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CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Briefing Book

Meeting of the Nonprescription Drugs Advisory Committee

December 2007

[Docket No. 2007P-0047]

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Briefing Book Sections — Page

1.0 EXECUTIVE SUMMARY

Phenylephrine had been on the market for decades when, in 1976, the Food and Drug Administration Over-the Counter (OTC) expert advisory review panel recommended that phenylephrine be classified as "generally recognized as safe and effective" (GRASE) at a 10 mg dose for OTC use. OTC medications such as phenylephrine are considered safe and effective treatments to help relieve nasal congestion.

Nasal congestion is one of the most common symptoms associated with acute and chronic rhinitis. Subjective interpretation and temporal changes of congestion, associated with a variety of factors including the nasal cycle, posture and mood, complicate the assessment of disease severity and treatment effectiveness in both clinical trials and by healthcare providers. Complications may result from the lack of treatment of this symptom.

FDA's meeting notice for the December 14, 2007 Nonprescription Drugs Advisory Committee meeting states that the committee will discuss the safety and effectiveness of phenylephrine as an OTC oral nasal decongestant. The meeting will address a Citizen's Petition submitted to FDA on February 1, 2007 requesting that the dose of oral phenylephrine in the OTC drug monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (CCABADP) be increased for patients ≥12 years and that additional studies be required to validate the Petitioners' assertion that a 25 mg dose would be more efficacious and just as safe as a 10 mg dose of phenylephrine hydrochloride every 4 hours.

The Citizen's Petition of February 1, 2007 also requested that approval for use in children <I2 years be withdrawn. Recently, FDA discussed safety and efficacy data for cough and cold medicines, including phenylephrine, in children at an October 18 and 19, 2007 joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee. As such, this report provides a thorough summary of phenylephrine data in adults only.

Consumer Healthcare Products Association (CHPA) convened a working group to critically assess all studies reviewed by the 1976 OTC expert advisory review panel and additional data on the efficacy and safety of phenylephrine in adults. This report summarizes the following:

- Consumer Need
- Clinical Pharmacology of Phenylephrine
- Efficacy of Phenylephrine

- Safety of Phenylephrine

The working group assessment of available scientific evidence concurs with previous findings of the FDA and OTC expert advisory review panel, that oral phenylephrine 10 mg is safe and effective as a nasal decongestant for OTC use.

This conclusion is based on the following key points:

Consumer Need

- Nasal congestion is one of the most common symptoms associated with acute and chronic rhinitis.

- Acute and chronic rhinitis results from a number of inciting triggers including allergens, infectious agents, or irritants.

Pharmacology

- Phenylephrine, a selective α_1-adrenergic receptor agonist, is an effective OTC nasal decongestant that can be administered orally and intranasally. Its dominant and direct effect is vasoconstriction of capacitance blood vessels of the nasal mucosa that decreases blood volume, leading to nasal decongestion.

- At the current OTC oral dose, phenylephrine does not have substantial agonist effect on β_1-adrenergic receptors of the heart, and it does not stimulate the β_2-adrenergic receptors of the bronchi or peripheral blood vessels.

- The oral bioavailability of phenylephrine in adults is about 38%, which is lower than that of some other decongestants. Comparison of oral bioavailability as a surrogate for relative drug efficacy is inappropriate and misleading because additional factors, including relative potency, drug concentrations at the target site, and receptor affinity contribute to clinical efficacy.

Efficacy

- Phenylephrine 10 mg is an effective OTC dose for nasal decongestion in adults.

- The effect of phenylephrine 10 mg on decreasing nasal airway resistance (NAR) has been proven in 5 randomized, double-blind, placebo-controlled clinical trials. Four of these studies also demonstrated significant improvement in subjective nasal symptom scores compared to placebo.

- A valid meta-analysis confirms the effectiveness of phenylephrine 10 mg demonstrated in the individual randomized, double-blind, placebo-controlled, clinical trials.

- There are no convincing data to support that increasing the dose of phenylephrine to 25 mg is necessary to produce clinically meaningful improvements in subjective symptoms of nasal congestion.

Safety

- Phenylephrine 10 mg has an acceptable safety profile and is an appropriate oral nasal decongestant for OTC use. The safety of phenylephrine 10 mg in adults has been demonstrated based on data from placebo-controlled clinical trials and from post-marketing data.

- Fifteen of 20 placebo-controlled studies have reported safety data.

    - Of 8 studies collecting data on adverse events, 4 studies reported no adverse events in subjects treated with single or multiple doses of phenylephrine ranging from 5 to 25 mg. While most adverse events reported by phenylephrine-treated subjects were reported at a frequency similar to placebo-treated subjects, nervousness was reported more frequently with phenylephrine 15 mg and 25 mg than with phenylephrine 10 mg or placebo.

    - Fifteen studies collected data on vital signs for phenylephrine doses ranging from 5 mg to 100 mg. Many studies reported no change in vital signs for various doses of phenylephrine at various time points, and both increases and decreases for pulse and blood pressure were observed.

        - In studies that included a 10 mg phenylephrine dose, there was no discernible relationship between changes in pulse and blood pressure, nor was there a clear pattern of vital sign changes at different time points.

        - Statistically significant differences from placebo in pulse were reported more frequently with doses of phenylephrine greater than 10 mg; some of the largest mean increases from baseline in pulse were observed with phenylephrine 25 mg. Mean increases from baseline in systolic blood pressure were larger with increasing phenylephrine dose. However, all mean increases in pulse compared to baseline were $\leq$ 11 beats per minute and mean increases in blood pressure

compared to baseline were less than 5 mm Hg and may not be clinically relevant.

- These results support that the current adult dose of phenylephrine 10 mg in the OTC monograph is well tolerated.

Conclusions

- Nasal congestion is one of the most common symptoms associated with acute and chronic rhinitis.

- This assessment of available scientific evidence concurs with previous findings of the FDA and the OTC expert advisory review panel, that oral phenylephrine 10 mg is safe and effective as a nasal decongestant for over-the-counter use in adults.

- There are insufficient data in adults to support the assertion that increasing the dose of phenylephrine to 25 mg is necessary to produce clinically meaningful improvements in nasal decongestion with a similar safety profile as the currently available 10 mg OTC monograph dose.

- OTC medications such as phenylephrine are considered safe and effective treatments to help relieve nasal congestion.

The materials provided in this document reflect the collective work and views of the following CHPA member companies who currently market products containing phenylephrine:

- Bayer HealthCare LLC
- GlaxoSmithKline
- McNeil Consumer Healthcare
- Novartis Consumer Health, Inc.
- Perrigo Company
- The Procter & Gamble Company
- Wyeth Consumer Healthcare

2.0 CONSUMER NEED

Key Points

- Nasal congestion is one of the most common symptoms associated with acute and chronic rhinitis.

- Acute and chronic rhinitis results from a number of inciting triggers including allergens, infectious agents, or irritants.

Nasal congestion associated with acute and chronic rhinitis is a universal experience seen in patients of all ages [McCaffrey 1986]. Total airway resistance is at its maximum in infancy, declines through childhood and adolescence, and does not increase again until middle age [Nathan 2007]. It is considered the most bothersome and difficult to treat of the symptoms of rhinitis [Davis 2004]. There is no difference in the localized physiologic response, whether the inciting trigger is an allergen, infectious agent or irritant. Nasal congestion is the result of the effect of local mediators by direct or reflex action on nasal blood vessels or on sympathetic nerve terminals [Nathan 2007]. During this vascular process, the nasal mucosa swells, impeding the sense of free breathing.

Severity of nasal congestion and effectiveness of treatment may be assessed by either objective or subjective measures. Clinically useful objective measures should be simple, non-invasive techniques which are standardized, reproducible, sensitive and universally applicable [Nathan 2007, Fisher 1997].

Subjective measures do not always correlate with objective endpoints. Patient descriptions of discomfort take into account a variety of aspects of congestion which are not always accounted for in the direct examination. The general feeling of congestion in a patient may be affected by factors such as mood, sinus congestion, Eustachian tube function, cold air receptors in the nasal mucosa and posture, as well as nasal resistance to airflow [Lund 1996]. Other issues affecting consistent measurement of symptom severity include a well established cadence effect of nasal congestion, both with regards to a circadian 24 hour time structure [Smolensky 1995] and a natural rhythm known as the nasal cycle, where severity of congestion alternates, in either regular or irregular patterns, between sides of the nose [Nathan 2007, Gallego 2006]. Topical and oral nasal decongestants provide immediate, effective relief of nasal congestion. Choice of an appropriate type of decongestant is important and may vary by patient and symptom severity.

Topical decongestants provide faster and more profound decrease in nasal air resistance, but have shorter duration and the potential to produce rebound congestion, whereas oral agents do not [Hendeles 1993]. Oral decongestants generally have a weaker effect on the relief of congestion, but they carry a much lower risk of rebound congestion that occurs after the effect has declined [Nathan 2007].

A range of potential medical complications may occur if a congested nose is left untreated. A congested nose blocks the sinus ostia [Lund 1996], which can lead to sinus pressure and possibly aid the progress of acute sinusitis [Falck 1989, Eccles 2005, Whittet 1992]. In addition, nasal congestion frequently blocks the nasopharyngeal opening to the Eustachian tube leading to muffled hearing and the onset of otitis media [Lund 1996]. When nasal congestion blocks the naso-lacrimal duct, a backup of tears and watery eyes can result [Eccles 2005]. A congested nose may block access of odorants to olfactory mucosa resulting in temporary loss of smell. Impaired olfaction and the change in sense of smell have been correlated to nasal congestion [Akerlund 1995].

In conclusion, nasal congestion is one of the most common symptoms associated with acute and chronic rhinitis. Subjective interpretation and temporal changes of congestion, associated with a variety of factors including the nasal cycle, posture and mood, complicate the assessment of disease severity and treatment effectiveness in both clinical trials and by healthcare providers. Complications may result from the lack of treatment of this symptom. Over-the-counter (OTC) medications such as phenylephrine are considered safe and effective treatments to help relieve nasal congestion.

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3.0 CLINICAL PHARMACOLOGY OF PHENYLEPHRINE

Key Points

- Phenylephrine, a selective α_1-adrenergic receptor agonist, is an effective OTC nasal decongestant that can be administered orally and intranasally. Its dominant and direct effect is vasoconstriction of capacitance blood vessels of the nasal mucosa that decreases blood volume, leading to nasal decongestion.

- At the current OTC oral dose, phenylephrine does not have substantial agonist effect on β_1-adrenergic receptors of the heart, and it does not stimulate the β_2-adrenergic receptors of the bronchi or peripheral blood vessels.

- The oral bioavailability of phenylephrine in adults is about 38%, which is lower than that of some other decongestants. Comparison of oral bioavailability as a surrogate for relative drug efficacy is inappropriate and misleading because additional factors, including relative potency, drug concentrations at the target site, and receptor affinity contribute to clinical efficacy.

3.1 Indication

Under the OTC Review nasal decongestant monograph, phenylephrine is indicated for the temporary relief of nasal congestion, a prominent symptom of the common cold, hay fever, and other upper respiratory allergies (allergic rhinitis) [21CFR 341.80(b)(1)]. OTC labeling text may describe the symptoms of nasal congestion as “nasal stuffiness” or “clogged up nose”. Additional language may be added to reflect the mechanism of action of decongestants: “reduces swelling of nasal passages”, “shrinks swollen membranes”, and “promotes nasal drainage”.

3.2 Pathophysiology of Nasal Congestion

Adults and children of all ages experience nasal congestion, although the prevalence varies with age. A greater percentage of children experience and report nasal congestion with upper respiratory infections compared with adults [Pappas 2007]. A recent national ambulatory medical care survey found that nasal congestion is mentioned in the top 20 reasons for a doctor’s office visit [Woodell 2004]. In the common cold and allergic rhinitis, congestion develops secondary to engorgement of the cavernous venous sinusoids in nasal turbinates, which leads to tissue swelling, reduced internal nasal diameter, and increased resistance to air flow [Gentile 2000]. The basic physiology associated with nasal congestion is substantially similar in children and adults. However, total nasal airway resistance is at a maximum in infancy and declines to a minimum by adolescence, at which point little change

occurs until middle age and the onset of tissue atrophy [Lund 1996]. This age-related difference is consistent with increases in anatomical size as children grow.

3.3 Pharmacology and Mechanism of Action

Nasal decongestants are sympathomimetic agents that mimic the action of norepinephrine. They bind to and activate two types of adrenergic receptors, α_1 and α_2. Phenylephrine HCl produces both direct and indirect sympathomimetic effects [Hoffman 2001]. The dominant and direct effect is selective agonism at α_1-adrenergic receptors. Phenylephrine also releases norepinephrine from its nerve terminal storage sites, which is an indirect effect. At the current OTC oral dose, phenylephrine does not have substantial agonist effect on the β_1-adrenergic receptors of the heart, and it does not stimulate the β_2-adrenergic receptors of the bronchi or peripheral blood vessels [Hoffman 2001].

Phenylephrine's stimulation of α_1-adrenergic receptors located on capacitance blood vessels of the nasal mucosa (postcapillary venules) results in vasoconstriction, decreased blood volume and a decrease in the volume of the nasal mucosa (nasal decongestion) [Gentile 2000]. In addition, the vasoconstrictive action reduces the extracellular fluid that is associated with congestion and rhinorrhea.

Compared with other sympathomimetic amines, phenylephrine is a more potent α_1-adrenergic receptor agonist than epinephrine, norepinephrine, and isoproterenol. Basal plasma levels of epinephrine and norepinephrine range from 20 to 50 pg/mL and 100 to 350 pg/mL, respectively [Cryer 1974, Christensen 1976]. Plasma concentrations of phenylephrine after a 10 mg oral dose, which yield nasal decongestant effects, range from 400 to 3400 pg/mL [McNeil 2007, Ptacek 2007]. The blood vessels of the nasal mucosa have been shown to be more sensitive than the heart to the effects of circulating epinephrine and this may explain why nasal decongestants cause decongestion without significant cardiac effects [Malcolmson 1959].

In the case of pseudoephedrine, which has weak direct agonist activity at α- and β-adrenergic receptors, its principal mechanism is indirect action related to presynaptic release of norepinephrine that binds postsynaptic α-adrenergic receptors [Hoffman 2001]. Peak plasma concentrations of pseudoephedrine after a 60 mg dose, which yield nasal decongestant effects, range from 180,000 to 270,000 pg/mL [McNeil 1992].

3.4 Pharmacokinetics and Metabolism

Phenylephrine is completely absorbed following oral administration and is believed to undergo high first-pass metabolism in the intestinal wall. In a study of 24 healthy adults given a 10 mg oral dose [McNeil 2007], maximum phenylephrine concentrations from 400 to

2000 pg/mL were attained within an average of 29 minutes (range: 15 to 60 minutes). In another study of 12 healthy men given a 10 mg dose [Ptacek 2007], maximum phenylephrine concentrations from 800 to 3400 pg/mL were attained within an average of 36 minutes (range: 15 to 60 minutes).

