Oral Phenylephrine as a Nasal Decongestant in the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) OTC Monograph

Nonprescription Drugs Advisory Committee
September 11-12, 2023

Theresa M. Michele, MD
Director, Office of Nonprescription Drugs

Objectives of the Advisory Committee Meeting

- Discuss the efficacy of oral phenylephrine as a nasal decongestant
- Consider potential safety and efficacy of higher than monograph doses

Phenylephrine (PE)

- One of two orally administered α1-adrenergic receptor agonists that are generally recognized as safe and effective (GRASE) in the CCABA OTC Monograph
- Indication: Temporary relief of nasal congestion
- PE is also
  - GRASE as a nasal decongestant by direct intranasal administration, for topical use for treatment of hemorrhoids, and for ocular use to relieve redness of the eye
  - Rx approved for intravenous treatment of hypotension
  - Rx approved for ocular use to dilate the pupil
- This meeting focuses on oral phenylephrine (hydrochloride and bitartrate salts)

CCABA Monograph Ingredients

Antihistamine	Decongestant	Expectorant	Antitussive	Bronchodilator
Oral Products				
Brompheniramine maleate Chlorcyclizine hydrochloride Chlorpheniramine maleate Dexbrompheniramine maleate Dexchlorpheniramine maleate Diphenhydramine citrate Diphenhydramine hydrochloride Doxylamine succinate Phenindamine tartrate Pheniramine maleate Pyrilamine maleate Thonzylamine hydrochloride Triprolidine hydrochloride	**Phenylephrine hydrochloride** **Phenylephrine bitartrate** **Pseudoephedrine hydrochloride** **Pseudoephedrine sulfate**	Guaifenesin	Chlophedianol hydrochloride Codeine Codeine phosphate Codeine sulfate Dextromethorphan Dextromethorphan hydrobromide Diphenhydramine citrate Diphenhydramine hydrochloride	Ephedrine Ephedrine hydrochloride Ephedrine sulfate Racephedrine hydrochloride
Topical and/or Inhaled Products				
	Levmetamfetamine Ephedrine Ephedrine hydrochloride Ephedrine sulfate Naphazoline hydrochloride Oxymetazoline hydrochloride **Phenylephrine hydrochloride** Propylhexedrine Xylometazoline hydrochloride		Camphor Menthol	Epinephrine Epinephrine bitartrate Racepinephrine hydrochloride

Phenylephrine Oral Dosage

Age Range	Phenylephrine Hydrochloride	Phenylephrine Bitartrate (tablets)*
Adults and children ≥12 y	**10 mg every 4 hours** NTE 60 mg in 24 hours	15.6 mg every 4 hours NTE 62.4 mg in 24 hours
6 to <12 years	5 mg every 4 hours NTE 30 mg in 24 hours	7.8 mg every 4 hours, NTE 31.2 mg in 24 hours
2 to <6 years	2.5 mg every 4 hours NTE 15 mg in 24 hours	Consult a doctor
<2 years	Consult a doctor	

* Bitartrate salt (PEB) effervescent tablets added in 2006 based on PK matching to PEH (**NO** efficacy data)
NTE = Not to exceed

Citizen Petitions

- 2007 CP*
  - Amend the dosage(s) of both oral PE salts by increasing the maximum dosage for patients ≥12 years of age
  - Withdraw approval for use in children <12 years of age
- 2015 CP**
  - Reclassify the oral PE salts as NOT GRASE due to lack of efficacy

* Leslie Hendeles, Pharm D; Randy C. Hatton, PharmD; Almut Winterstein, RPh, PhD at University of Florida

** Leslie Hendeles, Pharm D; Randy C. Hatton, PharmD at University of Florida

2007 NDAC Meeting

- Discussed the safety and effectiveness of oral phenylephrine as a nasal decongestant
  - Results are not consistent across studies for nasal airway resistance (NAR); symptoms should be the essential primary endpoint
  - Evidence of efficacy consists primarily of studies conducted 40 years ago and included fewer than 200 people
  - NAR results may not be generalizable to a wide population based on small studies
- Committee recommended additional trials
  - Multi-center, parallel, randomized, double blind, placebo-controlled trials, preferably with an active control such as pseudoephedrine, to evaluate nasal congestion scores and symptom relief
  - Characterization of PE dose response and dosing interval
  - Comparison of PK of single-ingredient products versus multiple-ingredient products
  - Safety evaluation of the effects of PE on blood pressure

2007 NDAC materials available at: https://wayback.archiveit.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs

OTC Drug Monograph Effectiveness Standard

- Effectiveness means a reasonable expectation that, in a significant portion of the target population, the pharmacological effect of the drug… will provide clinically significant relief of the type claimed
- Proof of effectiveness shall consist of controlled clinical investigations as defined in 21 CFR 314.126(b)
  - 314.126(b) is the definition of adequate and well controlled studies for New Drug Applications (NDAs)

21 CFR 330.10(a)(4)(ii)

Purpose of Proceedings Before an Advisory Committee

- An advisory committee is utilized to conduct public hearings on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner.
- The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee.

