Wyeth Consumer Healthcare

Phenylephrine Review

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Docket 76N-052N

TABLE OF CONTENTS

Executive Summary 3
Studies conducted by Wyeth Consumer Healthcare, not previously submitted to Docket 76N-052N 3
Studies reviewed by the FDA in 1976 6
Studies noted in Hendeles letter-to-the-editor 7
Overall Efficacy conclusions 9
Examination Of Dose-Response Across Studies 9
Conclusions and recommendations 10
References 18

EXECUTIVE SUMMARY

The recent series of communications between Representative Waxman and the FDA on the efficacy of phenylephrine prompted us to examine all studies of phenylephrine (PE) conducted by Wyeth Consumer Healthcare (WCH). The purpose of this communication is to submit information on three unpublished studies conducted between 1967 and 1983 that were not previously submitted to the OTC Monograph for Nasal Decongestant Drug Products, Docket 76N-052N. The study reports are appended and the results are summarized in this document. In our opinion, all three studies support the efficacy of 10 mg PE for nasal decongestion.

In addition to the review of the three clinical studies, this report summarizes the studies reviewed in 1976 by the FDA on this subject, as well as other published studies that were not part of the OTC Review. It is our conclusion that the total body of evidence supports the nasal decongestant efficacy of 10 mg of PE.

Furthermore, data are presented to show that there is no evidence that larger doses of PE result in greater efficacy. Therefore, we concur with the FDA's opinion that 10 mg of PE is a safe and effective decongestant.

STUDIES CONDUCTED BY WYETH CONSUMER HEALTHCARE, NOT PREVIOUSLY SUBMITTED TO DOCKET 76N-052N

Wyeth Consumer Healthcare (WCH), formerly AH Robins, conducted three double blind, randomized clinical trials which evaluated the efficacy of PE 10 mg for the treatment of nasal congestion. These are summarized in Table 1. Each study is discussed individually below:

1. **Study AHR-GIA** was a randomized, single-dose, double-blind, partial factorial, parallel group, single-center study conducted in 48 subjects (ages 19-74) with nasal congestion due to an upper respiratory infection (conducted in 1973). Subjects were enrolled within 24-72 hours of the onset of symptoms. The principal investigator was Burton M. Cohen, M.D. Subjects were randomly assigned to one of the following treatment groups: PE 10 mg (n=8), phenylpropanolamine (PPA) 10 mg (n=8), brompheniramine (BR) 8 mg (n=8), or PE+PPA+BR (n=24). Measurements of nasal inspiratory and expiratory resistances (using a Respiron instrument) and subjective assessments of nasal mucosal congestion, nasal mucosal hyperemia, nasal secretion, and ease of nasal breathing were assessed on 0-4 point

scales (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe or 0=normal, 1=mildly impaired, 2=moderately impaired, 3=severely impaired, 4=total obstruction) were completed at baseline and every 30 minutes post-dose for up to 4.5 hours. PE 10 mg alone resulted in statistically significant reductions from baseline in both inspiratory and expiratory resistances from 60 through 150 minutes after dosing ($p<0.05$), and marginally significant reductions in inspiratory resistance at 180-210 minutes after dosing ($p<0.10$). There were no statistically significant differences among the decongestant treatments. Results from the subjective assessments were consistent with those of the objective measures: PE significantly reduced (from baseline) nasal secretions from 30-180 minutes, congestion from 60-120 minutes (differences at 150-210 minutes were marginally significant), hyperemia from 30-180 minutes, and ease of breathing was significantly better at 60-150 minutes after dosing. There were no statistically significant differences between PE and PPA for any of the subjective assessments. WCH believes that this study is supportive of the efficacy of PE 10mg for the treatment of nasal congestion.

