Consumer Healthcare Products Association (CHPA) 
PHENYLEPHRINE TASK GROUP

Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults With Acute Nasal Congestion Due to Common Cold

Final Report (January 30, 2007)

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REPORT

Efficacy Meta-Analysis of Single-Dose 10 mg Phenylephrine vs. Placebo in Adults With Acute Nasal Congestion Due to Common Cold

1. BACKGROUND AND OBJECTIVES

Phenylephrine is a sympathomimetic drug which has been used as a nasal decongestant in the United States and globally since the 1940s. At that time, to be marketed in the US a drug had to be proven to be safe whereas proof of effectiveness was not required. Beginning in 1972, as a result of amendments to the US drug law, the FDA initiated the OTC Drug Review and determined on the basis of all available data which medicines could be deemed “generally recognized as safe and effective”. To accomplish this task, OTC companies and others submitted thousands of volumes of safety and efficacy information and the FDA assembled outside expert advisory panels which reviewed all available data and established OTC drug monographs for specific OTC drug categories. Similar to other active ingredients used in cough and cold medicines, phenylephrine was evaluated by the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. This panel conducted a review of the information available and deemed phenylephrine as generally recognized as safe and effective as a nasal decongestant at oral doses of 10 mg. The panel’s conclusions were published by the FDA in 1976 (Ref. 1). In 1994, the FDA issued the Final Monograph for OTC Nasal Decongestant Drug Products recognizing 10 mg phenylephrine as a safe and effective nasal decongestant (Ref. 2).

The issues associated with the illicit conversion of pseudoephedrine to methamphetamine caused OTC companies to replace pseudoephedrine with phenylephrine in many of their products, which in turn drew new attention to phenylephrine’s efficacy. In a recent publication, the authors questioned whether the FDA panel reached a correct conclusion on the basis of the available data at the time of the review in the 1970s (Ref. 3).

These developments prompted a task group of the Consumer Healthcare Products Association (CHPA) to obtain copies of all studies that were cited in the bibliography of the phenylephrine section of the 1976 OTC Review panel report on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products. In
addition, a literature search for additional studies investigating phenylephrine’s efficacy was conducted. A review of the data led to the conclusion that a meta-analysis would be both feasible for a set of studies and a meaningful contribution to the discussion regarding the efficacy of phenylephrine.

The objectives of the analyses of the CHPA Phenylephrine Task Group were:

- to compare single-dose 10 mg phenylephrine and placebo separately for each crossover and parallel group study of adult patients with acute nasal congestion due to head cold/common cold.

- to perform a pooled (individual-level) meta-analysis comparing 10 mg phenylephrine and placebo using all available raw data from placebo-controlled, single-dose crossover studies in adult patients with acute nasal congestion due to a common cold.

2. STUDIES AVAILABLE FOR THE ANALYSES

Three sources were used for identification and collection of placebo-controlled efficacy studies with orally administered phenylephrine used as single active ingredient.

A. The bibliography of the phenylephrine section of the 1976 OTC Review on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products (Ref. 1).

Within this set of data, 14 reports were identified as efficacy trials with single-active phenylephrine:

1) Memo to Hulme, N.A from H. Stander, “Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2”, 1968 (included in FDA OTC Volume 040298)

2) Memo to Blackmore from N.A. Hulme, “Neo-Synephrine – Elizabeth Biochemical Laboratories Study No. 5”, 1970 (included in FDA OTC Volume 040298)

3) Memo to Blackmore from N.A. Hulme, “Oral Neo-Synephrine – Cintest Labs Study No. 1”, 1969 (included in FDA OTC Volume 040298)
4) Memo to Blackmore from N.A. Hulme, “Oral Neo-Synephrine – Cintest Labs Study No. 2”, 1970 (included in FDA OTC Volume 040298)

5) Memo to Blackmore from N.A. Hulme, “Oral Neo-Synephrine – Cintest Labs Study No. 3”, 1970 (included in FDA OTC Volume 040298)

6) Memo to Blackmore from N.A. Hulme, “Oral Neo-Synephrine – Huntingdon Research Center Study No. 1”, 1969 (included in FDA OTC Volume 040298)