Phenylephrine undergoes rapid distribution into peripheral tissues. The estimated steady-state volume of distribution (340 ± 174 L) considerably exceeds body weight [Hengstmann 1982], indicating storage in certain organ compartments. The rapid uptake of phenylephrine by vesicular norepinephrine transporters into adrenergic storage vesicles is consistent with less drug circulating in the blood and with the two-compartment pharmacokinetic profile. The average *beta* elimination half-life is 2.5 hours for both oral [McNeil 2007] and intravenous [Hengstmann 1982] administration, with individual values ranging between 1 and 5 hours.

The principal routes of phenylephrine metabolism are sulfate conjugation (mainly in the intestinal wall) and oxidative deamination by both the A and B forms of monoamine oxidase [Suzuki 1979]. Glucuronidation also occurs, but to a lesser extent. In one study following 30 mg orally over eight hours [Ibrahim 1983], phenylephrine was metabolized to phenylephrine-sulfate, m-hydroxymandelic acid, phenylephrine-glucuronide and m-hydroxy-phenylglycol-sulfate at 47%, 30%, 12%, and 6% of the dose, respectively. Deamination is the predominant metabolic pathway after intravenous injection of phenylephrine [Hengstmann 1982], whereas sulfate conjugation is the predominant pathway after oral administration.

3.5 Pharmacokinetics in Children

The pharmacokinetics of oral phenylephrine have not been studied in children. CHPA member companies have committed to conduct a pharmacokinetic study in children, ages 2 to < 12 years, and will work with FDA on study design.

3.6 Oral Bioavailability

The oral bioavailability of phenylephrine was estimated using racemic ^{3}H-phenylephrine in 15 volunteers who had no evidence of renal or hepatic impairment [Hengstmann 1982]. Four volunteers received a short infusion (1 mg ^{3}H-phenylephrine in 2 mL isotonic saline over 12.5 to 20 minutes), while 10 volunteers received oral solution (^{3}H-phenylephrine 1 mg in 100 mL water) after an overnight fast.

The oral bioavailability of phenylephrine was estimated as 38%. Complete enteral absorption was assumed because the cumulative urinary excretion of ^{3}H-phenylephrine was not significantly different following intravenous or oral administration (86% and 80%,

respectively). The findings from this study should be interpreted with caution because the results were obtained from a small number of subjects, and the intravenous and oral pharmacokinetic data were obtained from different groups of subjects in a parallel design. Moreover the dose studied was 1 mg and the current adult oral dose is 10 mg, so linear pharmacokinetics are needed for the 10 mg dose to have comparable systemic bioavailability.

3.7 Oral Bioavailability is Only One Factor Associated with Clinical Efficacy

The petitioners' letter included the following statement on bioavailability: *"Phenylephrine, at the FDA-approved dose of 10 mg for adults, is unlikely to provide relief of nasal congestion. It has poor oral bioavailability because of extensive first-pass metabolism in the gut and liver. Only 38% of the dose reaches the systemic circulation, compared with 90% of a pseudoephedrine dose…."*

Oral bioavailability of a drug is only one factor associated with clinical efficacy. Pharmacological effects are mainly determined by drug concentrations that reach the target site of action. Comparison of oral bioavailability as a surrogate for relative drug efficacy is inappropriate and misleading because additional factors, including relative potency, drug concentrations at the target site, and receptor affinity contribute to clinical efficacy. Although phenylephrine has an estimated oral bioavailability of approximately 38% [Hengstmann 1982], it is one of the most potent α_1-adrenergic agonists. It is noteworthy that there are a number of effective drugs on the market with oral bioavailability less than 40% as listed in Table 3.1.

Table 3.1 Examples of Currently Marketed Drugs with Oral Bioavailability < 40%

Acyclovir 10-20%	Morphine 30%
Alendronate 0.6-0.7%	Omeprazole 30-40%
Atorvastatin 14%	Pentazocine 20%
Carvedilol 25-35%	Propranolol 26%
Lovastatin <5%	Pravastatin 17%
Metoprolol 12%	Verapamil 35%

(Package inserts, Drugdex)

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4.0 EFFICACY OF PHENYLEPHRINE AS A NASAL DECONGESTANT

Key Points

- Phenylephrine 10 mg is an effective OTC dose for nasal decongestion in adults.
- The effect of phenylephrine 10 mg on decreasing nasal airway resistance (NAR) has been proven in 5 randomized, double-blind, placebo-controlled clinical trials. Four of these studies also demonstrated significant improvement in subjective nasal symptom scores compared to placebo.
- A valid meta-analysis confirms the effectiveness of phenylephrine 10 mg demonstrated in the individual randomized, double-blind, placebo-controlled, clinical trials.
- There are no convincing data to support that increasing the dose of phenylephrine to 25 mg is necessary to produce clinically meaningful improvements in subjective symptoms of nasal congestion.

4.1 Clinical Evaluation of Nasal Decongestants

Nasal congestion is a symptom experienced by the general population resulting from a variety of causes, mostly from common colds and allergies. It is a symptom that is not always easily described by a patient and interpreted by a clinician [Davis 2004]. Patients and clinicians are interested in those aspects that cause discomfort and these symptoms may not always correlate with measures of nasal patency. Nasal itching, for example, is easily described by patients and understood by clinicians despite being difficult to measure objectively.

Patient sensation of nasal congestion can be influenced by a number of factors including mood, air temperature and cold receptors in the nasal airway. Menthol, for example, stimulates the cold receptors in the nasal passages and provides a sensation of relief even though it has no effect on NAR [Eccles 1994]. In addition, congestion of the ethmoid area, Eustachian tubes and the ostia of the paranasal sinuses may also give patients a subjective sensation of congestion that is unrelated to changes in NAR. All of the above factors make the translation of sensation of congestion to subjective symptom score scales, typically used in clinical trials, challenging. Despite these challenges, subjective assessment methods are used to determine efficacy of nasal decongestants.

Objective measurement of nasal congestion has also been used to determine the efficacy of nasal decongestants. Several different methods have been developed, all of which require specialized equipment and trained technicians, and thus are highly operator dependent. Hence these methods are not easily amenable to multi-center clinical trials. Peak nasal airflow may be measured during inspiration (PNIF) and expiration (PNEF). These methods are quick and non-invasive; however, these measurements are dependent on subject effort and may be affected by nasal secretions. Anterior and posterior rhinometry are used to calculate NAR from the nasal airflow and pressure required to achieve that flow.

Most clinical studies have used variations of the anterior or posterior rhinometry method to measure NAR. One challenge of utilizing this method in clinical trials is the “nasal cycle” where congestion occurs in one nostril and alternates to the other, possibly due to changes in sympathetic tone. Although it is unclear what percentage of the population experiences the “nasal cycle”, if bilateral measurements are taken, the magnitude of improvements in unilateral congestion may not be fully appreciated. Measurements for both anterior and posterior rhinometry can also be affected by the presence of mucus. Despite these challenges, both topical and oral nasal decongestants have been shown to reduce NAR.

In general, most clinical efficacy trials for OTC oral nasal decongestants have used both subjective and objective endpoints for analysis with agreement reported in some studies. The FDA and clinical experts accept the importance of evaluating both objective and subjective endpoints in determining efficacy.

4.2 Efficacy Studies

In 1976, an FDA OTC expert advisory review panel concluded that phenylephrine 10 mg is safe and effective for OTC use. The FDA standard for effectiveness for GRASE monograph substances is defined as follows: “Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed” “Such recognition of effectiveness must be based on published and/or unpublished controlled clinical trials which can be supported by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing.” [21 CFR 330.10 (3)(ii)].

Nasal congestion is a major symptom of both the common cold and allergic rhinitis. A meaningful reduction of severity and/or duration of nasal congestion is used to assess the efficacy of nasal decongestants. The studies presented below have demonstrated that orally administered phenylephrine 10 mg is clinically and statistically superior to placebo.

A CHPA working group reviewed all of the available clinical trials examining the efficacy of oral phenylephrine as a nasal decongestant. A total of 20 studies were identified for review, 14 of which were reviewed by the expert FDA OTC expert advisory review panel in 1976 for efficacy. Eight studies have shown positive effects of phenylephrine on NAR at doses ranging from 5 to 25 mg. All eight of these studies have shown statistically significant improvements in subjective scores for nasal congestion for at least one dose of phenylephrine.

Fifteen studies included a 10 mg dose of phenylephrine. Compared with placebo,

- 4 were positive for both NAR and subjective assessments [Elizabeth #2 1968, Cintest #1 1969, Cohen 1975, Cohen 1972]
- 1 was positive only for NAR [Elizabeth #5 1970]
- 1 was supportive of efficacy of phenylephrine 10 mg for NAR [AHR-4010-3 1983]
- 4 were negative [Bickerman 1971, AHR- 7032 1967, Huntingdon #1 1969, S-P Study P04579 2006]
- 5 studies were inconclusive (negative but lacked positive control to demonstrate sensitivity of the model or included a positive control which did not separate from placebo) [Memo to Lands from Luduena 1959, Cintest #2 1970, Cintest #3 1970, McLaurin 1961, Huntingdon #2 1969].

4.2.1 *Studies Reviewed by the FDA in 1976*

Copies of all studies that were cited in the bibliography of the phenylephrine section of the 1976 OTC Review of Cough, Cold and Allergy ingredients were obtained [Federal Register, vol. 41, no. 176, pages 38396-38400, September 9, 1976]. The FDA reviewed 14 studies for efficacy in 1976 (these studies are references 5-10 and 19-26 in 41 FR 38399-38400). Table 4.1 summarizes the design, pertinent strengths, weaknesses and findings from 12 of these studies. Reference 19 [Blanchard 1964] has been omitted from the table because this was a methodological paper that tested an oral combination product containing a vasoconstrictor (decongestant), an antihistamine and an analgesic whose specific ingredients were unknown. Additionally, reference 25 [Rodgers 1973] was not included because it was an abstract without any clinical data. All studies evaluated objective measures of nasal congestion by measuring reduction of NAR, using rhinometric methods. Furthermore, 11 of these 12 remaining studies measured subjective responses on a 5-point severity scale of nasal congestion and 1 on a 6-category scale.

Five of the 12 studies (references 5, 20, 21, 23, and 24) were negative or inconclusive, i.e., phenylephrine 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 makes it impossible to evaluate the sensitivity of the rhinometric assay performed. In another study (reference 5) the author noted that concerning the baseline NAR measurements, "…in the majority of cases there was no nasal congestion." In addition, the positive control failed to separate from placebo, again suggesting that the methods used were not sensitive. Thus 4 of these 5 studies were inconclusive.

The remaining negative study (reference 20) showed a statistically significant reduction in NAR by the positive control (phenylpropanolamine, PPA) and not by 10 and 25 mg phenylephrine suggesting a failure of phenylephrine efficacy under the conditions of that study. One would conclude, therefore, that of these 5 studies, there was <u>one</u> well-designed study that failed to demonstrate the efficacy of phenylephrine.

In contrast, seven double blind, randomized trials (references 6, 7, 8, 9, 10, 22, and 26) were positive, i.e., phenylephrine demonstrated a significant reduction in NAR at the doses tested, ranging from 5 to 25 mg. Four of the studies (references 7, 10, 22 and 26) included a 10 mg dose of phenylephrine. In each study, a clinically meaningful reduction in NAR was achieved at the 10 mg dose. A fifth study included a 5 mg dose which also significantly reduced NAR (reference 8).

Table 4.1 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 oral PE dose tested 10, 25, 50, 75 mg and PPA 25, 50 mg. n= 14-15 volunteers/arm Post-dose Obs at 1-5 h	**Inconclusive study.** With the exception noted below, oral active controls were not significantly different from PBO for NAR. PPA 50 mg was significant only at 1 hour. Analysis: Inadequate assay sensitivity, no systemic drugs demonstrated any effect. Volunteers did not appear to have congestion at baseline.
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 25 mg (n=12) Post-dose Obs at 15-120 min	**Positive study.** Both PE 25 mg and EPH significantly ↓'d NAR and subjective scores of nasal congestion compared to PBO.

Table 4.1 Studies Evaluated by FDA for Efficacy of Oral Phenylephrine

Study Reference #*	Basis of Review	Results/Comments
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 10 mg (n=16), 15 mg (n=10), 25 mg (n=6) Post-dose Obs at 15-120 min	**Positive study.** 10 mg, 15 mg and 25 mg PE significantly decreased NAR vs PBO. 10 mg PE significantly reduced NAR at all time points from 15 min through 2 hours (p=0.01); maximal reduction was 40% at 45 and 60 min post dose. Subjective scores for nasal congestion significantly ↓'d for PE 10 mg and 15 mg, and not for PE 25 mg.
Reference 8 Memo to Blackmore from Hulme June 2, 1969 Elizabeth Biochemical Labs #3	DB, PC, R incomplete crossover study in 42 subjects with congestion due to colds for 2 consecutive days. Studied oral PE doses of 5 mg (n=16), 15 mg (n=8) and 25 mg (n=9) and PPA 50 mg (n=9) Post-dose Obs at 15-240 min	**Positive study.** All actives significantly ↓'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 mg (n=6), 20 mg (n=5), and PE 25 mg (n=9) Post-dose Obs at 15-240 min	**Positive study.** 15 mg, 20 mg and 25 mg PE significantly ↓'d NAR compared to PBO as early as 45 min post dose. Only 20 mg PE significantly ↓'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 10 mg (n=10), 15 mg (n=6) and 25 mg (n=9) Post-dose Obs at 15-240 min	**Positive study.** All actives significantly ↓'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 significantly 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, 25 mg, and PPA 50 mg. n=16/arm Post-dose Obs at 15-240 min	**Negative study.** Neither PE dose separated from PBO on NAR. PPA significantly ↓'d NAR at 45 and 60 minutes. 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 49 subjects with congestion due to colds. Oral PE 10 mg (n=25), and 20 mg (n=24). Post-dose Obs at 15-240 min	**Inconclusive study.** No doses separated from PBO on NAR. No positive control. 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.

Table 4.1 Studies Evaluated by FDA for Efficacy of Oral Phenylephrine

Study Reference #*	Basis of Review	Results/Comments
Reference 22 Memo to Blackmore from Hulme. Apr 10, 1969 Cintest Labs #1	DB, PC, R incomplete crossover study in 47 subjects with congestion due to colds. PE 10 (n=16), and 25 mg (n=16), PPA 50mg (n=15). Post-dose Obs at 15-240 min	**Positive study.** 10, 25 mg PE and PPA significantly ↓'d NAR compared to PBO. PE 10 mg effect on NAR seen at 90 to 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 Cintest Labs #2	DB, PC, R incomplete crossover study in 46 subjects with congestion due to colds. Oral PE 10 mg (n=15), 15 mg (n=16), and 20 mg (n=15). Post-dose Obs at 15-240 min	**Inconclusive study.** No doses separate from PBO on objective and subjective measures. No positive control. No evidence of assay sensitivity
Reference 24 Memo to Blackmore from Hulme. May 18, 1970 Cintest Labs #3	DB, PC, R incomplete crossover study in 47 subjects with congestion due to colds. Oral PE 10 mg (n=15), 15 mg (n=16), and 25 mg (n=16). Post-dose Obs at 15-120 min	**Inconclusive study.** No dose of PE separated from PBO for NAR. No positive control. PE 15 mg significantly ↓'d subjective scores of nasal congestion (p=0.05).
Reference 26 OTC volume 040288B (Cohen, 1975)	DB, PC, parallel group study of 200 patients with nasal congestion due to head cold. Oral PE 10 mg administered every 4 hours for 4 doses, versus PBO Post-dose Obs at 15-120 min for NAR (n=25 per group), subjective assessments through 12 hr	**Positive study.** Significant reduction in NAR by PE 10 mg from 15-120 min compared to PBO (11-28%, $p \leq 0.05$). Subjective: PE was significantly better than PBO for sneezing, runny nose and stuffy nose, ($p < 0.05$).