2. **Study AHR-4010-3** was a randomized, six-center, multiple-dose, double-blind, parallel group study conducted in subjects with nasal congestion due to an upper respiratory infection conducted in 1983. Subjects were enrolled within 48 hours of the onset of symptoms. Subjects were required to take study medication every 4 hours over a 72-hour period. The study evaluated the following treatments: PE 10 mg, PPA 25 mg, PE 5 mg+PPA 12.5 mg, and placebo (PBO). Using a four-point categorical scale (0=not present, 1=mild, 2=moderate, 3=marked), subjective evaluations of runny nose, stuffy nose, sneezing and headache were provided by the subject at baseline, and at 24, 48 and 72 hours after taking the first dose of study medication, and by the Investigator at baseline and at 72 hours. Also using 4 and 5-point categorical scales (1=marked benefit, 2=moderate benefit, 3=minimal benefit, 4=no benefit, or 5=worse), both the subject and the investigator provided an overall evaluation of therapeutic effect at the end of the evaluation period. In addition to the patient and investigator subjective assessments, only subjects enrolled at one study site (site 0401) underwent objective assessments of nasal inspiratory and expiratory resistance at 15, 30, and 45 minutes, and 1-4 hours after the first dose of medication. The study enrolled a total of 274 subjects (ages 18-77 years) at 6 sites.

Site 0401 enrolled a total of 48 subjects, with 12 subjects randomized to each of the four treatment groups. PE 10 mg was found to be statistically significantly better than PBO for total nasal airway resistance (NAR) at 30-180 minutes after the first dose was administered, and was marginally better at 15 minutes. The total airway resistance improvement for PE

and PPA were similar. PE was also either significantly better, or marginally significantly better than placebo for the following subjective assessments: subjects' assessment of stuffy nose at 72 hours, investigator's assessment of stuffy nose at 72 hours ($p<0.10$), subjects' assessment of sneezing at 24 and 48 hours ($p<0.10$), and the investigator's assessment of sneezing at 72 hours ($p<0.10$). For the most part, both PE and PPA provided similar relief of runny nose, nasal congestion and sneezing, although the severity of the subjects' stuffy nose in those on PE was significantly lower than those on PPA at 72 hours.

There was a statistically significant ($p<0.01$) treatment-by-site interaction for both the subject and investigator's overall evaluations at 72 hours. The interaction became insignificant ($p<0.55$) when site 0401 was excluded from the analysis. The pooled data from the remaining 5 sites failed to show significant differences among the four treatments. Site 0401, other than being the only site to collect objective assessments, tended to have more severe nasal congestion and less severe runny nose at baseline (56% and 15% with severe stuffy nose and runny nose baseline ratings, respectively) compared to those enrolled at the other 5 sites (38% and 34% with severe stuffy nose and runny nose baseline ratings, respectively). Subjects at site 0401 also tended to be older (mean age = 47.7) than those from the other 5 sites (mean age = 33.9 years). It is not clear if any of the baseline differences between site 0401 and the other 5 sites could have contributed to the different outcomes. Nonetheless, WCH believes that this study is supportive of the efficacy of PE 10mg for nasal congestion.

3. **Study #7032** conducted in 1967 was a randomized, single-dose, single-blind, placebo controlled, full-factorial, 8-way crossover, single-center study conducted in 8 subjects (ages 8-60) with stable or chronic nasal congestion due to allergy. Each subject received each of the following treatments in random order on 8 separate treatment days: PE 10 mg, PPA 10 mg, BR 8 mg, PE+PPA, PE+BR, PPA+BR, and PE+PPA+BR and PBO. During each treatment period, NAR was measured at baseline and at 30, 60, and 120 minutes after dosing using a Respiron instrument. Subjects were required to have a NAR reading of at least 10 mm at baseline. PE 10 mg alone produced marginally statistically significant reductions ($p< 0.10$) in inspiratory and expiratory nasal airway resistances at 1 hour after dosing. Readings at 30 minutes and 2 hrs after dosing were numerically better, but not statistically different from placebo. The reductions seen in both inspired and expired nasal resistance at 30 minutes and 1 hour for PE were numerically greater than those seen with PPA. The two treatments were similar at 2 hours post-dose.

Two of these studies (AHR-GIA; AHR-4010-3) demonstrated with objective and subjective measures that in subjects with nasal congestion, PE 10 mg was significantly more effective than PBO or demonstrated significant improvements in NAR from baseline, whereas the third study (#7032) was weakly supportive.