7) Memo to Blackmore from N.A. Hulme, “Oral Neo-Synephrine – Huntingdon Research Center Study No. 2”, 1969 (included in FDA OTC Volume 040298)

8) Cohen, B.M., Kuebler W.F., “Conduct of a 200 patient doubleblind placebo controlled study to evaluate the effectiveness of phenylephrine hydrochloride (5 mg) tablets in relieving upper respiratory congestion and symptoms associated with the common cold”, Whitehall Laboratories / Bio-Evaluation Inc., 1975 (included in FDA OTC Volume 040288B)

9) Memo to Lands from F.P. Luduena, “Comparative Study of the Effects of Neo-Synephrine HCl and Propadrine HCl on Nasal Air Resistance (NAR), Blood Pressure and Pulse Rate of Volunteers”, 1959 (included in FDA OTC Volume 040298)

10) Memo to Suter from N.A. Hulme, “Nasal Decongestant Study by Elizabeth Biochemicals Laboratories No. 1”, 1967 (included in FDA OTC Volume 040298)

11) Memo to Blackmore from N.A. Hulme, “Oral Neo-Synephrine – Elizabeth Biochemical Study No. 3”, 1969 (included in FDA OTC Volume 040298)

12) Memo to Blackmore from N.A. Hulme, “Oral Neo-Synephrine – Elizabeth Biochemical Study No.4”, 1969 (included in FDA OTC Volume 040298)


B. A recently published review on nasal decongestants for the common cold conducted by the Cochrane Collaboration (Ref. 4).

In performing this comprehensive review, the Cochrane Collaboration searched for randomized, placebo-controlled trials with nasal decongestants (including phenylephrine) in adults and children suffering from the common cold. Databases that were searched for this review included MEDLINE, EMBASE, CENTRAL (the Cochrane Central Register of Controlled Trials), and Current Contents.

Only one placebo-controlled trial with oral single-active phenylephrine was identified. This was the publication of McLaurin et al. cited under 13 in Section A above.

C. A literature search conducted by CHPA via PubMed (a free service provided by the U.S. National Library of Medicine which provides access to MEDLINE and to articles in selected journals not included in MEDLINE).

In addition to studies already cited under Sections A and B above, this search yielded one placebo-controlled trial with oral phenylephrine:


In total, 15 studies were identified as placebo-controlled trials of oral phenylephrine used as single-active nasal decongestant.

3. STUDIES INCLUDED IN THE ANALYSES

For inclusion in the analyses, a study had to meet the following criteria:
1. Randomized single-dose, placebo-controlled trial
2. Orally administered, single-active phenylephrine at a dose of 10 mg
3. Adult patients with acute nasal congestion due to a common cold
4. Nasal airway resistance (NAR) was an efficacy endpoint
5. Study report contains sufficient individual subject data to allow reanalysis and/or meta-analysis for the comparison of the 10 mg dose level of phenylephrine and placebo
On the basis of these criteria, 8 studies were considered for the analyses.

1) Memo to Hulme, N.A from H. Stander, "Neo-Synephrine Oral Study – Elizabeth Biochemical Laboratories No. 2", 1968 (included in FDA OTC Volume 040298)

2) Memo to Blackmore from N.A. Hulme, "Neo-Synephrine – Elizabeth Biochemical Laboratory Study No. 5", 1970 (included in FDA OTC Volume 040298)

3) Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 1", 1969 (included in FDA OTC Volume 040298)

4) Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 2", 1970 (included in FDA OTC Volume 040298)

5) Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Cintest Labs Study No. 3", 1970 (included in FDA OTC Volume 040298)

6) Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 1", 1969 (included in FDA OTC Volume 040298)

7) Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Huntingdon Research Center Study No. 2", 1969 (included in FDA OTC Volume 040298)

8) Cohen, B.M., Kuebler W.F., "Conduct of a 200 patient doubleblind placebo controlled study to evaluate the effectiveness of phenylephrine hydrochloride (5 mg) tablets in relieving upper respiratory congestion and symptoms associated with the common cold", Whitehall Laboratories / Bio-Evaluation Inc., 1975 (included in FDA OTC Volume 040288B)