21 CFR 14.5


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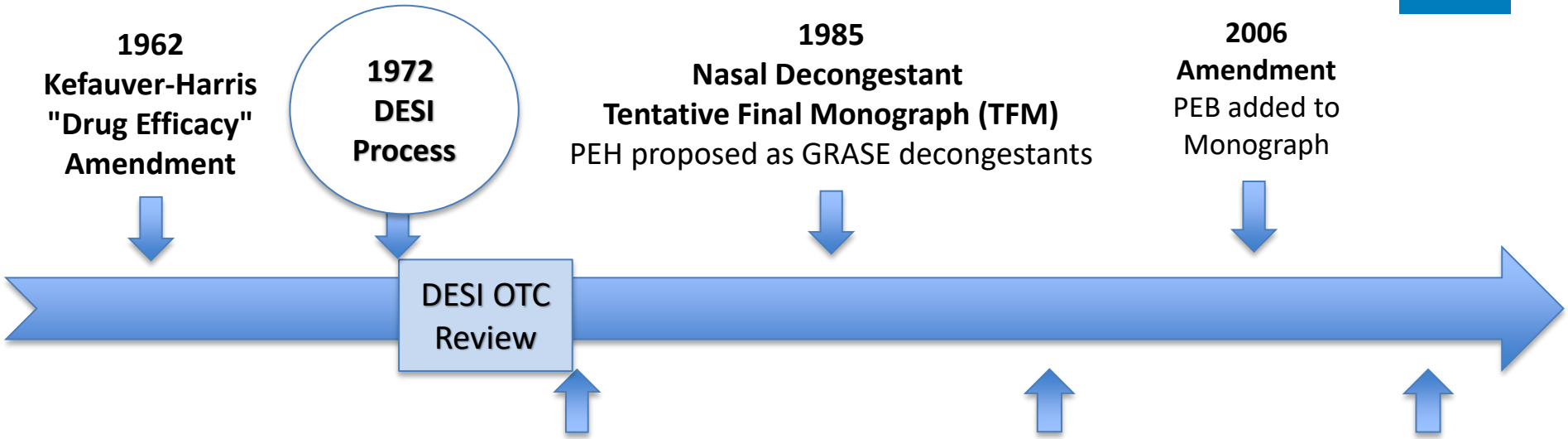
Background and Regulatory History of Oral Phenylephrine

Ben Bishop, PharmD
Regulatory Review Officer
Division of Nonprescription Drugs I
Office of Nonprescription Drugs

Decongestant Regulatory History Timeline



DESI Panel Review of OTC Drugs

- DESI (Drug Efficacy Study Implementation) was a process initiated in response to the 1962 Kefauver-Harris Amendment
  - Authorized a retrospective evaluation of ***effectiveness*** in addition to safety
- In 1972, FDA divided a list of over 400 ingredients being marketed without a prescription into 26 therapeutic categories and began the over-the-counter (OTC) DESI Review for each.
  - A therapeutic category for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) drugs was created and included nasal decongestants

Charge to the DESI Panels

- The DESI Panels were charged with:
  - Making recommendations based on available data at the time to establish conditions of use for dosing, directions, and warnings
  - Applying OTC drug effectiveness standards in accordance with 21 CFR § 330.10(a)(4)(ii)
    - "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."

DESI Panel Review of Oral Nasal Decongestants

The DESI Panel report published in 1976:

- Defined nasal decongestants as agents that reduce nasal congestion in patients with acute or chronic rhinitis
- Evaluated phenylephrine and pseudoephedrine as oral nasal decongestants
- **Concluded that phenylephrine hydrochloride is safe and effective as an orally administered nasal decongestant for nonprescription use at the specified dosage.**

OTC Monograph Rulemaking Process (Prior to the CARES Act)

- **1976**
  - DESI Review Panel reviewed all available data. Recommendations and rationale were published by the agency in an **Advance Notice of Proposed Rulemaking (ANPR).**
- **1985**
  - FDA reviewed the all data and comments submitted in response to the ANPR. A **Tentative Final Monograph (TFM)** was published as a proposed rule.
- **1994**
  - FDA reviewed all new data and comments submitted in response to the TFM. FDA published the **Nasal Decongestant Final Monograph (FM)** established the regulation in the Code of Federal Regulations (CFR).