STUDIES REVIEWED BY THE FDA IN 1976

WCH obtained copies of all studies that were cited in the bibliography of the PE section of the 1976 OTC Review of Cough, Cold and Allergy ingredients (Federal Register, vol. 41, no. 176, pages 38396-38400, September 9, 1976). We identified 14 studies reviewed by the FDA in 1976 (these studies are references 5, 6, 7, 8, 9, 10, 19, 20, 21, 22, 23, 24, 25, 26 in the 1976 Federal Register document). Of these, reference 19 was not evaluated further because this was a methodological paper that tested an oral combination product containing a vasoconstrictor, an antihistamine and an analgesic whose specific ingredients were unknown. Additionally, reference 25 was rejected because it was an abstract without any clinical data. Table 2 summarizes the design, pertinent strengths, weaknesses and findings from each of these studies. All studies evaluated objective measures of nasal congestion by measuring reduction of nasal airway resistance (NAR), using rhinometric methods. Furthermore, 11 of these 12 studies measured subjective responses on a 5-point severity scale of nasal congestion.

Five of the studies (references 5, 20, 21, 23, and 24) were negative, i.e., PE at doses ranging from 5 mg to 75 mg did not significantly reduce NAR compared to placebo. On examination of these studies, 3 of them (references 21, 23 and 24) did not include a positive control group which brings into question the sensitivity of the rhinometric assay performed. In another study (reference 5) the author noted that the baseline NAR measurements suggested "the majority of patients did not have baseline nasal congestion". In addition, the positive control failed to separate from placebo again suggesting that the methods used were not sensitive. Finally, another study (reference 20) showed a statistically significant reduction in NAR by the positive control (PPA) and not by 10 and 25 mg PE suggesting a true failure of PE efficacy under the conditions of that study. One would conclude therefore that of these 5 studies, there was <u>one</u> well-conducted study that failed to demonstrate the efficacy of PE. On the other hand, seven double blind (DB), randomized trials (R) [references 6, 7, 8, 9, 10, 22, and 26] were positive, i.e., PE demonstrated a significant reduction in NAR at the doses tested ranging from 5 – 25 mg. Four of the studies (references 7, 10, 22 and 26) included a 10 mg dose of PE and another study included a 5 mg dose (reference 8). In each study a

clinically significant reduction in NAR (20% or greater) was achieved at the 5 and 10 mg doses.

STUDIES NOTED IN HENDELES LETTER-TO-THE-EDITOR

WCH obtained all clinical studies cited in the Hendeles and Hatton letter-to-the-editor and conducted a computerized search for all published articles on the efficacy of PE. This latter search only revealed one completed but unpublished study by Schering Plough (http://clinicaltrials.gov/ct/show/NCT00276016). This study was conducted as a randomized, placebo-controlled, investigator–blind, three-way crossover trial to examine the efficacy of PE 12 mg and pseudoephedrine (PSE) 60 mg in 39 subjects with nasal congestion due to seasonal allergic rhinitis. Although PE failed to separate from PBO in the primary efficacy comparison of subjective nasal congestion scores, the authors believed that possible recall biases inherent in the crossover design may have influenced the result for PE.

Three additional studies were identified from the Hendeles and Hatton's 2006 letter-to-the-editor (Bickerman, 1971, Cohen, 1972 and McLaurin et al, 1961). Bickerman, 1971 corresponds to the FDA's abstract reference 25. The study by McLaurin et al, 1961 was evaluated by FDA for safety but not efficacy in their review. Cohen's study was published in 1972 but was not reviewed by the FDA in their 1976 review for reasons unknown to us. Table 3 summarizes these three studies.

McLaurin's study assessed the oral decongestant efficacy of PE 10 mg, PPA 25 mg, PSE 60 mg and ephedrine (EPH) 25 mg in a mixed population of patients with rhinitis. The quality of this study is questionable for the following reasons. First, the study population consisted of patients with rhinitis of mixed etiologies (common cold, sinusitis, allergy, vasomotor rhinitis, hypothyroidism). Second, the methods of randomization and blinding were not clear. Third, 42 out of 130 enrolled subjects (32%) were discontinued from the study and not included in the analyses, potentially biasing the results. Only one of the active treatment arms, i.e. EPH 25 mg but not PSE 60 mg or PPA 25 mg was found to significantly reduce NAR. Subjective assessment of nasal congestion did not reveal any significant treatment effects in contrast to Dr. Hendeles' conclusion that EPH showed efficacy in subjective endpoints as well. In our opinion this cannot be considered to be a valid study showing the lack of PE efficacy because the model's validity and assay sensitivity were not demonstrated.