The studies are identified in Table 1 (Studies 1 - 8). Of these 8 studies, 7 were of a similar design (i.e., randomized, double-blind, two-treatment, two-period, two-sequence crossover trials, NAR as efficacy endpoint) and were combined for meta-analysis (Studies 1 - 7). The eighth study was a double-blind, parallel group study and was not included in the meta-analysis of the crossover trials. This study (Study 8) was reanalyzed separately as were each of the 7 studies included in the meta-analysis.
There were a total of 163 patients available for analysis as follows:

**TABLE 1: STUDIES INCLUDED IN THE ANALYSES**

<table>
<thead>
<tr>
<th>Study No. (design)</th>
<th>Study ID</th>
<th>Baseline Nasal Airway Resistance (NAR) (Phenylephrine/Placebo)</th>
<th>Number of Subjects with Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (crossover)</td>
<td>Elizabeth No. 2</td>
<td>13.43 / 13.08*</td>
<td>16</td>
</tr>
<tr>
<td>2 (crossover)</td>
<td>Elizabeth No. 5</td>
<td>12.98 / 12.72*</td>
<td>10</td>
</tr>
<tr>
<td>3 (crossover)</td>
<td>Cintest No. 1</td>
<td>22.3 / 20.61*</td>
<td>16</td>
</tr>
<tr>
<td>4 (crossover)</td>
<td>Cintest No. 2</td>
<td>28.05 / 26.73*</td>
<td>15</td>
</tr>
<tr>
<td>5 (crossover)</td>
<td>Cintest No. 3</td>
<td>21.15 / 21.39*</td>
<td>15</td>
</tr>
<tr>
<td>6 (crossover)</td>
<td>Huntingdon No. 1</td>
<td>24.61 / 23.85*</td>
<td>16</td>
</tr>
<tr>
<td>7 (crossover)</td>
<td>Huntingdon No. 2</td>
<td>25.11 / 28.36*</td>
<td>25</td>
</tr>
<tr>
<td>8 (parallel group)</td>
<td>Bio-evaluation</td>
<td>5.29 / 4.99**</td>
<td>50 (25 per treatment)</td>
</tr>
</tbody>
</table>

* units
**cm H₂O/l/min @ 0.5 l/sec flow

There were 113 subjects included in the crossover trials comprising the meta-analysis. All subjects had data and were included in the analysis.

4. **STUDIES EXCLUDED FROM THE ANALYSES**

The following 7 studies were excluded from the analyses. Table 2 below provides characteristics of these studies and reasons for their exclusion.
9) Memo to Lands from F.P. Luduena, "Comparative Study of the Effects of Neo-Synephrine HCl and Propadrine HCl on Nasal Air Resistance (NAR), Blood Pressure and Pulse Rate of Volunteers", 1959 (included in FDA OTC Volume 040298)

10) Memo to Suter from N.A. Hulme, "Nasal Decongestant Study by Elizabeth Biochemicals Laboratories No. 1", 1967 (included in FDA OTC Volume 040298)

11) Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No. 3", 1969 (included in FDA OTC Volume 040298)

12) Memo to Blackmore from N.A. Hulme, "Oral Neo-Synephrine – Elizabeth Biochemical Study No. 4", 1969 (included in FDA OTC Volume 040298)


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**TABLE 2: STUDIES EXCLUDED FROM THE ANALYSES**

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study ID</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Lands from Luduena</td>
<td>Subjects were healthy volunteers</td>
</tr>
<tr>
<td>10</td>
<td>Elizabeth No. 1</td>
<td>Study investigated phenylephrine at dose levels other than 10 mg</td>
</tr>
<tr>
<td>11</td>
<td>Elizabeth No. 3</td>
<td>Study investigated phenylephrine at dose levels other than 10 mg</td>
</tr>
</tbody>
</table>
### 5. METHODS

**Efficacy Parameters:**

In all studies included in the meta-analysis, NAR was the efficacy endpoint. NAR was determined by an identical procedure (using a modified Butler-Ivy airflow device). According to the original study reports, five NAR measurements were taken at pre-dose and at all post-baseline time points for each study subject. However, these five measurements were not provided in these reports. The average of the five measurements was provided. These average values may have been rounded for listing in these reports.