*****Reference # refers to the bibliography from the FDA OTC Review (Federal Register, vol. 41, no. 176, pages 38399-38400, September 9, 1976)
†Denoted incomplete crossover since subjects received multiple treatments but not all of them. Specifically, each subject received one of the active treatments and placebo.
Abbreviations: R= randomized, DB= double-blind, PC= placebo-controlled, PBO= placebo, PE= phenylephrine, PPA= phenylpropanolamine, EPH= ephedrine

4.2.2 Additional Studies Identified from the Literature and Unpublished Data

Six additional studies were identified which were not included in the FDA review in 1976. These are summarized in Table 4.2. One study was positive [Cohen 1972] and another study was supportive [AHR 4010-3] while 3 studies [Bickerman 1971, AHR Study 7032 and S-P study P04579] were negative, and 1 study [McLaurin 1961] was inconclusive.

McLaurin's study (reference 11) assessed the oral decongestant efficacy of phenylephrine 10 mg, phenylpropanolamine 25 mg, pseudoephedrine 60 mg and ephedrine 25 mg compared with placebo 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 method of balancing the treatment order, if it was done at all, was not clear. Third, 42 out of 130 enrolled subjects (32%) were discontinued from the study and not included in the analysis, potentially biasing the results. Only one of the active treatment arms, i.e. ephedrine 25 mg but not phenylephrine 10 mg, pseudoephedrine 60 mg or phenylpropanolamine 25 mg, was found to significantly reduce NAR compared to placebo. Subjective assessment of nasal congestion did not reveal any significant treatment effects resulting from any of the 4 active treatments. This model's validity and assay sensitivity were not clearly demonstrated, therefore this cannot be considered to be a valid study showing the lack of phenylephrine efficacy.

Three studies were negative [S-P Study P04579, AHR Study 7032, Bickerman 1971]. Study S-P P04579 [2006] was conducted as a randomized, placebo-controlled, investigator–blind, three-way crossover trial to examine the efficacy of phenylephrine 12 mg and pseudoephedrine 60 mg in 39 subjects with nasal congestion due to seasonal allergic rhinitis. Although phenylephrine failed to separate from placebo in the primary efficacy comparison of subjective nasal congestion scores, the authors believed that possible recall biases inherent in the crossover design may have adversely influenced the result for phenylephrine. Objective measures were collected but results were not mentioned in the available synopsis.

AHR 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 18-60) 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: phenylephrine 10 mg, phenylpropanolamine 10 mg, brompheniramine 8 mg, phenylephrine and phenylpropanolamine, phenylephrine and brompheniramine, phenylpropanolamine and brompheniramine, and phenylephrine with phenylpropanolamine and brompheniramine and placebo. 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. Changes in NAR were not statistically significant between the four treatments including phenylephrine and the four treatments without phenylephrine. Phenylephrine alone was not compared to the other groups.

Bickerman [1971] evaluated the efficacy of oral phenylephrine 10 mg, pseudoephedrine 60 mg and phenylpropanolamine 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 pseudoephedrine and phenylpropanolamine but not pseudoephedrine reduced NAR from 30 minutes to 4 hours post dose. No subjective assessments of nasal congestion were made.

Study AHR-4010-3 is considered supportive. It was a randomized, 6-center, multiple-dose, double-blind, parallel group study conducted in subjects with nasal congestion due to an upper respiratory infection (URI). Subjects took study medication every 4 hours over a 72-hour period. The study evaluated phenylephrine 10 mg, phenylpropanolamine 25 mg, phenylephrine 5 mg plus phenylpropanolamine 12.5 mg, and placebo. Subjective symptom evaluations 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. Both the subject and the investigator provided an overall evaluation of therapeutic effect at the end of the evaluation period. Only subjects enrolled at one study site (site 0401) underwent objective assessments at 15, 30, and 45 minutes, and 1 to 4 hours after the first dose of medication. The study enrolled a total of 274 subjects (ages 18 to 77 years) at 6 sites.

Site 0401 enrolled a total of 48 subjects, with 12 subjects randomized to each of the 4 treatment groups. Phenylephrine 10 mg and phenylpropanolamine 25 mg were found to be statistically significantly better than placebo for NAR at 30 to 180 minutes after the first dose. At this site, phenylephrine 10 mg was statistically significantly better than placebo for subjective symptom assessments at 72 hours.

The pooled data from the remaining 5 sites failed to show significant differences among the 4 treatments for subjective assessments. Nonetheless, based on the NAR outcomes, this study is supportive of the efficacy of phenylephrine 10 mg for nasal congestion.

Table 4.2. Additional Placebo-controlled Studies on the Efficacy of Oral Phenylephrine

Study	Basis of Review	Results/Comments
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 mg (n=16) or 15 mg (n=16) or 25 mg (n=16). Post-dose Obs at 15-120 min	**Positive study.** All active doses significantly reduced NAR compared to PBO. 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. All doses significantly reduced subjective scores of nasal congestion from 30-120 minutes. Mean % reduction in subjective scores paralleled reduction in NAR for each dose.

Table 4.2. Additional Placebo-controlled Studies on the Efficacy of Oral Phenylephrine

Study	Basis of Review	Results/Comments
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 10 mg. Post-dose Obs at 30-240 min	**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 hr) whereas PE did not. No subjective assessments of nasal congestion were made.
Reference 11 McLaurin, 1961	Cross-over study in 88 subjects with nasal congestion due to a variety of causes including colds, sinusitis, allergy, vasomotor rhinitis and hypothyroidism. Compared oral PBO, PE 10 mg, PSE 60 mg, PPA 25 mg and EPH 25 mg. 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.	**Inconclusive study.** PSE did not separate from PBO. Only Ephedrine was found to significantly (p=0.05) lower NAR (38%). No significant differences in subjective assessments between PBO and the other treatment groups at either of the 2 time points. Significant methodologic issues: 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. Serial assessments not performed.
AHR-4010-3 December, 1983	R, PC, DB, parallel, multiple dose (every 4 hours), 3-day study in 274 patients with nasal congestion due to URI of less than 48 hours in duration <u>Treatments (n for NAR)</u> PE 5 mg + PPA 12.5 mg (n=12) PE 10 mg (n=12) PPA 25 mg (n=12) PBO (n=12) <u>Assessments</u> 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	**Supportive study.** Only 1 of 6 sites measured NAR (n=48). PE 10 mg significantly reduced NAR at 30-180 minutes compared to PBO, PE 10 mg was essentially equal to PPA at all time points In the analysis of the subjective assessment for this site, PE was significantly better than PBO for subjects' assessment of stuffy nose at 72 hours. 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 significant treatment-by-site interaction was observed for subject and investigator's overall evaluations at 72 hours. When the site that measured NAR was excluded, pooled data from the remaining 5 sites failed to show significant differences among the four treatments.

Table 4.2. Additional Placebo-controlled Studies on the Efficacy of Oral Phenylephrine

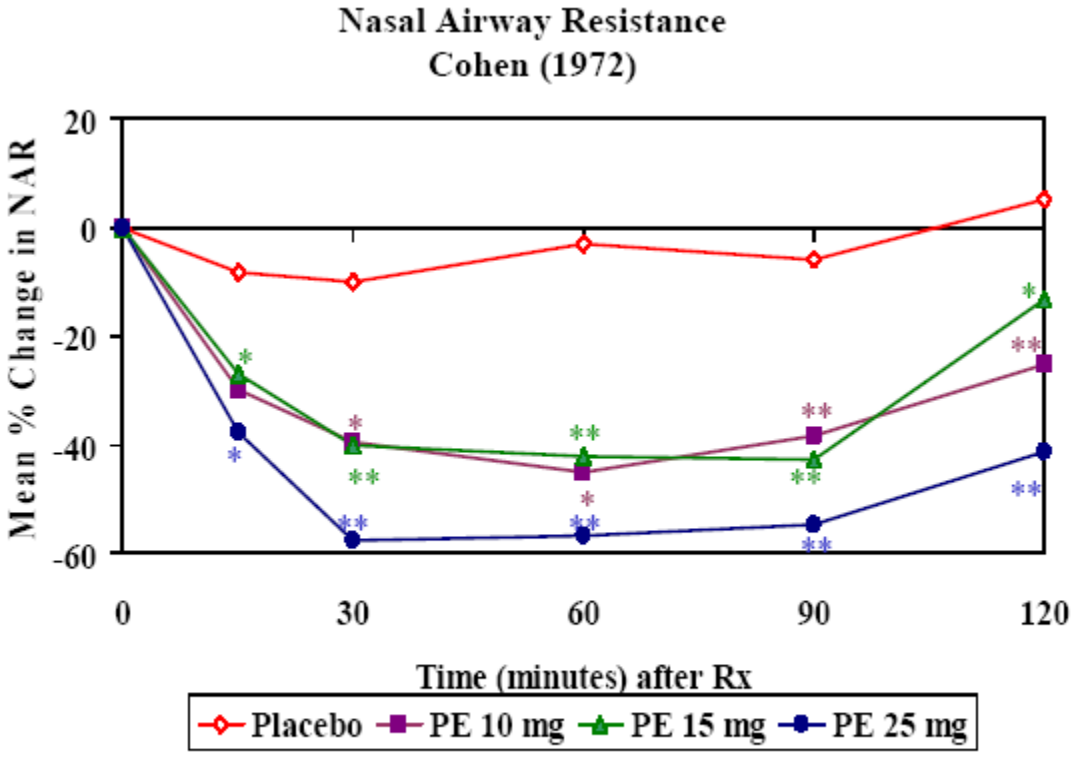
Study	Basis of Review	Results/Comments
AHR Study 7032 November, 1967	R, PC, SB, single dose, single-center crossover, 2 hr evaluation period in 8 subjects with stable or chronic nasal congestion Treatments PBO, PE 10 mg, PPA 10 mg, BROM 8 mg, PE + PPA, PE + BROM, PPA + BROM, PE + PPA + BROM (n=8) Assessments Inspiratory and expiratory NAR (electronic posterior rhinometry) Post-dose Obs at 30-120 min	**Negative Study** PE 10 mg monotherapy produced reductions ($p< 0.10$) in inspiratory and expiratory nasal airway resistances at 1 hour after dosing. Readings at 30 minutes and 2 hours after dosing were numerically better, but not statistically different from placebo.
Schering-Plough study P04579, January-February 2006	R, PC, SB, single dose, single center, 3-way crossover in 38 subjects with SAR. Treatments PBO, PE 12 mg, PSE 60 mg. Assessments Subjective symptom evaluations every 15 min over 6 hr, peak nasal inspiratory flow, NAR from rhinomanometry scores over 6 hours.	**Negative Study** NAR assessed but not reported. Overall reduction of nasal congestion scores from PE (-7.1%) was not different from PBO (-2.2%). PSE average reduction scores (-21.7%) was statistically greater than PBO ($p<0.01$) and PE ($p=0.01$). Authors noted a possible carryover effect.

Abbreviations: R= randomized, DB= double-blind, PC= placebo-controlled, SB= single-blind, PBO= placebo, PE= phenylephrine, PPA= phenylpropanolamine, EPH= ephedrine, PSE= pseudoephedrine, BROM= brompheniramine

4.2.3 Well Controlled Studies Establishing Efficacy of Phenylephrine 10 mg

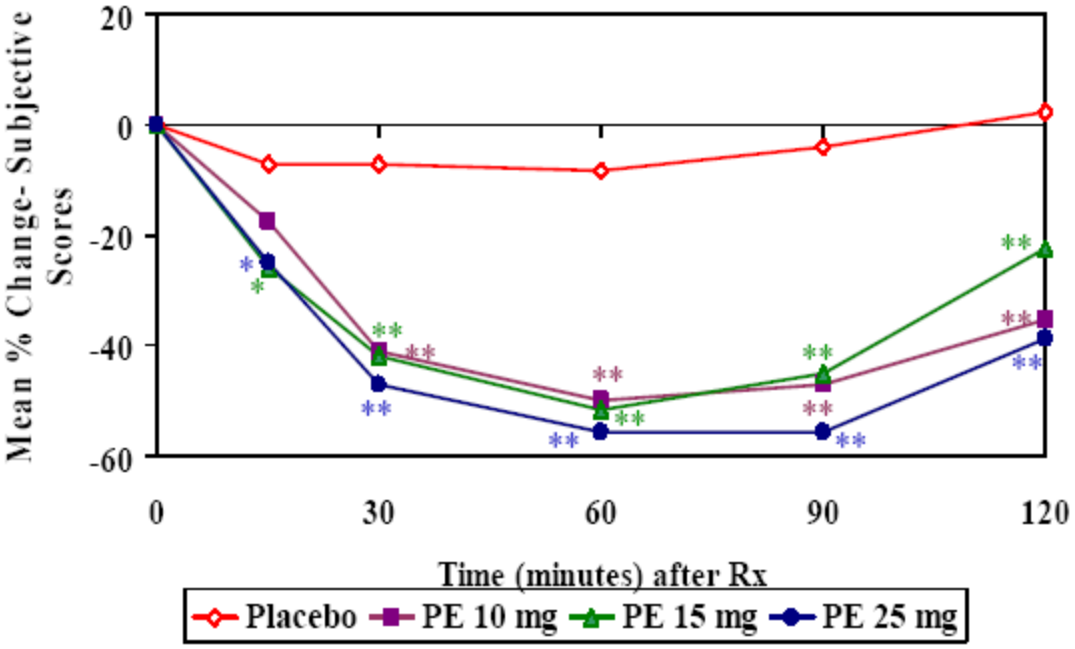
Five well-controlled studies demonstrating the efficacy of oral phenylephrine 10 mg as a nasal decongestant are presented in greater detail.

Cohen [1972] studied the efficacy of phenylephrine in 48 subjects with nasal congestion due to the common cold. This was a double blind, randomized, placebo controlled, incomplete two-way crossover study that tested the effects of phenylephrine 10 mg (n=16), 15 mg (n=16) and 25 mg (n=16) on NAR and improvement of subjective assessment of nasal congestion. Post-dose observations were made at 15 to 120 minutes. All doses of phenylephrine tested showed a significant reduction in NAR and improved subjective scores of nasal congestion compared to placebo. Furthermore, there was somewhat greater reduction in NAR produced by phenylephrine 25 mg compared to 10 mg and 15 mg doses. Subjective symptom scores separated from placebo for all phenylephrine groups, without notable differences between them. This study clearly demonstrates the efficacy of phenylephrine on objective and subjective measures. As mentioned previously, this study was not included in the FDA review in 1976. The results of this study for both objective and subjective endpoints are illustrated below.