Bickerman evaluated the efficacy of oral PE 10 mg, PSE 60 mg and PPA 40 mg compared to placebo in an unknown number of patients with chronic non-seasonal rhinitis in what the author described as a "representative crossover study". This study is generally lacking in details and appears to be more of a description and validation of a rhinometric method where a number of baseline measurements were made in patients with upper respiratory tract infections. The evaluation of pharmacological treatments seems to be a secondary objective. The results showed that PSE and PPA but not PE reduced NAR from 30 min to 4 h post dose. Dr. Hendeles constructed a table from the data in this study and published it in his 2006 letter to the editor citing it as evidence of the lack of effect of PE. He further described the study as a double-blind, placebo-controlled, randomized crossover study in 20 patients with nasal stuffiness. We have been unable to verify this statement given the information in the manuscript. Dr. Hendeles had used the same data in a previous paper he authored in 1993 (Pharmacotherapy 1993;13: 129S-134S). In that paper he noted that "the report did not indicate how many patients were studied". Therefore the robustness of these data cannot be established. The on-line repository cited in his letter to the editor does not contain any additional information about this study.

Cohen, studied the efficacy of PE in 48 subjects with nasal congestion due to colds. This was a double blind, randomized, placebo controlled, crossover study which tested the effects of PE 10 mg, 15 mg and 20 mg on NAR and improvement of subjective assessment of nasal congestion. All doses of PE tested showed a significant reduction in NAR and subjective scores of nasal congestion. Furthermore there was statistically significant greater reduction in NAR produced by PE 25 mg compared to 10 mg and 15 mg doses. This is one of the only studies to demonstrate a significant dose response effect. Hendeles criticizes this paper - "it is noteworthy that in the cohort treated with 10mg, baseline nasal airway resistance was significantly different on the 2 study days, making the results difficult to interpret". He is correct in that there was no apparent adjustment for this baseline imbalance (and the data are unavailable to do it now). However, the PE group was consistently numerically less severe post-baseline compared to placebo despite it starting out as more severe. Also, the PE 15 mg group, which did not differ from placebo at baseline, also showed a significant reduction in NAR compared to placebo treatment. Finally, PE 10mg and placebo subjective symptom scores were comparable at baseline, and the scores in the PE 10mg group improved significantly more than in the placebo group.

In our opinion Dr. Hendeles unduly discredits the positive study (Cohen) while emphasizing the two negative studies (McLaurin, Bickerman). At best it can be argued that the data in his

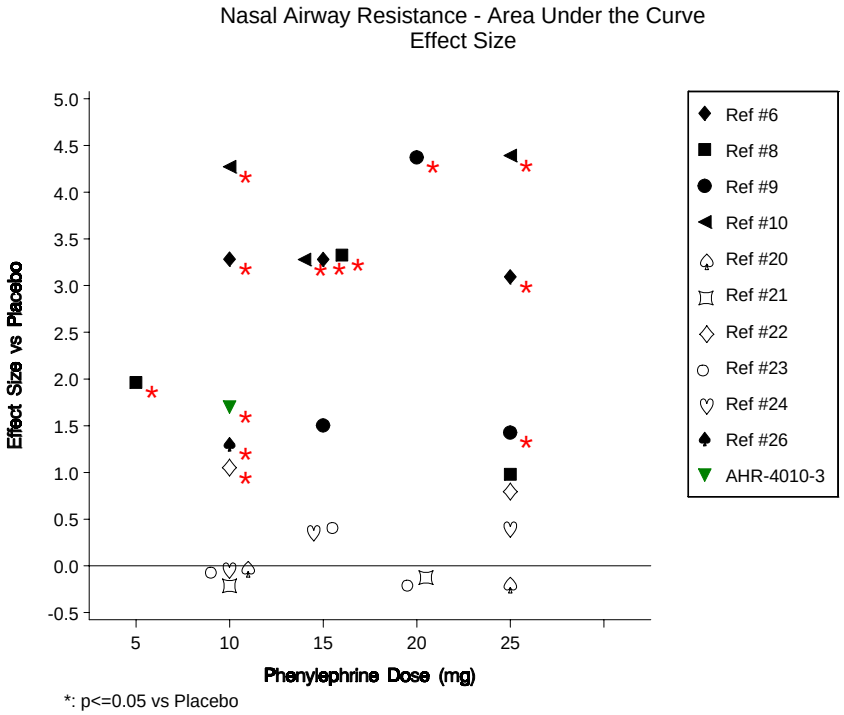
letter-to-the-editor shows one positive (Cohen) and one negative (Bickerman) study with respect to PE. The third study (McLaurin) cannot be relied upon to draw any valid conclusions about PE efficacy.