Subjective impressions of changes in nasal congestion were scored in the studies, but there were insufficient data for analysis.

Two parameters were analyzed for the meta-analysis and for the analysis of each study:

1. Change from baseline (pre-dose) NAR at each post-baseline time point (15, 30, 45, 60, 90, 120, 180, and 240 minutes post-dose), defined as post-baseline NAR - baseline NAR.

2. LN-ratio NAR [defined as LN (NAR at a post-baseline time point) – LN (baseline NAR)] at each post-baseline time point (15, 30, 45, 60, 90, 120,
180, and 240 minutes post-dose). At each time point, this is mathematically identical to the natural logarithm of the ratio of the post-baseline to baseline values, LN (post-baseline NAR at a time point / baseline NAR).

Note that the 45, 90, 180, and 240 minute post-baseline time points were not included in the design of Study 8; the 180 and 240 minute time points were also not included in the designs of Studies 1 and 5.

**Criteria for Evaluation:**

On the basis of medical considerations and consumer expectations the following criteria were chosen:

- Statistical significance at the 30 minute and 60 minute post-dosing time points (primary time points).

- 20% reduction from baseline NAR for phenylephrine. A 20% reduction from baseline is a reduction noticeable by patients (*Ref. 5*).

**Statistical Methods:**

**Analyses by Study:**

In the original study reports, the investigators used analysis of variance (without a covariate adjustment for baseline) to analyze the NAR measurements. However, for this report, the individual data values for each crossover study were analyzed using analysis of covariance (adjusting for pre-dose baseline average measurement, a covariate). For these crossover studies, the statistical model included 'patient' as a random factor. Information on which treatment sequence a patient was randomized to was not available in the original study reports; therefore, treatment sequence and period could not be included in the statistical model and a test for first-order carryover could not be done. Patient was a random factor for the analysis of Study 8 also, but was not included in the statistical model as this was a parallel group study.

**Pooled Meta-Analyses:**

Since Study 8 was a parallel group study and not a crossover study, it was not included in the meta-analysis.

For all meta-analyses performed for each efficacy parameter, the individual data values for each crossover study were included. Analysis of covariance
(ANCOVA), adjusting for pre-dose baseline average measurement (a covariate) was performed for all analyses.

First, prior to the use of statistical models to compare treatments, an analysis was performed to test “heterogeneity” at each post-dose time point, that is, to determine if the treatment difference between phenylephrine and placebo varied in direction or magnitude from study to study at a post-dose time point. This would further determine if phenylephrine differed from placebo in some studies and not others or if the treatment difference between phenylephrine or placebo was larger for some studies than for others at a post-dose time point. This test for “heterogeneity” is a test of the “treatment-by-study interaction” term from the following statistical models:

- **Model 1**: a fixed effects meta-analysis model using parametric ANCOVA, adjusting for baseline (a covariate), with terms for patient, study (a fixed factor), treatment (a fixed factor), and the treatment-by-study interaction. This model was used twice:
  
  Model 1.a: assuming patient as a fixed factor with unequal within-subject variance components across studies
  
  Model 1.b: assuming patient as a random factor with unequal within-subject and between-subject variance components across studies.

For the meta-analyses, two statistical models were used to perform analysis of covariance comparing the efficacy of phenylephrine and placebo at each post-dose time point:

- **Model 2**: a fixed effects meta-analysis model which is Model 1 above, but without the treatment-by-study interaction term. Study is again assumed to be fixed. This model was used twice:
  
  Model 2.a: assuming patient as a fixed factor with unequal within-subject variance components across studies
  
  Model 2.b: assuming patient as a random factor with unequal within-subject and between subject variance components across studies.