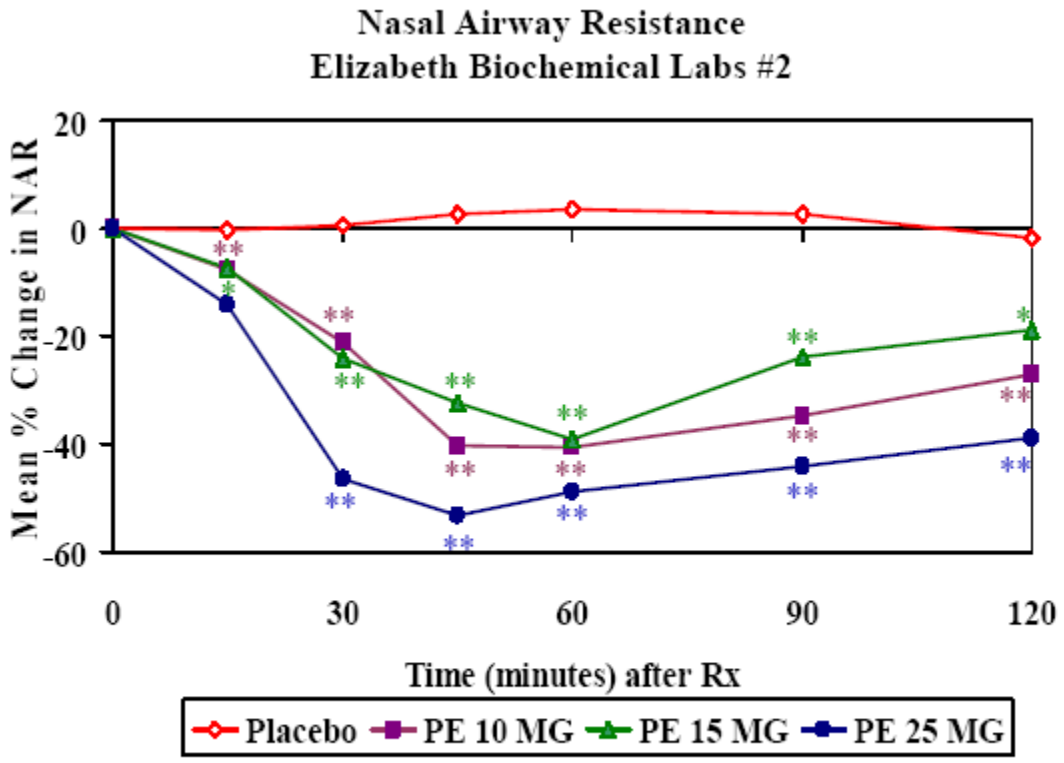
* $p \leq 0.05$; ** $p \leq 0.01$ vs placebo
Note: Statistical testing versus placebo was among only subjects who received that particular dose.

Subjective Scores of Nasal Congestion
Cohen (1972)



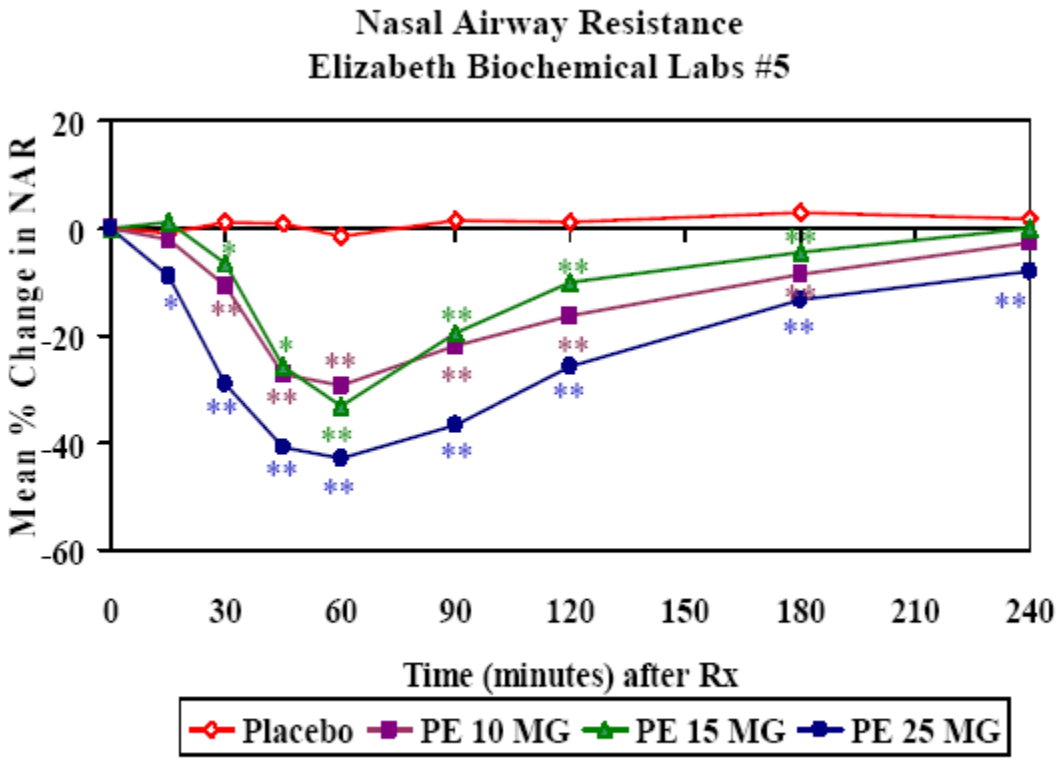
* $p \leq 0.05$; ** $p \leq 0.01$ vs placebo
Note: Statistical testing versus placebo was among only subjects who received that particular dose.

The “Elizabeth #2” study (Ref #7 in: FDA OTC Volume 040298. January 12, 1968) was a randomized, double-blind, placebo-controlled, single-dose, incomplete crossover study in 38 subjects with congestion due to colds, who received oral ephedrine 50 mg (n=6), and phenylephrine 10 mg (n=16), 15 mg (n=10), or 25 mg (n=6). Post-dose observations were made at 15 to 120 minutes. Each active dose statistically separated from placebo. Phenylephrine 10 mg significantly reduced NAR at all time points from 15 minutes through 2 hours (p=0.01). Maximal reduction was 40% at 45 and 60 minutes post dose. Subjective scores for nasal congestion were significantly decreased for phenylephrine 10 mg and 15 mg (p=0.01) and for ephedrine 50 mg (p=0.05) compared to placebo, but not for phenylephrine 25 mg. The results of this study for the objective NAR endpoint are illustrated below.



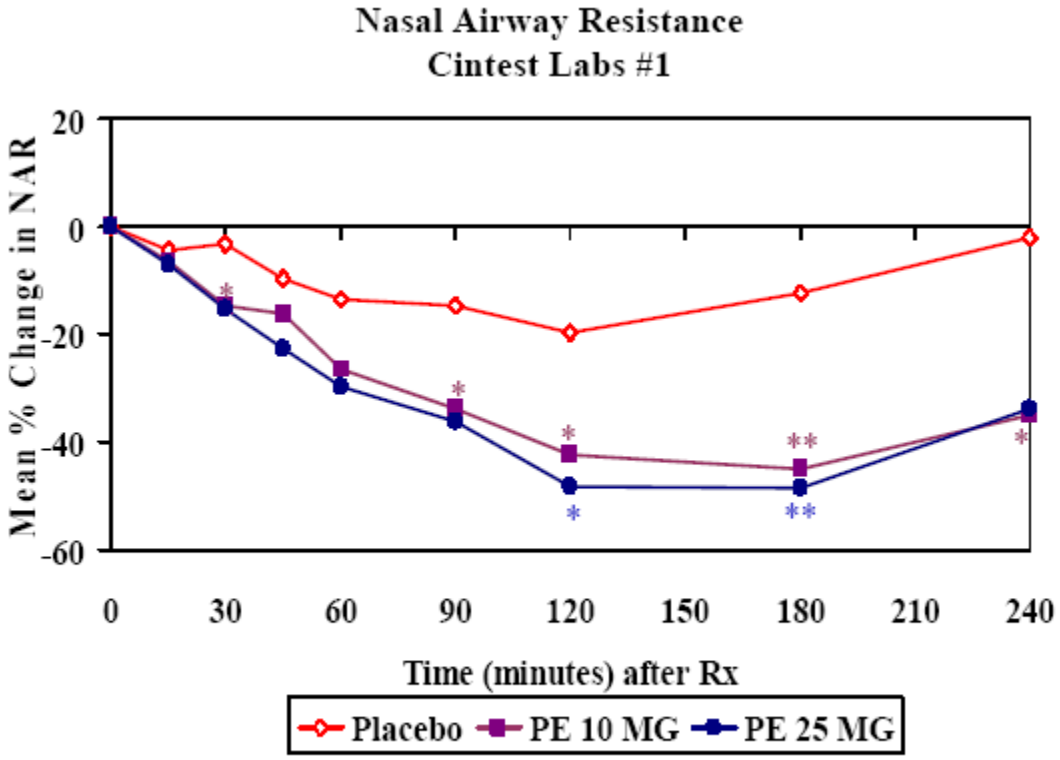
* $p \leq 0.05$; ** $p \leq 0.01$ vs placebo
Note: Statistical testing versus placebo was among only subjects who received that particular dose.

The “Elizabeth #5” study (Ref #10 in: FDA OTC Volume 040298. May 27, 1970) was a randomized, double-blind, placebo-controlled, single-dose, incomplete crossover study in 25 subjects with nasal congestion due to colds. Oral doses of phenylephrine 10 mg (n=10), 15 mg (n=6) and 25 mg (n=9) were studied. Post-dose observations were made at 15 to 240 minutes. NAR decreased significantly in all active groups compared to placebo as early as 30 minutes after dosing and lasted through 180 minutes. The peak effect for phenylephrine 10 mg was at 60 minutes (29% decrease, p=0.01). Only the 25 mg dose significantly reduced subjective scores of nasal congestion. The results of this study for the objective NAR endpoint are illustrated below.



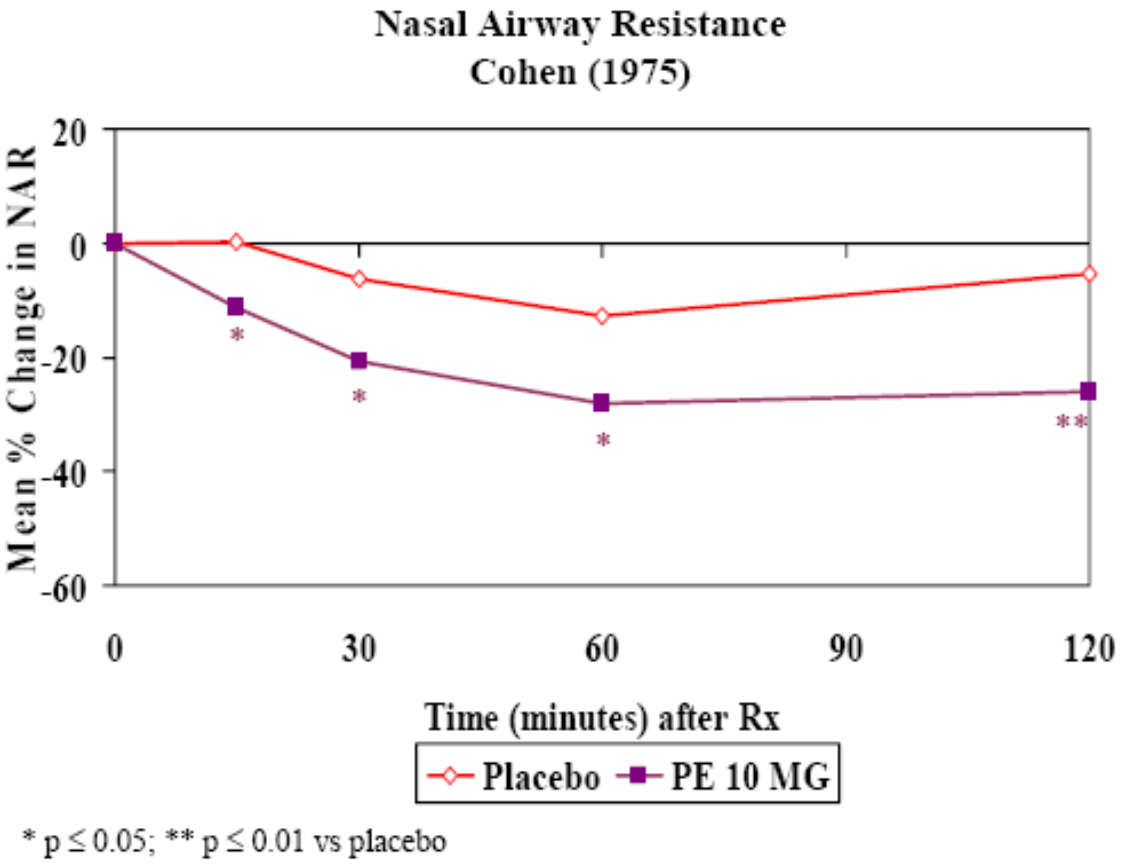
* $p \leq 0.05$; ** $p \leq 0.01$ vs placebo
Note: Statistical testing versus placebo was among only subjects who received that particular dose.

A study performed by Cintest labs, study #1 (Ref #22 in: FDA OTC Volume 040298. April 10, 1969), was a randomized, double-blind, placebo-controlled, single-dose, incomplete crossover study in 47 subjects with congestion due to colds. Treatments studied were phenylephrine 10 mg (n=16) and 25 mg (n=16), phenylpropanolamine 50 mg (n=15), and placebo. Post-dose observations were made from 15 to 240 minutes. All active treatments significantly decreased NAR compared to placebo. Phenylephrine 10 mg produced a significant effect on NAR at 90 to 180 minutes. Phenylephrine 10 mg and phenylpropanolamine 50 mg significantly reduced subjective scores for nasal congestion. The results of this study for the objective NAR endpoint are illustrated below.



* $p \leq 0.05$; ** $p \leq 0.01$ vs placebo
Note: Statistical testing versus placebo was among only subjects who received that particular dose.

In addition to the 4 positive single-dose studies, the efficacy of phenylephrine 10 mg has been established in one multi-dose study. Cohen [1975] performed a randomized, double-blind, placebo-controlled, multi-dose parallel group study of 200 patients with nasal congestion due to head cold. Phenylephrine 10 mg was administered orally every 4 hours for 4 doses. Post-dose observations were made at 15 through 120 minutes for NAR (n=50); subjective assessments continued through 12 hours. Phenylephrine 10 mg produced significant reductions in NAR compared to placebo from 15 to 120 minutes (11 to 28%; $p \leq 0.05$). Changes in subjective symptom scores for phenylephrine were significantly better than placebo for sneezing, runny nose and stuffy nose ($p < 0.05$). The results of this study for the objective NAR endpoint are illustrated below.