OVERALL EFFICACY CONCLUSIONS

Of the 19 studies presented above evaluating PE for nasal congestion, 11 studies show benefit of PE in both objective and subjective findings; 3 well conducted studies failed to show the efficacy of PE; and 5 studies demonstrated inadequate model validation and assay sensitivity thereby not allowing efficacy conclusions to be made.

Examination Of Dose-Response Across Studies

We further examined the studies cited above, where data were available, to determine whether a dose-response relationship could be demonstrated for PE. The following figure shows the effect size, which is a measure of the difference between the active treatments and placebo, standardized by the within-study standard deviations (between subjects).



These data show that there is no clear dose response associated with increasing doses of PE. This suggests that doses of PE greater than 10 mg do not produce a larger effect size (or more decongestant effect) than 5-10 mg doses, hence obviating the need to recommend or

further study the efficacy of 25 mg of PE. Given the possibility of increased cardiovascular risks with increasing doses of any sympathomimetic amine and the desire to maximize the benefit risk ratio of these OTC drugs, we disagree with Dr. Hendeles' suggestion that higher doses are warranted.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, WCH concurs with the Agency opinion that 10mg phenylephrine is a safe and efficacious oral nasal decongestant.

We respectfully disagree with Hendeles and Hatton's conclusions regarding the lack of efficacy of PE. The authors suggested that the 1976 US FDA review panel that concluded that PE was safe and effective, reached a "specious conclusion that was not based on a systematic review of the available data". The authors state that the panel reviewed only four studies showing efficacy of the 10mg dose of PE compared with seven studies showing no difference between PE and placebo. As described above, the data reviewed by WCH, which includes all studies that were submitted to the FDA, as well as others published subsequently, along with three unpublished studies conducted by our company, demonstrate that 10mg of PE is effective in both objective and subjective measures of nasal congestion relief.

Drs Hendeles and Hatton also allege that the "poor oral bioavailability" of PE may be a reason that it is unlikely to provide relief of nasal decongestion. It is important to note that bioavailability in itself is not a reason for lack of efficacy. The critical components in this regard are the amount of drug that reaches the appropriate receptor sites and the affinity of the drug for those receptors. There are many examples of highly effective drugs that have "low bioavailability", e.g., the bioavailability of the bisphosphonates is <1%, omeprazole, 30-40% and morphine 40%.

In the final analysis, consumers will decide whether PE is effective for them. As discussed, data from numerous studies suggests that PE is effective. Available market research data also suggests that consumers are as satisfied with PE containing medicines as they were with PSE containing medicines. GfK Group conducted a study comparing consumer satisfaction and future purchase intent for Pfizer's PSE containing Sudafed compared to Sudafed PE. Among approximately 450 users, the satisfaction was similar (50% and 51%) while future purchase intent was higher for Sudafed PE than for the PSE formulation (54% vs. 44%, respectively), (GfK Arbor LLC, 2006).

Consumers have several choices among OTC products for nasal congestion. First, they can select PE products off-the-shelf. If they experience adequate relief, consumers are likely to be satisfied with such products. If they find that they are not experiencing adequate relief, they can seek out PSE-containing medicines, which are available behind the counter. Alternatively, they can seek recommendations for other OTC treatment from the pharmacist with respect to their symptoms.