- **Model 3**: a random effects meta-analysis model, with baseline, patient, treatment, study, and treatment-by-study interaction in the model, but with patient, study, and treatment-by-study interaction considered random.
The SAS System Version 8.2 PROC MIXED code to generate results from all models analyzed is given in Appendix 1.

The assumptions of the parametric statistical models noted above, normality and equality of variance, were checked by inspection of plots of residuals vs. predicted values and boxplots of residuals for each treatment group (seen in Appendix 2 for by-study analyses and in Appendix 3 for the meta-analysis). Although variances of the two treatments appear to be equal, there appears to be a departure from normality for some analyses, although sometimes the distributions of residuals appear symmetrical. There appears to be comparability between the two efficacy parameters with regard to how well the normality and equality of variance assumptions fit the data for the treatment factor in the model. Differences between studies in term of patient variability were noted in the original reporting of these studies; therefore, within and between-subject variances components were allowed to vary for analyses using Models 1, 2, and 3 (as described above).

All p-values for treatment effect terms in Models 2 and 3 were considered statistically significant if \( p \leq 0.05 \).

The results of Model 2.a were generally comparable to those for Model 2.b. Determinations concerning the efficacy of phenylephrine are primarily based on the results from Model 2.b and Model 3 for the change from baseline parameter, a more commonly used parameter. A sensitivity analysis was performed using the LN-ratio parameter. Results of analyses of the change from baseline parameter and the LN-ratio parameter were generally comparable. Therefore, the results of the Model 2.b and 3 change from baseline analyses are presented in the Results section of this report. A summary table of results of the analyses of the change from baseline and LN-ratio parameters is provided in Appendix 4 (Appendix 4.1 for by-study analyses and Appendix 4.2 for meta-analyses).

Appendix 5 contains a listing of the standard errors of treatments for Models 2.a, 2.b, and 3 for both efficacy parameters for all analyses performed. The 95% confidence intervals on the difference between treatments (generated from PROC MIXED) are also provided; the difference between treatments provided is based on adjusted (least squares) treatment means. Forest plots are provided in Figures 1 to 8 to show the confidence intervals on the treatment difference by post-dose time point for each study (assuming patient is random) and for the meta-analyses (based on Models 2.b and 3).
Treatments means are plotted by post-dose time point for each parameter by study (assuming patient is a random factor) and for the meta-analyses (using all models) in Figures 9 to 16. For figures representing the results of analyses of the change from baseline parameter, percent change from baseline for a treatment is plotted against time. Percent change for a treatment is calculated as: \((\text{least squares adjusted treatment mean} \times 100) / \text{(baseline mean for a treatment)}\). The lower and upper 95% confidence interval limits plotted for a treatment in these figures are the lower and upper confidence limits for the adjusted treatment mean converted to percent change from baseline.

6. RESULTS

RESULTS BY STUDY:

Figures 1 to 8 show an estimate of the treatment difference between phenylephrine and placebo with corresponding 95% confidence interval for each post-dose time point. Estimates and confidence intervals are provided for each study (assuming patient is random) and for the meta-analyses (based on Models 2, b and 3). Confidence intervals that do not contain 0 are statistically significantly in favor of phenylephrine over placebo.

Statistically significant differences in favor of phenylephrine over placebo were found in Studies 1, 2, 3 and 8. The results are indicated in Table 3.

Statistically significance differences were not found between phenylephrine and placebo for Studies 4, 5, 6, and 7, but directional differences were found as shown in Table 4. The maximum percent changes from baseline achieved for phenylephrine in these studies were 29%, 17%, 17%, and 16%, for Studies 4, 5, 6, and 7, respectively. However, for placebo, the maximum percent changes from baseline were 32%, 21%, 22%, and 20%, respectively.
**TABLE 3: RESULTS OF STUDIES WITH STATISTICALLY SIGNIFICANT DIFFERENCES**