* $p \leq 0.05$; ** $p \leq 0.01$ vs placebo

In summary, phenylephrine 10 mg has been demonstrated in multiple randomized, placebo-controlled trials to be effective in relieving nasal congestion in adults.

4.2.4 Meta-analyses of the Phenylephrine Data

The drug approval process relies upon the principle of replication of results from well-designed, placebo-controlled, appropriately powered clinical trials to verify drug efficacy. Multiple clinical trials have demonstrated the efficacy of phenylephrine 10 mg. In addition to individual clinical trials, two meta-analyses of phenylephrine study data have been published. The first, performed by the petitioners [Hatton 2007], showed no beneficial effect of phenylephrine 10 mg. The second meta-analysis was conducted on behalf of CHPA [Kollar 2007] and demonstrated statistically significant efficacy of phenylephrine 10 mg on NAR. Although both analyses were conducted using the data obtained primarily from the same studies, different statistical methodologies were employed and different endpoints were evaluated. The 2 meta-analyses arrived at different conclusions about the efficacy of phenylephrine 10 mg as an oral decongestant. In this section, the meta-analyses are compared, and possible explanations for their different results are explored.

4.2.4.1 Methods and Results

4.2.4.1.1 Study Selection Criteria

Hatton [2007] selected randomized, placebo-controlled clinical trials that evaluated the efficacy of oral phenylephrine as a single agent used as a nasal decongestant for inclusion in the primary analysis. Studies that used combination products or compared phenylephrine with another oral decongestant were excluded. The meta-analysis was performed using aggregated treatment means and standard errors.

To be included in the Kollar analysis [Kollar 2007], studies had to have used a single-dose, randomized, placebo-controlled design with an orally administered product in which phenylephrine at a dose of 10 mg was the single active ingredient. These studies enrolled adult patients with acute nasal congestion due to the common cold; had the efficacy end point of NAR; and contained sufficient data in the study report (i.e., individual data for each patient and/or treatment group means and standard error of the mean, SE) to allow reanalysis and/or meta-analysis of phenylephrine 10 mg versus placebo. Studies not meeting these criteria were excluded. Meta-analyses were performed using individual data for each patient.

Both meta-analyses included the same seven studies with the exception of a randomized, parallel-group study [Cohen 1975], which Hatton included in the meta-analysis. Although Kollar analyzed this study separately, the results were not included in their meta-analysis due to its different (parallel) design.

4.2.4.1.2 Consideration of Endpoints

In the Hatton meta-analysis the sole endpoint that was analyzed was the maximum percentage reduction in NAR during the first 120 minutes after dosing (the most commonly studied period in the studies). Based on this endpoint, Hatton concluded that phenylephrine 10 mg was ineffective as an oral nasal decongestant.

While understanding a drug's maximum effect is one measure of clinical interest, more clinically relevant endpoints to evaluate are those that examine treatment response over time. Such a time-point analysis is in accordance with the FDA Guidance for Industry on allergic rhinitis [FDA 2000]. This was the approach used in the Kollar meta-analysis, which analyzed the treatment effect of phenylephrine at all available time-points (from 15 to 120 minutes after dosing in the 7 studies, and up to 240 minutes after dosing in 5 studies). This analysis showed that phenylephrine 10 mg was significantly more effective than placebo at 30, 60 and 90 minutes.

In order to possibly explain the differences between the two analyses, CHPA attempted to replicate the Hatton meta-analysis using the same data and the identical statistical methodology, evaluating both the maximal effect variable used by Hatton and the endpoints used by Kollar. Rather than re-analyzing all the individual time points, a single endpoint that best combines the results of the individual time points is area-under-the-curve (AUC), which essentially averages the results over the individual time points. Because the treatment effect over time is derived from multiple assessments, it is less variable, and therefore more sensitive, than the maximum effect, which is derived from a single assessment that can occur at different times (see AUC methodology description in appendix 1). Using the maximum effect endpoint yielded point estimates that differed slightly from those reported by Hatton, but only by approximately 2%, with a p-value of 0.15 (no significant treatment effect for phenylephrine 10 mg). When AUC was used as the endpoint, it yielded a p-value of 0.02 (significant treatment effect for phenylephrine 10 mg). Since the endpoint was the only difference between the two meta-analyses, these results indicate that the clinical endpoint selected is the major factor for the difference in conclusions between the Hatton and Kollar meta-analyses.

4.2.5 Examination of Dose-Response Across Studies

Where data were available, further examination was undertaken of the studies to determine whether a dose-response relationship could be demonstrated for phenylephrine.

The efficacy of a 10 mg dose of phenylephrine was compared to a 25 mg dose in the 4 studies in which model sensitivity was demonstrated (i.e., the positive studies versus placebo). The doses were compared based on their relative effects over placebo, where the

effect was based on the AUC of the percent NAR improvement over baseline. In 3 of the studies, the effects were compared by analysis of covariance with dose and treatment as fixed effects, baseline NAR as a covariate, and subject as a repeated measure (each subject received placebo and either phenylephrine 10 mg or phenylephrine 25 mg). The fourth study [Cohen 1972], provided neither raw data nor summary data to estimate standard errors; so only the effect size estimates are presented. Table 4.3 shows the results.

Table 4.3. Comparison of % Change in NAR (AUC) PE 10 mg versus PE 25 mg

	PE 10 mg	PE 25 mg	Difference (PE 25 mg – PE 10 mg)	
Study	LS Mean % change in AUC ± S.E.	LS Mean % change in AUC ± S.E.	LS Mean % change in AUC ± S.E.	p
Elizabeth #2	29.3 ± 3.6	38.8 ± 5.9	9.4 ± 6.9	0.19
Cintest #1	11.6 ± 6.0	9.9 ± 6.0	-1.7 ± 8.4	0.84
Elizabeth #5	18.1 ± 2.5	31.0 ± 2.7	12.9 ± 3.7	0.003
Cohen (1972)*	31.7	38.6	6.9	

*The article provided insufficient information to compute standard errors

In summary, these results show that in only one study was there a statistically significant difference between the 10 mg and 25 mg treatment groups. Thus the evidence is insufficient to conclude that 25 mg is a more effective dose. While suggestive of some incremental response with increasing doses of phenylephrine, limited data comparing phenylephrine 10 mg against higher doses do not strongly support the presence of a dose-response for reduction in NAR or improvement in symptoms of nasal congestion. Only one [Elizabeth #5 1970] of the 4 studies demonstrated improved subjective response when the dose was increased to 25 mg. Doses greater than phenylephrine 10 mg do not consistently produce greater decongestant effect as measured by NAR.

4.3 Overall Efficacy Conclusions

There is substantial evidence for efficacy of phenylephrine 10 mg in the symptomatic treatment of nasal congestion, from studies using objective measures (NAR) and the subjective measures of symptom improvement. Of the 18 studies presented above evaluating phenylephrine for nasal congestion, 8 studies show benefit of phenylephrine in doses ranging from 5 mg to 25 mg on both objective and subjective measures. In particular, 5 randomized, placebo-controlled, clinical trials found phenylephrine 10 mg to be superior to placebo on objective measures of NAR. Furthermore, 4 of those studies also demonstrated statistically significant improvements in subjective symptoms of nasal congestion. Several of these studies also included a positive control that separated from placebo, establishing the sensitivity of the assay.

As supportive data, the meta-analysis conducted by Kollar, which evaluated outcomes at multiple time points, demonstrated that phenylephrine 10 mg was superior to placebo. When the analysis performed by the petitioners was repeated including an AUC endpoint, the results confirmed that phenylephrine 10 mg was superior to placebo.

Finally, there is insufficient evidence to support the assertion that increasing the dose of phenylephrine to 25 mg will produce improvements in decongestant effects.

4.4 Reference List

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5.0 SAFETY REVIEW OF PHENYLEPHRINE

Key Points

- Phenylephrine 10 mg has an acceptable safety profile and is an appropriate oral nasal decongestant for OTC use. The safety of phenylephrine 10 mg in adults has been demonstrated based on data from placebo-controlled clinical trials and from post-marketing data.

- Fifteen of 20 placebo-controlled studies have reported safety data.

    - Of 8 studies collecting data on adverse events, 4 studies reported no adverse events in subjects treated with single or multiple doses of phenylephrine ranging from 5 to 25 mg. While most adverse events reported by phenylephrine-treated subjects were reported at a frequency similar to placebo-treated subjects, nervousness was reported more frequently with phenyleprine 15 mg and 25 mg than with phenylephrine 10 mg or placebo.

    - Fifteen studies collected data on vital signs for phenylephinre doses ranging from 5 mg to 100 mg. Many studies reported no change in vital signs for various doses of phenylephrine at various time points, and both increases and decreases for pulse and blood pressure were observed.

        - In studies that included a 10 mg phenylephrine dose, there was no discernible relationship between changes in pulse and blood pressure, nor was there a clear pattern of vital sign changes at different time points.

        - Statistically significant differences from placebo in pulse were reported more frequently with doses of phenylephrine greater than 10 mg; some of the largest mean increases from baseline in pulse were observed with phenylephrine 25 mg. Mean increases from baseline in systolic blood pressure were larger with increasing phenylephrine dose. However, all mean increases in pulse compared to baseline were $\leq$ 11 beats per minute and mean increases in blood pressure compared to baseline were less than 5 mm Hg and may not be clinically relevant.

- These results support that the current adult dose of phenylephrine 10 mg in the OTC monograph is well tolerated.

5.1 Summary of Safety of Phenylephrine from Placebo-Controlled Trials

5.1.1 OTC Expert Advisory Review Panel Report Published in 1976

A review of oral phenylephrine safety and efficacy as a nasal decongestant was published in 1976 as part of the establishment of the OTC drug monograph for cold, cough, allergy, bronchodilator and antiasthmatic drug products [FDA 1976]. There were 9 placebo-controlled studies discussed in the expert advisory panel review of safety [Memo to Bird from Stander 1968, Memo to Luduena from Stander 1967, Memo to Hulme from Bird 1968, Memo to Lands from Luduena 1959, Elizabeth #1 1967, Elizabeth #2 1968, Elizabeth #3 1969, Elizabeth #4 1969, Elizabeth #5 1970, McLaurin 1961]. The OTC expert advisory review panel concluded that phenylephrine hydrochloride was safe and effective as an oral decongestant for OTC use.

The OTC expert advisory review panel stated the following: “Clinical experience has confirmed that phenylephrine hydrochloride is safe in the dosage ranges used as an oral nasal decongestant. Keys and Violante reported that oral doses of 40 to 60 mg phenylephrine are necessary for consistent clinically meaningful cardiovascular effects such as increased diastolic pressure and reflex cardiac slowing [Keys 1942]. Various reports reinforce the impression that in normal volunteers, blood pressure and pulse rate responses to 10 to 15 mg oral doses are equal to or only minimally greater than placebo. The maximum blood pressure increase does not exceed 2 to 7 mm Hg and the pulse rate changes do not exceed ± 6 beats/minute. At doses of 25 mg, blood pressure increases up to 7 mm Hg and pulse changes of ± 4 to 13 beats per minute were occasionally noted at some time intervals [Keys 1942, Memo to Bird from Stander 1968, Memo to Luduena from Stander 1967, Memo to Hulme from Bird 1968, Memo to Lands from Luduena 1959, Elizabeth #1 1967, Elizabeth #2 1968, Elizabeth #3 1969, Elizabeth #4 1969, Elizabeth #5 1970, McLaurin 1961].”

The following was noted by the expert advisory review panel concerning side effects in the central nervous system: “Overtly perceived side effects at 10 mg doses approximate the incidence and pattern of a placebo response, whereas 15 to 25 mg doses are associated with an increasing incidence of symptoms related to mild central nervous system stimulation [Keys 1942].”

5.1.2 Current Review of Placebo-Controlled Trials

Twenty placebo-controlled studies of phenylephrine in adults have been identified. This includes 9 placebo-controlled studies discussed in the 1976 OTC panel report of safety [Memo to Bird from Stander 1968, Memo to Luduena from Stander 1967, Memo to Hulme

from Bird 1968, Memo to Lands from Luduena 1959, Elizabeth #1 1967, Elizabeth #2 1968, Elizabeth #3 1969, Elizabeth #4 1969, Elizabeth #5 1970, McLaurin 1961], 4 additional studies with safety data that were included in the discussion of effectiveness in the 1976 review [Huntingdon #2 1969, Cintest #2 1970, Cintest #3 1970, Cohen 1975], 2 studies also discussed in the OTC review of effectiveness that lacked safety data [Cintest #1 1969, Huntingdon #1 1969], and an additional 5 studies [Cohen 1972, Schering Plough 2006, Bickerman 1971, AHR-4010-3 1983, AHR-7032 1967]. These 20 placebo-controlled studies are identified below in Table 5.1. Safety data were reported in 15 of these 20 studies. Safety data included adverse event data and group-level information on vital signs measurements of pulse rate, systolic blood pressure, and diastolic blood pressure. The type of information provided by each study is listed in Table 5.1. Adverse event reporting was included in 8 of these studies. Changes in vital signs were reported in 15 of these studies. A summary of each of the 20 studies is provided in Appendix 2.

Table 5.1. Availability of Safety Data From Placebo-Controlled Studies

Study	Adverse Event Data	Vital Signs Data
Memo to Bird from Stander 1968 [Ref 2][a], Memo to Hulme from Bird 1968 [Ref 4]	No	Yes (Pulse, SBP, DBP)
Memo to Luduena from Stander 1967 [Ref 3]	No	Yes (Pulse, SBP, DBP)
Memo to Lands from Luduena 1959 [Ref 5]	No	Yes (Pulse, SBP, DBP)
Elizabeth Study #1 1967 [Ref 6]	No	No
Elizabeth Study #2 1968 [Ref 7]	No	No
Elizabeth Study #3 1969 [Ref 8]	Yes	Yes (Pulse, SBP, DBP)
Elizabeth Study #4 1969 [Ref 9]	No	Yes (Pulse, SBP, DBP)
Elizabeth Study #5 1970 [Ref 10]	No	Yes (Pulse, SBP, DBP)
McLaurin et al 1961 [Ref 11]	Yes	Yes (Pulse, SBP)
Huntingdon Study #2 1969 [Ref 21]	Yes	Yes (Pulse, SBP, DBP)
Cintest Study #2 1970 [Ref 23]	No	Yes (Pulse, SBP, DBP)
Cintest Study #3 1970 [Ref 24]	No	Yes (Pulse, SBP, DBP)
Cohen BM 1975 [Ref 26]	Yes	Yes (SBP, DBP)
Cintest Study #1 1969 [Ref 22]	No	No
Huntingdon Study #1 1969 [Ref 20]	No	No
Cohen BM 1972	Yes	Yes (Pulse, SBP, DBP)
Schering-Plough Study P04579 2006	Yes	Yes (not stated)
Bickerman 1971	No	No
AHR-4010-3 1983	Yes	Yes (Pulse, SBP, DBP)
AHR-7032 1967	Yes	Yes (Pulse, SBP, DBP)

a: Reference numbers provided in brackets are from 1976 OTC expert advisory review panel
Abbreviations: DBP = diastolic blood pressure, SBP = systolic blood pressure.