Abbreviations

AE	Adverse event
BROM	Brompheniramine
DB	Double-blind
EPH	Ephedrine
NAR	Nasal airway resistance
PBO	Placebo
PC	Placebo-controlled
PE	Phenylephrine
PPA	Phenylpropanolamine
R	Randomized
ss	Statistically significant

Table 1. Summary of AH Robins Studies Evaluating Phenylephrine

Study	Basis of Review	Results/Comments
AHR-GIA May, 1973	R, DB, single-dose, partial factorial, parallel group, single-center studying 48 adults with nasal congestion due to URI of 24-72 hrs in duration Treatments PE 10 mg + PPA 10 mg + BROM 8 mg (n=24) PE 10 mg (n=8) PPA 10 mg (n=8) BROM 8 mg (n=8) Assessments Inspiratory and expiratory NAR (electronic posterior rhinometry) at baseline and every 30 minutes post-dose for up to 4.5 hours, Subjective measures (5-point severity scale of nasal congestion, nasal mucosal hyperemia, nasal secretion and ease of nasal breathing)	**Positive study.** NAR (inspiration and expiration): Significant change from baseline* for PE at 60-150 min, and marginally better at 180-210 min PPA numerically better than PE at 120-240 min; the two treatments essentially equal at 30-90 min Subjective Nasal Mucosal Congestion – ss reduced from baseline* for PE sign at 60-120 and marginally better at 150-210 min. Nasal secretions - ss reduced from baseline for PE *30-180 min, hyperemia 30-180 min. Subjective ease of nasal breathing - ss reduced from baseline* for PE sign at 60-150 min. No consistent difference between PE and PPA * within-group comparison

AHR-4010-3 December, 1983	R, DB, parallel, multiple dose (every 4 hours), 3-day study in 48 patients with nasal congestion due to URI of less than 48 hours in duration Treatments PE 5 mg + PPA 12.5 mg (n=12) PE 10 mg (n=12) PPA 25 mg (n=12) PBO (n=12) Assessments NAR (electronic posterior rhinometry) at 15, 30, 45, 60, 120, 180, and 240 min after first dose Subjective symptomatic measures (4-point categorical scale) at 24, 48 and 72 hrs; Investigator symptomatic evaluation at 72 hrs; Overall (global) evaluation by both subject and Investigator at 72 hours	**Positive study.** These data suggest that PE separated from PBO in subjective and NAR assessments and equal to a PPA dose of 25mg. PE significantly reduced NAR at 30-180 minutes compared to PBO and was marginally better at 15 minutes. PE was essentially equal to PPA at all time points PE was either significantly better, or marginally significantly better than PBO for the following subjective assessments: subjects' assessment of stuffy nose at 72 hours, Investigator's assessment of stuffy nose at 72 hours ($p<0.10$), subjects' assessment of sneezing at 24 and 48 hours ($p<0.10$), and the Investigator's assessment of sneezing at 72 hours ($p<0.10$). For the most part, both PE and PPA provided similar relief of runny nose, nasal congestion and sneezing, although the severity of the subjects' stuffy nose for PE was significantly lower than PPA at 72 hours. A WCH re-analysis of the global assessments, based on the data provided in the report, indicates that PE 10mg was significantly better than placebo.
Study 7032 November, 1967	R, PC, SB, single dose, single-center crossover, 2 hr evaluation period in 8 subjects with stable or chronic nasal congestion Treatments PBO, PE 10 mg, PPA 10 mg, BROM 8 mg, PE + PPA, PE + BROM, PPA + BROM, PE + PPA + BROM (n=8) Assessments Inspiratory and expiratory NAR (electronic posterior rhinometry)	**Trending Study (Positive trend)** PE 10 mg alone produced marginally statistically significant reductions ($p< 0.10$) in inspiratory and expiratory nasal airway resistances at 1 hour after dosing. Readings at 30 minutes and 2 hrs after dosing were numerically better, but not statistically different from placebo. The reductions seen in both inspired and expired nasal resistance at 30 minutes and 1 hour for PE were numerically greater than those seen with PPA. The two treatments were similar at 2 hours post-dose.