Phenylephrine Bitartrate (PEB)

- PEB is an effervescent tablet dosage form formed with the bitartrate salt
- FDA received a Citizen Petition in 2002 which requested that the CCABA OTC Monograph be amended to add this dosage form
- The petition included:
  - Domestic and global marketing history data
  - Pharmacokinetic (PK) data showing that phenylephrine hydrochloride salt (PEH) and PEB have comparable bioavailability profiles
- **The petition did NOT include efficacy data**
- FDA issued a Proposed Rule in 2004 and a Final Rule in 2006, and PEB is now a monograph condition, or 'Generally Recognized as Safe and Effective' (GRASE)

Other Oral Decongestants

- **Combat Methamphetamine Epidemic Act (2006)**
  - Moved pseudoephedrine products “behind-the-counter”
  - Introduced daily and monthly limits on the legally purchased quantity
- **Phenylpropanolamine (PPA)**
  - Alpha-1 adrenergic receptor agonist reviewed by the Panel and recommended as safe and effective oral nasal decongestant
  - However, FDA did not find it GRASE in either the Tentative or Final Monograph due to safety concerns
  - PPA was removed from OTC use after a large safety study showed that it was associated with hemorrhagic stroke in women of childbearing age

The 2020 CARES Act and CCABA Deemed Final Order

- The Coronavirus Aid, Relief, and Economic Security Act (CARES Act) amended the Food, Drug, and Cosmetic Act:
  - Reformed and modernized the regulation of OTC Monograph drugs
  - Replaced the rulemaking process with an administrative order process for issuing, revising, and amending OTC monographs
- All OTC Monographs have now been reviewed and posted as orders
- A Deemed Final Administrative Order for the CCABA OTC Monograph (M012) was posted on October 14, 2022
  - Available at: https://dps.fda.gov/omuf/monographsearch/monograph_m012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Clinical Pharmacology of Oral Phenylephrine

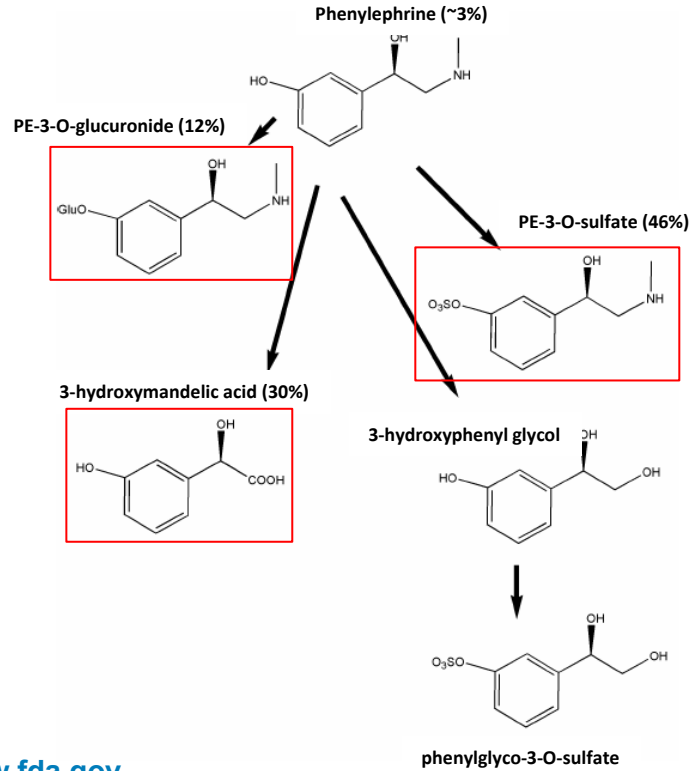
Yunzhao Ren, MD, PhD
Acting Team Leader
Division of Inflammation & Immune Pharmacology (DIIP)
Office of Clinical Pharmacology (OCP)

Overview

- Metabolism and pharmacology of phenylephrine
- Very low bioavailability of phenylephrine following oral administration
- Small systemic α1-adrenergic agonistic effect of phenylephrine following a 10 mg oral dose

Metabolism of Phenylephrine Following Oral Route

Urine excretion of PE and its metabolites*



- Most of metabolism of PE occurs in the small intestine wall by multiple enzymes (Monoamine oxidase [MAO], sulfotransferase, and glucuronidases, etc.) before entering systemic circulation.
- Three major metabolites identified in the circulation (PE-glucuronide, PE-sulfate, and hydroxymandelic acid).
- ~ 80% of PE oral dose is excreted in urine within 48-hour post-oral dose with three major metabolites counting for ~ 90% of the excretion. Parent PE only counts for 3% of urine excretion.