5.1.2.1 Summary of Adverse Events

Reporting of adverse events was provided in 8 of the 15 studies reporting safety data [McLaurin 1961, Huntingdon #2 1969, Elizabeth #3 1969, Cohen 1972, Cohen 1975, Schering Plough 2006, AHR-4010-3 1983, AHR-7032 1967]. Four of the studies reported

no adverse events in subjects treated with single doses of phenylephrine ranging from 5 mg to 25 mg [Huntingdon #2 1969, Schering Plough 2006, Elizabeth #3 1969, AHR-7032 1967].

In the other 4 studies that reported adverse events, specific adverse events reported by subjects treated with phenylephrine 10 mg included feeling warm, dizzy, extrasystoles, flushing, nasal dryness, slightly shaky, dry mouth, lightheadedness, and nausea [Cohen 1972, Cohen 1975, McLaurin 1961, AHR-4010-3 1983]. Specific adverse events reported by subjects treated with phenylephrine 15 mg included dry nose, nervousness, and lightheadedness [Cohen 1972]. Specific adverse events reported by subjects treated with phenylephrine 25 mg included dry mouth, dry nose, circumoral paresthesias, irritability, nervousness, malaise, lightheadedness, breathlessness, and gaseousness [Cohen 1972].

In a multiple-dose parallel study of 200 subjects [Cohen 1975], numerically fewer phenylephrine 10 mg-treated subjects (8%) reported adverse events compared to placebo-treated subjects (11%). In a single-dose study [Cohen 1972], the number of adverse events appeared dose-dependent with 12.5% of phenylephrine 10 mg-treated subjects reporting adverse events, a rate comparable to the 12.5% of placebo-treated subjects reporting adverse events, compared with 43.8% of phenylephrine 15 mg-treated subjects, and 81.25% of phenylephrine 25 mg-treated subjects. Adverse events reported by more than one subject in any phenylephrine dose group included circumoral paresthesias (2 phenylephrine 25 mg-treated subjects), malaise (2 phenylephrine 25 mg-treated subjects), and nervousness (6 phenylephrine 15 mg-treated subjects, 5 phenylephrine 25 mg-treated subjects, and 1 placebo-treated subject). In a multiple-dose study [McLaurin 1961] where subjects were treated with one dose in the clinic and another dose at bedtime, the percent of subjects reporting nervousness was less with phenylephrine 10 mg (37%) than with ephedrine 25 mg (71%), pseudoephedrine 60 mg (53%), and placebo (42%), but not phenylpropanolamine 25 mg (26%). In this study, placebo-treated subjects reported the largest numbers of cases of headache (11), dizzy and lightheadedness (10), and drowsiness (9), while phenylephrine 10 mg-treated subjects reported the largest number of cases of nausea (8).

In summary, 3 of the 8 studies that reported adverse events were dose-ranging studies. Of these 3 studies, 2 reported no adverse events with phenylephrine 5 mg, 15 mg, and 25 mg [Elizabeth #3 1969] and phenylephrine 10 mg and 20 mg [Huntingdon #2 1969]. The third study [Cohen 1972] evaluated phenylephrine 10 mg, phenylephrine 15 mg, and phenylephrine 25 mg. In this study, nervousness was reported more frequently with phenylephrine 15 mg and 25 mg than with phenylephrine 10 mg or placebo [Cohen 1972].

5.1.2.2 Summary of Vital Signs

Vital signs were assessed in all 15 studies that reported safety data. Results are presented below individually by the specific vital sign assessed (pulse, systolic blood pressure, diastolic blood pressure).

5.1.2.2.1 Pulse

A summary of the results for pulse is provided by study in Table 5.2. Pulse was specified as being evaluated in 13 of 15 studies that reported safety data. Pulse was not evaluated by Cohen in 1975. In the Schering Plough study, the vital signs assessed were not specified, although it was stated that no treatment differences were observed in vital signs.

In 3 of the 13 studies that evaluated pulse, no statistically significant differences in pulse were observed in subjects treated with single and multiple doses of phenylephrine ranging from 10 mg to 75 mg versus placebo [Cintest #2 1970, McLaurin 1961, Lands from Luduena 1959]. In 2 studies, it was indicated that there was no clinically relevant effect of treatment on pulse [AHR-4010-3 1983, AHR-7032 1967].

Of the 8 dose-ranging studies that reported statistically significant differences in pulse between phenylephrine and placebo, 3 studies [Huntingdon #2 1969, Bird from Stander 1968, Luduena from Stander 1967] reported a decrease in pulse at phenylephrine doses ranging from 10 mg to 100 mg, 4 studies [Elizabeth #5 1970, Cintest #3 1970, Cohen 1972, Elizabeth #4 1969] reported increases at doses ranging from 5 mg to 25 mg, and 1 study [Elizabeth #3 1969] reported both increases and decreases at doses ranging from 5 mg to 25 mg. When statistically significant mean differences from placebo in pulse were reported, mean decreases from baseline ranged from 2.29 to 11.54 beats per minute and mean increases from baseline ranged from 0.71 to 11 beats per minute. A greater number of statistically significant increases compared to placebo were reported with phenylephrine 25 mg than with lower doses of phenylephrine. In addition, some of the largest mean increases from baseline were observed with 25 mg of phenylephrine. All mean increases from baseline in pulse were $\leq$ 11 beats per minute. These changes were relatively small and may not be clinically relevant.

Table 5.2. Summary of Evaluation of Pulse – Comparisons Versus Placebo

Study	Time (min)						
Drug and Dose	15	30	60	90	120	180	240
Bird from Stander 1968							
PE 15 mg	NS	S↓	NS	--	NS	--	--
PE 20 mg	NS	NS	NS	--	NS	--	--
PE 25 mg	NS	S↓	NS	--	NS	--	--
PPA 50 mg	NS	NS	NS	--	NS	--	--
Luduena from Stander 1967							
PE 10 mg	NS	NS	NS	--	NS	--	--
PE 25 mg	NS	NS	S↓	--	NS	--	--
PE 50 mg	NS	NS	S↓	--	NS	--	--
PE 100 mg	NS	S↓	S↓	--	NS	--	--
Lands from Luduena 1959[a]							
PE 10, 25, 50, 75 mg, and PPA 25, 50 mg	--	--	NS	--	NS	--	--
Elizabeth #3 1969							
PE 5 mg	--	S↑	NS	S↑	NS	NS	NS
PE 15 mg	--	NS	NS	NS	NS	NS	NS
PE 25 mg	--	S↑	NS	NS	NS	NS	S↓
PPA 50 mg	--	NS	NS	NS	NS	NS	NS
Elizabeth #4 1969							
PE 15 mg	--	NS	NS	NS	NS	NS	NS
PE 20 mg	--	NS	NS	NS	S↑	S↑	NS
PE 25 mg	--	NS	NS	NS	NS	S↑	NS
Elizabeth #5 1970							
PE 10 mg	--	NS	NS	NS	S↑	NS	NS
PE 15 mg	--	NS	S↑	S↑	NS	NS	NS
PE 25 mg	--	S↑	NS	S↑	S↑	S↑	S↑
McLaurin 1961							
PE 10 mg, Eph 25 mg, PSE 60 mg, and PPA 25 mg	--	--	NS	--	--	--	--
Huntingdon #2 1969							
PE 10 mg	--	NS	NS	S↓	NS	NS	NS
PE 20 mg	--	NS	NS	NS	NS	NS	NS
Cintest #2 1970							
PE 10, 15, and 20 mg	--	NS	NS	NS	NS	NS	NS
Cintest #3 1970							
PE 10 mg	--	NS	NS	NS	NS	--	--
PE 15 mg	--	NS	NS	S↑	NS	--	--
PE 25 mg	--	NS	NS	NS	NS	--	--
Cohen 1972							
PE 10 mg	NS	S↑	NS	S↑	S↑	--	--
PE 15 mg	NS	S↑	NS	NS	NS	--	--
PE 25 mg	NS	S↑	S↑	S↑	S↑	--	--
Schering Plough[b] 2006							
PE 12 mg, PSE 60 mg							
AHR-4010-3 1983							
PE 10 mg, PPA 25 mg, and PE 5 mg + PPA 12.5 mg	NCR	NCR	NCR	--	NCR	--	NCR
AHR-7032 1967							
PE 10 mg, PPA 10 mg, BR 8 mg, and 4 combination products	--	NCR	NCR	--	NCR	--	--

a: Also no significant differences at 5 hours post dose.
b: No treatment differences were observed in vital signs. No additional detail provided.
Abbreviations: BR = brompheniramine, Eph = ephedrine, NCR = not clinically relevant, NS = not significant, PE = phenylephrine, PPA = phenylpropanolamine, PSE = pseudoephedrine, S = statistically significant compared to placebo, -- = not assessed at that time point, ↓ = decrease compared to baseline, ↑ = increase compared to baseline

5.1.2.2.2 Systolic Blood Pressure

A summary of the results for systolic blood pressure is provided by study in Table 5.3. Systolic blood pressure was specified as being evaluated in 14 of the 15 studies that reported safety data. In the Schering Plough study, the vital signs assessed were not specified, although it was stated that no treatment differences were observed in vital signs.

In 7 of the 14 studies that evaluated systolic blood pressure, no statistically significant differences were observed in systolic blood pressure in subjects treated with single and/or multiple doses of phenylephrine ranging from 10 mg to 75 mg versus placebo [Cintest #2 1970, Cohen 1975, McLaurin 1961, Cohen 1972, Elizabeth #4 1969, Lands from Luduena 1959, Bird from Stander 1968]. In 2 studies, it was indicated that there was no clinically relevant effect of treatment on systolic blood pressure [AHR-4010-3 1983, AHR-7032 1967].

There were 5 studies that reported statistically significant differences in systolic blood pressure between phenylephrine and placebo, of which 2 [Huntingdon #2 1969, Cintest #3 1970] reported decreases in systolic blood pressure at phenylephrine doses ranging from 10 mg to 25 mg while 3 [Elizabeth #3 1969, Elizabeth #5 1970, Luduena from Stander 1967] reported increases at doses ranging from 5 mg to 100 mg. When statistically significant mean differences from placebo in systolic blood pressure were reported, mean decreases from baseline ranged from 1.08 to 2.26 mm Hg and mean increases from baseline ranged from 1.25 to 4.38 mm Hg. While mean increases in systolic blood pressure were larger with increasing dose, all mean increases in blood pressure compared to baseline were less than 5 mm Hg and may not be clinically relevant.

Table 5.3. Summary of Evaluation of Systolic Blood Pressure – Comparisons Versus Placebo

Study Drug and Dose	Time (min) 15	30	60	90	120	180	240
Bird from Stander 1968							
PE 15 mg	NS	NS	NS	--	NS	--	--
PE 20 mg	NS	NS	NS	--	NS	--	--
PE 25 mg	NS	NS	NS	--	NS	--	--
PPA 50 mg	NS	NS	S↑	--	S↑	--	--
Luduena from Stander 1967							
PE 10 mg	NS	NS	NS	--	NS	--	--
PE 25 mg	NS	NS	NS	--	NS	--	--
PE 50 mg	NS	NS	NS	--	NS	--	--
PE 100 mg	NS	S↑	S↑	--	NS	--	--
Lands from Luduena 1959[a]							
PE 10, 25, 50, 75 mg, and PPA 50 mg	--	--	NS	--	NS	--	--
PPA 50 mg	--	--	S↑	--	S↑	--	--
Elizabeth #3 1969							
PE 5 mg	--	NS	NS	NS	S↑	NS	NS
PE 15 mg	--	NS	NS	NS	S[b]	NS	NS
PE 25 mg	--	NS	NS	NS	NS	NS	NS
PPA 50 mg	--	S↑	S↑	S↑	S↑	NS	NS
Elizabeth #4 1969							
PE 15, 20, 25 mg	--	NS	NS	NS	NS	NS	NS
Elizabeth #5 1970							
PE 10 mg	--	NS	S↑	S↑	S↑	S↑	NS
PE 15 mg	--	NS	NS	S↑	NS	NS	NS
PE 25 mg	--	NS	S↑	S↑	S↑	NS	S↑
McLaurin 1961							
PE 10 mg, Eph 25 mg, PSE 60 mg, and PPA 25 mg	--	--	NS	--	--	--	--
Huntingdon #2 1969							
PE 10 mg	--	NS	NS	NS	NS	S↓	NS
PE 20 mg	--	NS	NS	NS	NS	NS	NS
Cintest #2 1970							
PE 10, 15, and 20 mg	--	NS	NS	NS	NS	NS	NS
Cintest #3 1970							
PE 10 mg	--	NS	NS	NS	NS	--	--
PE 15 mg	--	NS	S↓	NS	NS	--	--
PE 25 mg	--	NS	S↓	NS	NS	--	--
Cohen 1975							
PE 10 mg	NS	NS	NS	--	NS	--	--
Cohen 1972							
PE 10, 15, and 25 mg	NS	NS	NS	NS	NS	--	--
Schering Plough[c] 2006							
PE 12 mg, PSE 60 mg							
AHR-4010-3 1983							
PE 10 mg, PPA 25 mg, and PE 5 mg + PPA 12.5 mg	NCR	NCR	NCR	--	NCR	--	NCR
AHR-7032 1967							
PE 10 mg, PPA 10 mg, BR 8 mg, and 4 combination products	--	NCR	NCR	--	NCR	--	--

a: Also no significant differences at 5 hours post dose.

b: Mean SBP for PE 15 mg did not change from baseline but was significantly different from placebo because mean SBP for placebo decreased.

c: No treatment differences were observed in vital signs. No additional detail provided.

Abbreviations: BR = brompheniramine, Eph = ephedrine, NCR = not clinically relevant, NS = not significant, PE = phenylephrine, PPA = phenylpropanolamine, PSE = pseudoephedrine, S = statistically significant compared to placebo, -- = not assessed at that time point, ↓ = decrease compared to baseline, ↑ = increase compared to baseline

5.1.2.2.3 Diastolic Blood Pressure

A summary of the results for diastolic blood pressure is provided by study in Table 5.4. Diastolic blood pressure was specified as being evaluated in 13 of 15 studies that reported safety data. Diastolic blood pressure was not evaluated by McLaurin in 1961. In the Schering Plough study, the vital signs assessed were not specified, although it was stated that no treatment differences were observed in vital signs.

In 4 of the 13 studies that evaluated diastolic blood pressure, no statistically significant differences were observed in diastolic blood pressure in subjects treated with single and/or multiple doses of phenylephrine ranging from 10 mg to 100 mg versus placebo [Cintest #2 1970, Cohen 1975, Lands from Luduena 1959, Luduena from Stander 1967]. In 2 studies, it was indicated that there was no clinically relevant effect of treatment on diastolic blood pressure [AHR-4010-3 1983, AHR-7032 1967].