Table 2. Studies Evaluated by FDA for Efficacy of Oral Phenylephrine

Study Reference #	Basis of Review	Results/Comments
Reference 5 Memo to Lands from Luduena April 23, 1959	DB, PC, incomplete crossover study. Topical PE and PPA and Oral PE dose tested 10, 25, 50, 75 mg and PPA 25, 50 mg. N= 14-15 volunteers/arm	**Negative study.** Actives did not separate from PBO for NAR. Analysis: Inadequate assay sensitivity, no systemic drugs demonstrated any effect.
Reference 6 Memo to Suter from Hulme. June 27, 1967 Elizabeth Biochemical Labs #1	DB, PC, R, incomplete crossover study in 25 subjects with congestion due to colds. Studied oral EPH. 8 mg (n=13) and PE 25mg (n=12)	**Positive study.** Both PE 25 mg and EPH ↓ NAR (peak ↓ ~ 5 units) and subjective scores of nasal congestion significantly ↓ by both treatments compared to PBO.
Referred to in Reference 7 Memo to Wessinger from Hulme. Jan 12, 1968 Elizabeth Biochemical Labs #2	DB, PC, R, incomplete crossover study in 38 subjects with congestion due to colds. Studied oral ephedrine 50 mg (n=6) and PE 10mg (n=16), 15mg (n=10), 25mg (n=6)	**Positive study.** 10 mg, 15mg and 25mg PE separated from PBO. 10 mg PE significantly reduced NAR at all time points from 15 min through 2 hours (p=0.01). Maximal reduction was 5.3 units at 45 and 60 min post dose. All doses ↓ subjective scores of nasal congestion.
Reference 8 Memo to Blackmore from Hulme June 2, 1969 Elizabeth Biochemical Labs #3	DB, PC, R incomplete crossover study in 46 subjects with congestion due to colds for 2 consecutive days. Studied oral PE doses of 5mg (n=16), 15mg (n=10) and 25mg (n=10) and PPA 50mg (n=10)	**Positive study.** All actives ↓'d NAR compared to PBO. No demonstration of dose-response. Only PE 15 mg and PPA 50 mg significantly reduced subjective scores of nasal congestion (p=0.05).
Reference 9 Memo to Blackmore from Hulme. August 11, 1969 Elizabeth Biochemical Labs #4	DB, PC, R incomplete crossover study in 20 subjects with congestion due to colds. PE 15 (n=6), and 20 mg (n=5), PE 25mg (n=9)	**Positive study.** 15 mg, 20 mg and 25 mg PE ↓'d NAR compared to PBO beginning at 45 min post dose. Only 20 mg PE ↓'d subjective scores of nasal congestion.
Reference 10 Memo to Blackmore from Hulme May 27, 1970 Elizabeth Biochemical Labs #5	DB, PC, R incomplete crossover study in 25 subjects with congestion due to colds. Studied oral PE doses of 10mg (n=10), 15mg (n=6) and 25mg (n=9)	**Positive study.** All actives ↓'d NAR compared to PBO as early as 30 minutes after dosing. PE 10 mg duration up to 180 min, peak effect at 60 min (29%↓,P=0.01). Subjective: only 25 mg PE reduced subjective scores of nasal congestion.
Reference 20 Memo to Blackmore from Hulme May 13, 1969 Huntingdon Research Center #1	DB, PC, R, incomplete crossover study in 48 subjects with congestion due to colds. Oral PE 10, and 25 mg, PPA 50mg. N= 16/arm	**Negative study.** No PE doses separated from PBO. PPA positive at 45 and 60 min. Subjective results not reported due to lack of objective effect.