<table>
<thead>
<tr>
<th>Study No. (design)</th>
<th>Study ID</th>
<th>Statistic</th>
<th>Post-dose time points statistically significant (p ≤ 0.05) in favor of phenylephrine over placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (crossover)</td>
<td>Elizabeth No. 2</td>
<td>Significant?</td>
<td>p ≤ 0.05 p ≤ 0.05 p ≤ 0.05 p ≤ 0.05 p ≤ 0.05 p ≤ 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>-1.26 (-1.87, -0.65) -3.11 (-3.97, -2.26) -5.74 (-6.60, -4.87) -5.44 (-6.64, -4.25) -4.70 (-6.03, -3.38) -3.44 (-4.91, -1.96)</td>
</tr>
<tr>
<td>2 (crossover)</td>
<td>Elizabeth No. 5</td>
<td>Significant?</td>
<td>NS p ≤ 0.05 p ≤ 0.05 p ≤ 0.05 p ≤ 0.05 p ≤ 0.05 p ≤ 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>-0.05 (-0.44, 0.35) -1.68 (-2.33, -1.03) -3.51 (-4.38, -2.65) -3.82 (-4.64, -3.01) -2.90 (-3.65, -2.15) -2.09 (-2.80, -1.38) -1.17 (-1.71, -0.63) -0.38 (-1.05, 0.30)</td>
</tr>
<tr>
<td>3 (crossover)</td>
<td>Cintest No. 1</td>
<td>Significant?</td>
<td>NS p ≤ 0.05 NS NS p ≤ 0.05 p ≤ 0.05 p ≤ 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>-0.17 (-1.70, 1.36) -2.24 (-4.36, -0.12) -1.90 (-4.53, 0.73) -3.14 (-7.01, 0.74) -4.75 (-8.90, -0.59) -4.88 (-8.80, -0.95) -6.81 (-11.09, -2.52) -6.66 (-12.38, -0.94)</td>
</tr>
<tr>
<td>8 (parallel group)</td>
<td>Bio-evaluation</td>
<td>Significant?</td>
<td>p ≤ 0.05 p ≤ 0.05 # #</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>-0.60 (-1.14, -0.07) -0.67 (-1.23, -0.11) -0.68 (-1.28, -0.09) -0.96 (-1.48, -0.44)</td>
</tr>
</tbody>
</table>

Source: Appendix 4.1 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

# The design of Study 1 did not include the 180 and 240 min. time points

## # The design of Study 8 did not include the 45, 90, 180, and 240 min. time points

NS = not statistically significant
### TABLE 4: DIRECTIONAL DIFFERENCES IN STUDIES 4, 5, 6, AND 7

<table>
<thead>
<tr>
<th>Study No. (design)</th>
<th>Study ID</th>
<th>Statistic</th>
<th>15 mins</th>
<th>30 mins</th>
<th>45 mins</th>
<th>60 mins</th>
<th>90 mins</th>
<th>120 mins</th>
<th>180 mins</th>
<th>240 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (crossover)</td>
<td>Cintest No. 2</td>
<td>Directional?</td>
<td>D</td>
<td>-</td>
<td>-</td>
<td>D</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>-0.13 (-1.85, 1.60)</td>
<td>0.31 (-1.40, 2.02)</td>
<td>0.13 (-2.47, 2.74)</td>
<td>-1.81 (-4.90, 1.29)</td>
<td>0.39 (-2.92, 3.70)</td>
<td>1.05 (-3.22, 5.31)</td>
<td>0.63 (-4.62, 5.67)</td>
<td>0.68 (-5.75, 7.12)</td>
</tr>
<tr>
<td>5 (crossover)</td>
<td>Cintest No. 3</td>
<td>Directional?</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>-</td>
<td>-</td>
<td>#</td>
<td>#</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>-0.58 (-1.93, 0.77)</td>
<td>-0.21 (-2.44, 2.03)</td>
<td>-0.07 (-2.46, 2.31)</td>
<td>-0.13 (-2.75, 2.48)</td>
<td>0.15 (-2.93, 3.23)</td>
<td>0.93 (-2.19, 4.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (crossover)</td>
<td>Huntington No. 1</td>
<td>Directional?</td>
<td>D</td>
<td>D</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>-0.57 (-2.82, 1.68)</td>
<td>-0.06 (-3.29, 3.17)</td>
<td>1.11 (-1.22, 3.43)</td>
<td>1.53 (-2.37, 5.43)</td>
<td>0.17 (-3.62, 3.96)</td>
<td>2.70 (-2.45, 7.84)</td>
<td>0.83 (-4.25, 5.91)</td>
<td>-1.65 (-9.22, 5.92)</td>
</tr>
<tr>
<td>7 (crossover)</td>
<td>Huntington No. 2</td>
<td>Directional?</td>
<td>-</td>
<td>D</td>
<td>-</td>
<td>-</td>
<td>D</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference (Confidence Interval)</td>
<td>0.99 (-0.98, 2.95)</td>
<td>-0.36 (-3.61, 2.89)</td>
<td>2.09 (-0.88, 5.05)</td>
<td>1.44 (-2.81, 5.70)</td>
<td>-0.18 (-4.00, 3.63)</td>
<td>2.89 (-0.69, 6.48)</td>
<td>1.49 (-1.05, 4.02)</td>
<td>1.61 (-2.82, 6.03)</td>
</tr>
</tbody>
</table>