There were 7 studies that reported statistically significant differences in diastolic blood pressure between phenylephrine and placebo, of which 4 [Huntingdon #2 1969, Cintest #3 1970, Cohen 1972, Elizabeth #4 1969] reported decreases in diastolic blood pressure at phenylephrine doses ranging from 15 mg to 25 mg, while 3 [Elizabeth #3 1969, Elizabeth #5 1970, Bird from Stander 1968] reported increases at phenylephrine doses ranging from 5 mg to 25 mg. When statistically significant mean differences from placebo in diastolic blood pressure were reported, mean decreases from baseline ranged from 0.7 to 3.25 mm Hg and mean increases from baseline ranged from 0.80 to 2.29 mm Hg. All mean increases in blood pressure compared to baseline were less than 5 mm Hg and may not be clinically relevant.

Table 5.4. Summary of Evaluation of Diastolic Blood Pressure – Comparisons Versus Placebo

Study	Time (min)						
Drug and Dose	15	30	60	90	120	180	240
Bird from Stander 1968							
PE 15 mg	NS	NS	NS	--	S↑	--	--
PE 20 mg	NS	NS	NS	--	NS	--	--
PE 25 mg	NS	NS	NS	--	NS	--	--
PPA 50 mg	NS	NS	NS	--	NS	--	--
Luduena from Stander 1967							
PE 10, 25, 50, 100 mg	NS	NS	NS	--	NS	--	--
Lands from Luduena 1959[a]							
PE 10, 25, 50, 75 mg, and PPA 25, 50 mg	--	--	NS	--	NS	--	--
Elizabeth #3 1969							
PE 5 mg	--	NS	NS	S↑	NS	NS	NS
PE 15 mg	--	NS	NS	NS	S↑	NS	NS
PE 25 mg	--	NS	NS	NS	NS	NS	NS
PPA 50 mg	--	NS	S↑	S↑	NS	NS	NS
Elizabeth #4 1969							
PE 15 mg	--	NS	NS	NS	NS	NS	NS
PE 20 mg	--	NS	NS	NS	NS	NS	NS
PE 25 mg	--	NS	NS	NS	S↓	NS	NS
Elizabeth #5 1970							
PE 10 mg	--	NS	S↑	S↑	NS	NS	NS
PE 15 mg	--	NS	NS	NS	NS	NS	NS
PE 25 mg	--	NS	NS	NS	NS	NS	NS
Huntingdon #2 1969							
PE 10 mg	--	NS	NS	NS	NS	NS	NS
PE 20 mg	--	NS	NS	NS	NS	NS	S↓
Cintest #2 1970							
PE 10, 15, and 20 mg	--	NS	NS	NS	NS	NS	NS
Cintest #3 1970							
PE 10 mg	--	NS	NS	NS	NS	--	--
PE 15 mg	--	NS	NS	NS	NS	--	--
PE 25 mg	--	NS	NS	S↓	S[b]	--	--
Cohen 1975							
PE 10 mg	NS	NS	NS	--	NS	--	--
Cohen 1972							
PE 10 mg	NS	NS	NS	NS	NS	--	--
PE 15 and 25 mg[c]						--	--
Schering Plough[d] 2006							
PE 12 mg, PSE 60 mg							
AHR-4010-3 1983							
PE 10 mg, PPA 25 mg, and PE 5 mg + PPA 12.5 mg	NCR	NCR	NCR	--	NCR	--	NCR
AHR-7032 1967							
PE 10 mg, PPA 10 mg, BR 8 mg, and 4 combination products	--	NCR	NCR	--	NCR	--	--

a: Also no significant differences at 5 hours post dose.

b: Mean DBP for PE 25 mg did not change from baseline but was significantly different from placebo because mean DBP for placebo decreased.

c: PE 15 and PE 25 significantly decreased DBP at 4 of the 10 time points (5 per each PE dose). No additional detail provided.

d: No treatment differences were observed in vital signs. No additional detail provided.

Abbreviations: BR = brompheniramine, Eph = ephedrine, NCR = not clinically relevant, NS = not significant, PE = phenylephrine, PPA = phenylpropanolamine, PSE = pseudoephedrine, S = statistically significant compared to placebo, -- = not assessed at that time point, ↓ = decrease compared to baseline, ↑ = increase compared to baseline

5.1.3 Conclusions from Placebo-Controlled Trials

In summary, 15 of 20 studies reported safety data. Of the 8 studies collecting data on adverse events, 4 studies reported no adverse events in subjects treated with single doses of phenylephrine ranging from 5 mg to 25 mg. In the other 4 studies, most adverse events reported by phenylephrine-treated subjects were reported at a frequency similar to placebo-treated subjects. Nervousness was reported more frequently with phenylephrine 15 mg and 25 mg than with phenylephrine 10 mg or placebo.

Fifteen studies collected data on vital signs for phenylephrine doses ranging from 5 mg to 100 mg. Many studies reported no change in vital signs for various doses of phenylephrine at various time points, and both increases and decreases for pulse and blood pressure were observed. In studies that included a 10 mg phenylephrine dose, there was no discernable relationship between changes in pulse and blood pressure, nor was there a clear pattern of vital sign changes at different time points.

Statistically significant differences from placebo in pulse were reported more frequently with doses of phenylephrine greater than 10 mg; some of the largest mean increases from baseline in pulse were observed with phenylephrine 25 mg. Mean increases from baseline in systolic blood pressure were larger with increasing phenylephrine dose. However, all mean increases in pulse compared to baseline were $\leq$ 11 beats per minute and mean increases in blood pressure compared to baseline were less than 5 mm Hg and may not be clinically relevant.

These results support that the current adult dose of phenylephrine 10 mg in the OTC monograph is well tolerated.

5.2 Post-Marketing Safety Data for Phenylephrine

CHPA has commissioned the Rocky Mountain Poison and Drug Center (RMDPC) to perform an additional independent analysis of post-marketing data for orally-administered phenylephrine-containing products. The RMDPC will review serious adverse events and fatalities from member companies' post-marketing safety databases. In addition, they will review the medical literature and poison center data. It is anticipated that the results of these analyses will be presented at the December 14, 2007 NDAC meeting.

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6.0 CONCLUSIONS

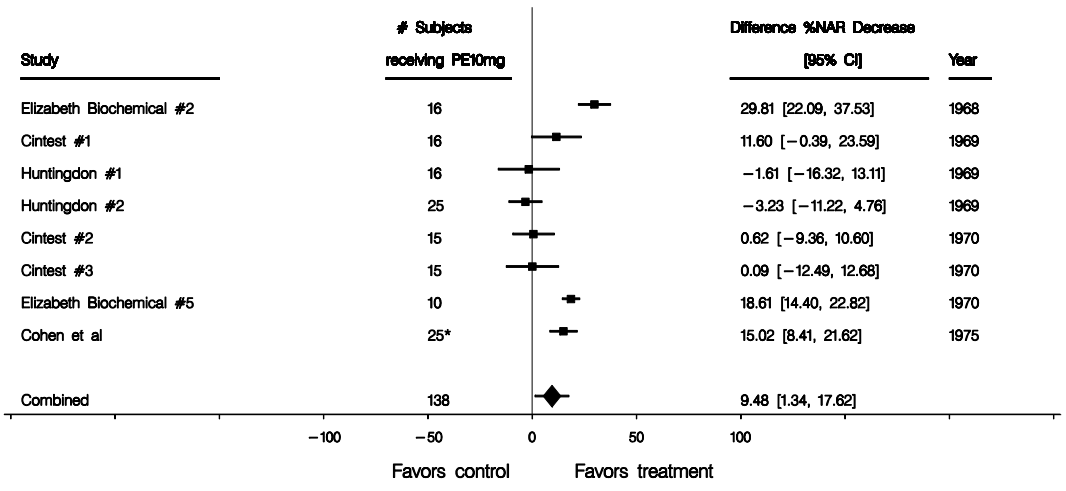
- Nasal congestion is one of the most common symptoms associated with acute and chronic rhinitis.
- This assessment of available scientific evidence concurs with previous findings of the FDA and the OTC expert advisory review panel, that oral phenylephrine 10 mg is safe and effective as a nasal decongestant for over-the-counter use in adults.
- There are insufficient data in adults to support the assertion that increasing the dose of phenylephrine to 25 mg is necessary to produce clinically meaningful improvements in nasal decongestion with a similar safety profile as the currently available 10 mg OTC monograph dose.
- OTC medications such as phenylephrine are considered safe and effective treatments to help relieve nasal congestion.

7.0 APPENDICES

Appendix 1

CHPA Meta-analysis Methods

Area-under-the curve (AUC), which is essentially a weighted average across the time points, is a useful, single endpoint to capture overall data over a time period. In order to directly compare this endpoint to the maximum percentage reduction endpoint that Hatton et al. used, we analyzed this AUC endpoint over the same 2-hour interval with the same eight placebo-controlled, randomized studies (7 crossover studies and 1 parallel study), and we performed the analysis using their methodology. We summarized the results of the studies using a random effects meta-analysis model with the aggregated treatment means and standard errors. For the crossover studies, we used the mean and standard error of the within-subject difference between the relative change in NAR during the phenylephrine and placebo periods, and for the parallel-group study, we used the difference between the mean changes and the pooled standard errors. Again, this is exactly the method that Hatton et al used, except that our endpoint is the AUC of the relative changes, and their endpoint was the maximum relative change. The individual study data were analyzed by the within-group t-test on the within-subject differences in the changes from baseline for the crossover studies and the independent groups t-test on the within-subject changes from baseline for the parallel study; apparently Hatton et al did the same. All pairwise tests were two-sided. The results are shown in the figure below.



*: Parallel study, the same number of subjects were in the placebo group

Appendix 2

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Memo to Bird from Stander 1968 [Ref 2 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 120 min	Phenylephrine 15 mg Phenylephrine 20 mg Phenylephrine 25 mg PPA 50 mg Placebo Single Dose	Oral Oral Oral Oral Oral	20 20 20 20 20	NA NA NA NA NA	**Study Population:** Healthy volunteers. **Safety:** Mean **pulse rate** (bpm): • at 30 min [PE 15 mg (-7.21), Pbo (-3.40); p=0.01] and [PE 25 mg (-6.50), Pbo (-3.40); p=0.05] Mean **SBP** (mm Hg): • at 60 min [PPA (+4.31), Pbo (-0.55); p=0.01], at 120 min [PPA (+7.70), Pbo (+2.33); p=0.01]. Mean **DBP** (mm Hg): • at 120 min [PE 15 mg (+1.77), Pbo (+5.63); p=0.05]. Adverse events were not reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Memo to Luduena from Stander 1967 [Ref 3 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 120 min	Phenylephrine 10 mg	Oral	20	(24-49) 20M, 0F	**Study Population:** Healthy volunteers. **Safety:** Mean **pulse rate** (bpm): • at 30 min [PE 100 mg (-9.46), Pbo (-3.06); p=0.05] • at 60 min [PE 25 mg (-8.81), Pbo (-4.91); p=0.05], [PE 50 mg (-10.19), Pbo (-4.91; p=0.01], [PE 100 mg (-11.54), Pbo (-4.91); p=0.01]. Mean **SBP** (mm Hg): • at 30 min [PE 100 mg (+3.82), Pbo (-0.68); p=0.05] • at 60 min [PE 100 mg (+4.38), Pbo (-0.23); p=0.05]. • No significant differences were observed between any PE dose and Pbo for **DBP**. Adverse events were not reported.
		Phenylephrine 25 mg	Oral	20	(24-49) 20M, 0F	
		Phenylephrine 50 mg	Oral	20	(24-49) 20M, 0F	
		Phenylephrine 100 mg	Oral	20	(24-49) 20M, 0F	
		Placebo Single Dose	Oral	20	(24-49) 20M, 0F	

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Memo to Lands from Luduena 1959 [Ref 5 in 1976 OTC Review]	DB PC CO Duration of Follow-up: 5 h Data are avail-able for topical admini-stration in the report and are not pre-sented in this sum-mary.	Phenylephrine 10 mg Phenylephrine 25 mg Phenylephrine 50 mg Phenylephrine 75 mg PPA 25 mg PPA 50 mg Placebo Single Dose	Oral Oral Oral Oral Oral Oral Oral	15 15 14 14 15 14 87	(20-46)	**Study Population:** 15 healthy volunteers. **Safety:** Mean **SBP** with PE 75 mg was higher at 1 h and 2 h compared to baseline; however, the difference was only a few mm Hg and was not significant. Differences observed in mean SBP with lower PE doses were smaller. Similar increases in mean **DBP** were observed for PE 75 mg with smaller increases observed for lower PE doses. No clinically important differences in **pulse rate** were noted for any PE dose. A small but significant increase in mean **SBP** compared to baseline was observed with PPA 50 mg at 1h and 2h; increases compared with baseline were (+8.1) at 1h and (+8.4) at 2h for PPA 50 mg. Changes in mean **DBP** were similar (+6 at 1 h, +6 at 2 h). Adverse events were not reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Elizabeth Study #1 1967 [Ref 6 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 120 min	Phenylephrine 25 mg	Oral	12	NA	**Study Population:** Subjects with head colds. **Safety:** Safety was not reported.
		Ephedrine 8 mg	Oral	13	NA	
		Placebo Single Dose	Oral	25	NA	

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Elizabeth Study #2 1968 [Ref 7 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 120 min	Phenylephrine 10 mg	Oral	16	NA	**Study Population:** Subjects with nasal congestion on 2 consecutive days. **Safety:** Safety was not reported.
		Phenylephrine 15 mg	Oral	10	NA	
		Phenylephrine 25 mg	Oral	6	NA	
		Ephedrine 50 mg	Oral	6	NA	
		Placebo	Oral	38	NA	
		Single Dose				

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Elizabeth Study #3 1969 [Ref 8 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 240 min	Phenylephrine 5 mg	Oral Capsule	16	NA	**Study Population:** Subjects with head colds and having confirmed nasal congestion on 2 consecutive days. **Safety:** Mean **pulse rate** (bpm): • at 30 min [PE 5 mg (+0.71), Pbo (-2.26); p=0.05] and [PE 25 mg (+1.62), Pbo (-0.82); p=0.05], at 90 min [PE 5 mg (+2.85), Pbo (-1.51); p=0.01], at 240 min [PE 25 mg (-3.24), Pbo (+1.64); p=0.05]. Mean **SBP** (mm Hg): • at 30 min [PPA (+6.83), Pbo (no change); p=0.05], at 60 min [PPA (+9.57), Pbo (no change); p=0.01], at 90 min [PPA (+8.20), Pbo (no change); p=0.01],at 120 min [PE 5 mg (+1.25), Pbo (-1.26); p=0.05], [PE 15 mg (no change), Pbo (-2.74);p=0.05], [PPA (+5.47), Pbo (no change); p=0.05]. Mean **DBP** (mm Hg): • at baseline [PPA (79.89), Pbo (85.33); p=0.05], at 60 min [PPA (+4.00), Pbo (-2.56); p=0.05], at 90 min [PE 5 mg (+2.29), Pbo (-0.76); p=0.05] and [PPA (+2.40), Pbo (-3.41); p=0.05], at 120 min [PE 15 mg (+0.80), Pbo (-1.63); p=0.05]. No side effects were reported by any subject treated with any dose of PE. One subject reported increased heart rate and a nauseous feeling about 20 min after taking PPA.
		Phenylephrine 15 mg	Oral Capsule	8	NA	
		Phenylephrine 25 mg	Oral Capsule	9	NA	
		PPA 50 mg	Oral Capsule	9	NA	
		Placebo Single Dose	Oral Capsule	42	NA	