Reference 21 Memo to Blackmore from Hulme. June 26, 1969 Huntingdon Research Center #2	DB, PC, R incomplete crossover study in 50 subjects with congestion due to colds. Oral PE 10, and 20 mg. N= 25/arm	**Negative study.** No doses separated from PBO. Author cited possible reasons for failure: 1) larger variability (compared to other congestion studies), 2) insufficient training of technicians, 3) use of different technicians pre and post-dosing. Subjective results not reported due to lack of effect on NAR.
Reference 22 Memo to Blackmore from Hulme. Apr 10, 1969 Clintest Labs #1	DB, PC, R incomplete crossover study in 48 subjects with congestion due to colds. PE 10, and 25 mg, PPA 50mg. N= 16/arm	**Positive study.** 10, 25 mg PE and PPA ↓'d NAR compared to PBO. PE 10mg effect on NAR seen 90 180 minutes. PE 10 mg and PPA significantly reduced subjective scores for nasal congestion (p=0.05, p=0.01, respectively).
Reference 23 Memo to Blackmore from Hulme. Jan 23, 1970 Clintest Labs #2	DB, PC, R incomplete crossover study in 48 subjects with congestion due to colds. Oral PE 10, 15, and 25 mg. N= 16/arm	**Negative study.** No doses separate from PBO on objective and subjective measures. No positive control.
Reference 24 Memo to Blackmore from Hulme. May 18, 1970 Clintest Labs #3	DB, PC, R incomplete crossover study in 48 subjects with congestion due to colds. Oral PE 10, 15, and 25 mg. N= 16/arm	**Negative study.** 10 mg PE does not separate from PBO. 15mg and 25 mg are marginal. No positive control. PE 15 mg ↓'d subjective scores of nasal congestion (p=0.05).
Reference 26 OTC volume 040288B	DB, PC, parallel group study of 200 patients with nasal congestion due to head cold. PE 10mg administered orally Q4h x 4 doses, versus PBO	**Positive study.** Significant reduction in NAR by PE 10mg from 15-120 min compared to PBO (11-28%, $p \leq 0.05$). Placebo group was somewhat more severe at baseline, for which there was no adjustment. Subjective: PE was significantly better than PBO for sneezing (115%), runny nose (85%) and stuffy nose (57%), $p < 0.05$.

Table 3. Other Studies in the Literature on the Efficacy of Phenylephrine

Study	Basis of Review	Results/Comments
McLaurin, 1961	Cross-over study in 88 subjects with nasal congestion due to a variety of causes, colds, sinusitis, allergy, vasomotor rhinitis and hypothyroidism. Compared oral PBO, PE 10mg, PSE 60mg, PPA 25mg and Eph 25mg. Measured NAR (McLaurin's Rhinometric method) at baseline and 60 minutes post dose. Subjective change of the nasal airway (6 category scale) recorded 60 min post dose and the following a.m. after taking a second dose 1 hr prior to bedtime the previous evening. Vital signs.	**Negative study. PE did not separate from PBO.** Only Ephedrine was found to significantly (p=0.05) lower NAR (38%). No significant differences between PBO and treatment groups at either 2 time points. Significant methodologic issues: Unclear how this study was blinded or randomized. Almost 1/3 of the subjects (42/130) who entered the study dropped out before completion and were excluded from all analyses. This could have severely biased the results as well since, to some extent, only responders were analyzed. Statistical methods were not provided.
Bickerman, 1971	This study was described by the author as a "Representative DB crossover study". An unknown number of subjects with chronic non-seasonal rhinitis received oral PBO, PSE 60mg, PPA 40 mg or PE 10mg.	**Negative Study. PE did not separate from PBO.** PSE and PPA showed significant reduction of NAR compared to PBO at all post-dose time points (30 min – 4 h) whereas PE did not. No subjective assessments of nasal congestion were made.
Cohen, 1972	DB, PC, R incomplete two way crossover study of 48 subjects with nasal congestion due to the common cold. Each subject received oral PBO and PE 10 (n=16) or 15 (n=16) or 25 mg (n=16).	**Positive study.** All active doses reduced NAR compared to PBO. PE 25mg showed greater ↓ in NAR compared to 10mg and 15mg doses. For PE 10 mg, significant reduction was seen from 30-120 min ($p \leq 0.01$- 0.05). Peak reduction of ~40% at 60 min post dose. Mean % reduction in subjective scores paralleled reduction in NAR for each dose. This study clearly demonstrates the efficacy of PE on objective and subjective measures. There is a statistically significant dose-response effect between 25 mg and 10mg doses. A greater number of AEs were seen at the 25 mg dose.

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