ibuprofen alone, in the treatment of nocturnal enuresis as determined by the primary study endpoint of mean change from baseline in the number of wet nights during the 14-day treatment period. In addition, while ibuprofen alone was significantly superior to placebo, pseudoephedrine alone was not.

- Combined treatment with ibuprofen and pseudoephedrine was significantly superior to placebo for mean percent reductions in wet nights during the 14-day treatment period of at least 50%, 40%, 30% and 25%. Ibuprofen alone was significantly superior to placebo for mean percent reductions in wet nights of at least 30% and 25%. There were no significant differences between pseudoephedrine and placebo in the mean percent reductions in wet nights.

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- The mean number of wet nights during the 14-day treatment period was significantly lower for the combined treatment and ibuprofen groups (8.6 and 9.3, respectively), than for the placebo group (10.2); there was no significant difference between pseudoephedrine (10.4) and placebo.
- All study treatments were well tolerated and no safety issues were identified in this study. There was no significant difference among the treatment groups in the overall incidence of adverse events in this study. No serious adverse events or deaths were reported.

Date of the report: December 18, 2003

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