Source: Appendix 4.1 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence Interval on the treatment difference (phenylephrine minus placebo)

# The design of Study 5 did not include the 180 and 240 min. time points.
RESULTS OF META-ANALYSES:

Using Model 1 results, statistically significant treatment-by-study interactions (all p-values ≤0.217) occurred for all time points (15 through 240 minutes) as expected given results of by-study analyses shown above (interaction p-values not provided in any table, but available in Appendix 3). Directional differences in favor of phenylephrine over placebo were seen in all studies, but not at all time points post-dose (Table 4 and Appendix 4.1). Directional treatment differences in favor of phenylephrine over placebo were seen for at least 2 and up to 6 time points in the 8 studies available for analysis.

For meta-analyses, statistical significance in favor of phenylephrine over placebo was achieved at the primary time points (30 and 60 minutes post-dose) and also for the 90 minute post-dose time point for both Models 2.b and 3. Statistical significance in favor of phenylephrine over placebo was also seen for the 45, 120, and 180 minute post-dose time points using Model 2.b (Table 5).

Note that there was a reduced sample size for the 180 and 240 minute time points as compared to earlier time points since only five studies were available for analysis at the 180 and 240 minute time points. Lack of statistical significance seen at the 120 and 180 minute post-dose time points (for Model 3) and at the 240 minute post-dose time point (for Models 2.b and 3) may be due to reduced power given increased variance and/or reduced sample size seen at these time points (Appendix 5).

Using estimates taken from both Models 2.b and 3, the percent changes from baseline for phenylephrine were at most 4%, 9%, 15%, 21%, 21%, 23%, 25%, and 20% for the 15, 30, 45, 60, 90, 120, 180, and 240 minute time points, respectively. Percent changes from baseline were at least 6 percentage points higher and at most 16.6 percentage points higher for phenylephrine as compared to placebo between 30 and 90 minutes post-dose (6 percentage points at 30 and 45 minutes and as high as 16.6 percentage points at 60 minutes).

The average change from baseline NAR for phenylephrine was approximately two-thirds to 2 times greater than that for placebo between 15 and 90 minutes post-dose.
### TABLE 5: RESULTS OF META-ANALYSIS