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Elizabeth Study #4 1969 [Ref 9 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 240 min	Phenylephrine 15 mg Phenylephrine 20 mg Phenylephrine 25 mg Placebo Single Dose	Oral Capsule Oral Capsule Oral Capsule Oral Capsule	6 5 9 20	NA NA NA NA	**Study Population:** Subjects with head colds and having confirmed nasal congestion on 2 consecutive days. **Safety:** Mean **pulse rate** (bpm): • at 120 min [PE 20 mg (+1.52), Pbo (-4.70); p=0.05], • at 180 min [PE 20 mg (+3.04), Pbo (-5.49); p=0.01], • at 180 min [PE 25 mg (+0.82), Pbo (-3.15); p=0.05]. No significant differences were observed in mean **SBP** for any of the PE doses compared with Pbo at any time point. Mean **DBP** (mm Hg): at 120 min [PE 25 mg (-3.25), Pbo (+2.49); p=0.05]. Adverse events were not reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Elizabeth Study #5 1970 [Ref 10 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 240 min	Phenylephrine 10 mg Phenylephrine 15 mg Phenylephrine 25 mg Placebo Single Dose	Oral Oral Oral Oral	10 6 9 25	NA NA NA NA	**Study Population:** Subjects with head colds and confirmed nasal congestion on 2 consecutive days. **Safety:** Mean **pulse rate** (bpm): • at 30 min [PE 25 mg (+3.02), Pbo (-2.29); p=0.05], • at 60 min [PE 15 mg (+5.69), Pbo (no change); p=0.05], • at 90 min [PE 15 mg (+3.25), Pbo (-2.46); p=0.05] and [PE 25 mg (+5.29), Pbo (-2.29); p=0.01], • at 120 min [PE 10 mg (+2.27), Pbo (-0.76); p=0.05] and [PE 25 mg (+3.02), Pbo (-3.06); p=0.05], • at 180 min and 240 min [PE 25 mg (+3.78), Pbo (-0.76); p=0.05]. Mean **SBP** (mm Hg): • at 60 min [PE 10 mg (+1.30), Pbo (-1.33); p=0.05] and [PE 25 mg (+3.99), Pbo (-1.35); p=0.05], • at 90 min [PE 10 mg (+1.30), Pbo (-2.66), p=0.01] and [PE 15 mg (+1.39), Pbo (-2.8); p=0.05], and [PE 25 mg (+3.99), Pbo (-2.7); p=0.01], • at 120 min [PE 10 mg (+2.60), Pbo (-3.99); p=0.01] and [PE 25 mg (+2.66), Pbo (-2.7); p=0.05], • at 180 min [PE 10 mg (+2.60), Pbo (-2.66); p=0.01], • at 240 min [PE 25 mg (+2.66), Pbo (-1.35); p=0.05]. Mean **DBP** (mm Hg): • at 60 min [PE 10 mg (+1.47), Pbo (-2.26); p=0.05], • at 90 min [PE 10 mg (+2.21), Pbo (-1.50); p=0.01. No adverse event data were reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
McLaurin et al 1961	R DB PC	Phenylephrine 10 mg	Oral Capsule	88	NA	**Study Population:** Subjects with complaint of nasal obstruction and the clinical findings that confirmed a soft tissue congestion and edema.
[Ref 11 in 1976 OTC Review]	CO	Ephedrine 25 mg	Oral Capsule	88	NA	**Safety:** None of the active drugs or Pbo had a statistically significant effect on **SBP** assessed 60 min post dose. No statistically significant effects were observed with any of the active drugs or Pbo for **heart rate** assessed 60 min post dose, although PE resulted in a 10 or more bpm rate increase for 9 subjects compared to 3 for Pbo. % of subjects reporting **nervousness** 1h after treatment in the clinic and at bedtime: PE (37), ephedrine (71), PSE (53), PPA (26), Pbo (42). AEs reported included headache (34), nausea (21), dizzy and lightheaded (22), and drowsy (13). Pbo subjects reported the largest numbers of headache (11), dizzy and lightheaded (10), and drowsy (9). PE subjects reported the largest number of cases of nausea (8). Other AEs were reported infrequently.
	Duration of Follow-up: 2 days	PSE 60 mg	Oral Capsule	88	NA	
		PPA 25 mg	Oral Capsule	88	NA	
		Placebo	Oral Capsule	88	NA	
		Multiple dose, initial and 1 h prior to bedtime				

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Huntingdon Study #2 1969 [Ref 21 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 240 min	Phenylephrine 10 mg Phenylephrine 20 mg Placebo Single Dose	Oral Capsule Oral Capsule Oral Capsule	25 24 49	NA NA NA	**Study Population:** Subjects with head colds and confirmed nasal congestion on 2 consecutive days. **Safety:** Mean **pulse rate** (bpm): • at 90 min [PE 10 mg (-2.29), Pbo (+3.24); p=0.05]. Mean **SBP** (mm Hg): • at 180 min [PE 10 mg (-2.26), Pbo (+2.20); p=0.05]. Mean **DBP** (mm Hg): • at 240 min [PE 20 mg (-0.73), Pbo (+4.39); p=0.05]. No subjects reported side effects with any treatment.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Cintest Study #2 1970 [Ref 23 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 240 min	Phenylephrine 10 mg Phenylephrine 15 mg Phenylephrine 20 mg Placebo Single Dose	Capsule Oral Capsule Oral Capsule Oral Capsule Oral	15 16 15 46	NA NA NA NA	**Study Population:** Subjects with head colds and confirmed nasal congestion on 2 consecutive days. **Safety:** No significant differences between any of the PE doses and Pbo were observed for pulse rate, diastolic blood pressure, or systolic blood pressure. Adverse events were not reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Cintest Study #3 1970 [Ref 24 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 120 min	Phenylephrine 10 mg Phenylephrine 15 mg Phenylephrine 25 mg Placebo Single Dose	Capsule Oral Capsule Oral Capsule Oral Capsule Oral	15 16 16 47	NA NA NA NA	**Study Population:** Subjects with head colds and confirmed nasal congestion on 2 consecutive days. **Safety:** Mean **pulse rate** (bpm): • at 90 min [PE 15 mg (+3.83), Pbo (+0.77); p=0.01]. Mean **SBP** (mm Hg): • at 60 min [PE 15 mg (-1.1), Pbo (-3.36); p=0.01] and [PE 25 mg (-1.08), Pbo (+1.08); p=0.05]. Mean **DBP** (mm Hg): • at 90 min [PE 25 mg (-0.7), Pbo (+4.66); p=0.05], at 120 min [PE 25 mg (no change), Pbo (+ 4.66); p=0.05]. Adverse events were not reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Cohen BM 1975 [Ref 26 in 1976 OTC Review]	**Phase 1** R DB PC Duration of Follow-up: 120 min	Phenylephrine 10 mg Single Dose	Oral Tablet	25	53.7 (21-80) 9M, 16F	**Study Population:** Subjects with upper respiratory congestion associated with the common cold.
		Placebo	Oral Tablet	25	46.6 (13-75) 13M, 12F	**Safety:** **Phase 1** Mean (range) SBP with PE compared to Pbo was 1.3 mm Hg (0.2 to 1.4) higher. Mean (range) DBP with PE compared to Pbo was 0.56 (-0.2 to 0.6) lower with one exception. None of these differences were statistically significant. Pulse was not assessed.
	Phase 2 Duration of Follow-up: 12 h	Phenylephrine 10 mg q4h	Oral Tablet	75	50.0 (16-83) 26M, 49F	**Phase 1 and 2 Combined** Number of subjects reporting AEs: PE-8, Pbo-11. AEs included: dizzy (PE-1, Pbo-3), felt warm (PE-3, Pbo-1), dry mouth (Pbo-3), nausea (Pbo-2), dizzy and flushing (Pbo-1), headache (Pbo-1), extrasystoles (PE-1), flush (PE-1), nasal dryness (PE-1), slightly shaky (PE-1).
		Placebo q4h Multiple Dose	Oral Tablet	75	55.0 (16-78) 36M, 39F	

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Cintest Study #1 1969 [Ref 22 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 240 min	Phenylephrine 10 mg Phenylephrine 25 mg PPA 50 mg Placebo Single Dose	Capsule Oral Capsule Oral Capsule Oral Capsule Oral	16 16 15 47	NA NA NA NA	**Study Population:** Subjects with head colds and confirmed nasal congestion on 2 consecutive days. **Safety:** Safety was not reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Huntingdon Study #1 1969 [Ref 20 in 1976 OTC Review]	R DB PC CO Duration of Follow-up: 240 min	Phenylephrine 10 mg Phenylephrine 25 mg PPA 50 mg Placebo Single Dose	Oral Oral Oral Oral	16 16 16 48	NA NA NA NA	**Study Population:** Subjects with head colds and confirmed nasal congestion on 2 consecutive days. **Safety:** Safety was not reported.

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Cohen BM 1972	R DB PC CO Duration of follow-up: 120 min	Phenylephrine 10 mg Phenylephrine 15 mg Phenylephrine 25 mg Placebo Single Dose	Oral Tablet Oral Tablet Oral Tablet Oral Tablet	16 16 16 48	NA NA NA NA	**Study Population:** Subjects with nasal congestion due to a common cold of 24 to 48 h duration. **Safety:** **Blood Pressure**: • No significant differences were observed between PE 10 mg and Pbo in mean SBP or DBP over 120 min or between PE 15 mg and PE 25 mg compared to Pbo for mean SBP over 120 min. • PE 15 mg and PE 25 mg significantly (p≤0.05) reduced mean DBP at 4 of the 10 time points (5 per PE dose). Mean **heart rate** (bpm): • at 30 min [PE 10 mg (+8), Pbo (+3); p=0.05], [PE 15 mg (+6), Pbo (-1); p=0.05], [PE 25 mg (+8), Pbo (-1); p=0.05]. • at 60 min [PE 25 mg (+11), Pbo (-2); p≤0.01]. • at 90 min [PE 10 mg (+6), Pbo (+1); p≤0.01], [PE 25 mg (+7), Pbo (-2); p≤0.01]. • at 120 min [PE 10 mg (+4), Pbo (+1); p=0.05], [PE 25 mg (+6), Pbo (-2); p≤0.01]. Number of subjects reporting AEs appears to be dose-related: PE 10 mg-2, PE 15 mg-7, PE 25 mg-13, Pbo-6. AEs included: dry mouth (PE 10 mg-1, PE 25 mg-1, Pbo-4), dry nose (PE 10 mg-1, PE 15 mg-1, PE 25 mg-1, Pbo-3), circumoral paresthesias (PE 25 mg-2), irritability (PE 25 mg-1), nervousness (PE 15 mg-6, PE 25 mg-5, Pbo-1), malaise (PE 25 mg-2), lightheadedness (PE 15 mg-1, PE 25 mg-1), breathlessness (PE 25 mg-1), gaseousness (PE 25 mg-1).

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Schering-Plough Study P04579 2006	R IB PC CO SC	Phenylephrine 12 mg	Oral Capsule			**Study Population:** Subjects with seasonal allergic rhinitis exposed to pollen for 6 h in the Vienna Challenge Chamber. **Safety:** PE and PSE were both well tolerated. No adverse events were reported. No treatment differences were observed in vital signs.
		PSE 60 mg	Oral Tablet			
		Placebo	Oral Capsule			
	Duration of Follow-up: 7.5 h	Single Dose		Overall: 39	Overall: (19-46)	

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
Bickerman 1971	DB CO PC	Phenylephrine 10 mg	Oral	20[a]	NA	**Study Population:** Subjects with chronic nonseasonal rhinitis.
		PSE 60 mg	Oral	20	NA	**Safety:** Safety was not reported.
	Duration of Follow-up: 4 h	PPA 40 mg	Oral	20	NA	a: the number of subjects per treatment group was not clear in the 1971 article; 20 was obtained from a letter to the editor in 2006 that contained these data: Hendeles and Hatton. *J Allergy Clin Immunol*. 118:279-80.
		Placebo	Oral	20	NA	

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
AHR-4010-3 1983	R DB PC P MC	Phenylephrine 10 mg q4h			NA	**Study Population:** Subjects with nasal congestion due to upper respiratory tract infection of less than 48 h duration.
		PPA 25 mg q4h			NA	**Safety:** All treatments were well tolerated. Reported AEs included lightheadedness (PE 10 mg-1, Pbo-1), very dry throat (PE+PPA-1), dizziness (PPA-1), eructation (Pbo-1), gaseousness (Pbo-1). Examination and analysis of blood pressure and pulse rate recordings pre and post study resulted in no meaningful changes.
	Duration of Follow-up: NAR, 240 min	Phenylephrine 5 mg + PPA 12.5 mg q4h			NA	
		Placebo q4h			NA	
	Subject-ive assess-ments, 72 h	Multiple Dose 3 days		Overall: 274	Overall: (18-77)	

Summary of Published and Unpublished Placebo-Controlled Studies of Phenylephrine in Adults

Citation [Reference]	Study Design	Medication Dose Duration	Dosage Form Route	N Safety	Mean Age (Range), y Gender	Study Results
AHR-7032 1967	R SB PC CO SC Duration of Follow-up: 120 min	Phenylephrine 10 mg		8		**Study Population:** Subjects with stable or chronic nasal congestion due to allergy. **Safety:** No adverse events were reported. There was no clinically significant effect of any treatment on blood pressure or pulse in any treatment.
		PPA 10 mg		8		
		BROM 8 mg		8		
		Phenylephrine 10 mg + PPA 10 mg		8		
		Phenylephrine 10 mg + BROM 8 mg		8		
		PPA 10 mg + BROM 8 mg		8		
		Phenylephrine 10 mg + PPA 10 mg + BROM 8 mg		8		
		Pbo		8		
		Single Dose			Overall (18-60)	

Abbreviations: BROM = brompheniramine, CO = crossover, DB = double-blind, DBP = diastolic blood pressure, IB = investigator-blind, MC = multicenter, MD = multiple dose, NA = not available, NAR = nasal airway resistance, P = parallel, Pbo = placebo, PC = placebo-controlled, PE = phenylephrine, PPA = phenylpropanolamine, PSE = pseudoephedrine, q4h = every four hours, R = randomized, SB = single-blind, SBP = systolic blood pressure, SC = single center, SD = single dose