<table>
<thead>
<tr>
<th>Model</th>
<th>Statistic</th>
<th>15 mins</th>
<th>30 mins</th>
<th>45 mins</th>
<th>60 mins</th>
<th>90 mins</th>
<th>120 mins</th>
<th>180 mins</th>
<th>240 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Significant?</td>
<td>NS</td>
<td>p ≤ 0.05</td>
<td>p ≤ 0.05</td>
<td>p ≤ 0.05</td>
<td>p ≤ 0.05</td>
<td>p ≤ 0.05</td>
<td>p ≤ 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>2.b</td>
<td>Treatment Difference</td>
<td>-0.27</td>
<td>-1.68</td>
<td>-2.71</td>
<td>-3.68</td>
<td>-2.80</td>
<td>-2.02</td>
<td>-1.09</td>
<td>-0.33</td>
</tr>
<tr>
<td></td>
<td>(Confidence Interval)</td>
<td>(-0.61, 0.08)</td>
<td>(-2.23, -1.14)</td>
<td>(-3.57, -1.85)</td>
<td>(-3.39, -2.97)</td>
<td>(-3.54, -2.06)</td>
<td>(-2.67, -1.37)</td>
<td>(-1.61, -0.58)</td>
<td>(-1.21, 0.55)</td>
</tr>
<tr>
<td>3</td>
<td>Significant?</td>
<td>NS</td>
<td>p ≤ 0.05</td>
<td>NS</td>
<td>p ≤ 0.05</td>
<td>p ≤ 0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Treatment Difference</td>
<td>-0.41</td>
<td>-1.32</td>
<td>-1.38</td>
<td>-2.30</td>
<td>-2.24</td>
<td>-1.01</td>
<td>-0.95</td>
<td>-0.32</td>
</tr>
<tr>
<td></td>
<td>(Confidence Interval)</td>
<td>(-1.18, 0.36)</td>
<td>(-2.56, -0.09)</td>
<td>(-3.51, 0.74)</td>
<td>(-4.34, -0.26)</td>
<td>(-4.17, -0.31)</td>
<td>(-3.42, 1.40)</td>
<td>(-4.85, 2.96)</td>
<td>(-1.21, 0.57)</td>
</tr>
</tbody>
</table>

Source: Appendix 4.2 and Appendix 5

Confidence Interval = Lower and Upper Limits of a 95% Confidence interval on the treatment difference (phenylephrine minus placebo)

NS = not statistically significant
7. SUMMARY AND CONCLUSIONS

Eligible studies:
- Eight out of 14 reviewed studies fulfilled the criteria for inclusion in the analyses (Studies No. 1 – 8). One other trial, the study conducted by Cohen (Study No. 15), met all selection criteria except for providing individual patient data. It is important to note that this study demonstrated that 10 mg phenylephrine significantly improved NAR compared to placebo. So it is justifiable to assume that the results of the meta-analysis would still be positive had Study No. 15 been included.

Analyses of individual studies:
- Statistically significant differences in favor of 10 mg phenylephrine over placebo were seen in 4 of 8 individual studies analyzed.
- Although the direction and the size of the treatment difference was not consistent for all studies at all post-dose time points (Model 1), directional treatment differences in favor of 10 mg phenylephrine over placebo were seen for at least 2 and up to 6 time points in the 8 studies available for analysis.

Meta-analysis:
- For the meta-analysis including 7 crossover studies (Studies No. 1 – 7), phenylephrine was statistically significantly superior to placebo at the primary time points, 30 and 60 minutes post-dose, and at 90 minutes post-dose (using the results of both Models 2.b and 3). Also, phenylephrine was statistically significantly favored over placebo at the 45, 120, and 180 minute post-dose time points (Model 2.b).
- Reductions from baseline were on the order of 20%, a reduction considered to be noticeable by the patient. In one model (Model 2.b), reductions from baseline for phenylephrine were at least 21% from 60 to 180 minutes post-dose. In the second model (Model 3), reductions were 18% at 60 minutes post-dose, and at least 20% from 90 to 180 minutes post-dose.
- Study No. 8 was a parallel group study and was not included in the meta-analysis. In this study, phenylephrine was shown to be statistically significantly superior to placebo at the four time points assessed (15, 30, 60, and 120 minutes post-dose). Therefore, it can be assumed that the results of the meta-analysis would have remained positive had Study No. 8 been included.
In conclusion, both the meta-analysis of seven crossover studies and the results of a parallel group study demonstrated that phenylephrine at a dose of 10 mg is an effective decongestant.

References:

Ref. 1  FDA, Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. Federal Register, Vol. 41, No.176, p.38399-38400, 1976

Ref. 2  FDA, Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use; Final Monograph for OTC Nasal Decongestant Drug Products. Federal Register, Vol. 59, No.162, p.43386-43412, 1994