* As percentage of urine excretion amount

Sources:

- Schering-Plough briefing document for 2007 NDAC meeting
- Hengstmann JH, *Eur J Clin Pharmacol.* 1982; 21: 335-341

In Vitro α-Adrenergic Agonistic EC_{50} Values of Phenylephrine

α Receptor	EC_{50} of Parent PE (ng/mL)	PE-3-O-sulfate	PE-3-O-glucuronide	3-Hydroxy mandelic acid
α1a	16.9*	No Activity	No Activity	No Activity
α1b	2.3*	No Activity	No Activity	No Activity
α2a	37.6#	No Activity	No Activity	No Activity
α2b	390.3#	No Activity	No Activity	No Activity
α2c	147.8#	No Activity	No Activity	No Activity

Abbreviations: EC_{50}, half maximal effective concentration; PE, phenylephrine

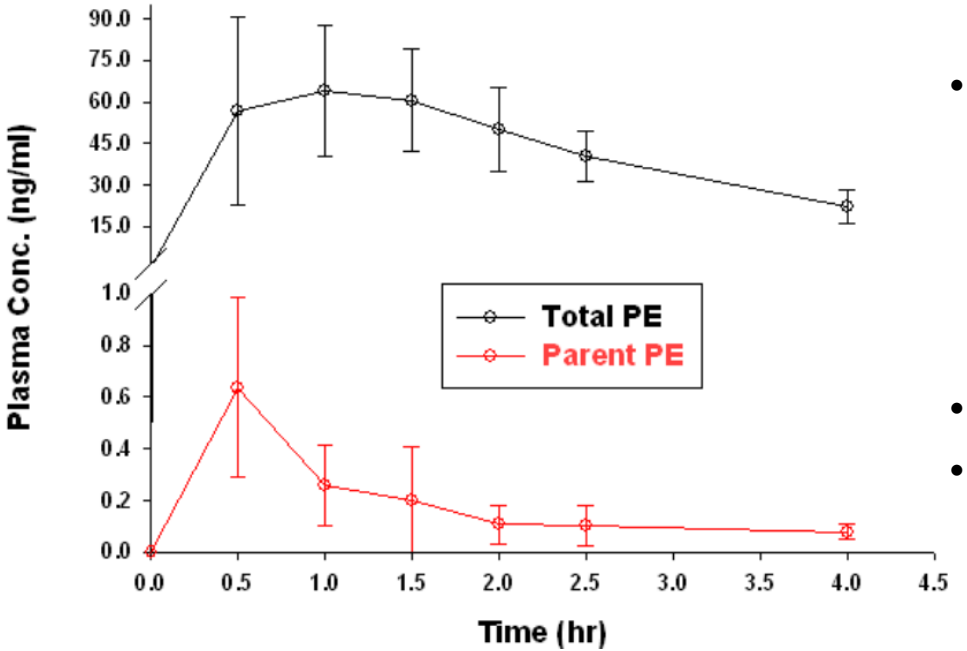
* As measured by cell-based calcium flux response

\# As measured by [^{35}S]-GTPγS binding exchange assay

Source: Schering-Plough 2007 Nonprescription Drugs AC meeting presentation

- None of PE major metabolites has *in vitro* α-adrenergic agonistic effect
- NDA 204300 phenylephrine injection label: "*The metabolites (i.e., m-hydroxymandelic acid and sulfate conjugates) are considered not pharmacologically active.*"

Parent and Total Phenylephrine PK Profile Following 10 mg Oral Dose



Source: Schering-Plough Study CL2005-07, 2005

- Total PE:
  - Parent PE
  - PE-3-O-glucuronide
  - PE-3-O-sulfate
- Plasma C_{max} of parent PE ~1% of total PE
- Plasma AUC of parent PE <1% of total PE

In Vitro α-Adrenergic Agonistic EC_{50} Values of Phenylephrine

α Receptor	EC_{50} of Parent PE (ng/mL)	PE-3-O-sulfate (nM)	PE-3-O-glucuronide (nM)	3-Hydroxy mandelic acid (nM)
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α1b	**2.3***	No Activity	No Activity	No Activity
α2a	37.6#	No Activity	No Activity	No Activity
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α2c	147.8#	No Activity	No Activity	No Activity

PE: phenylephrine

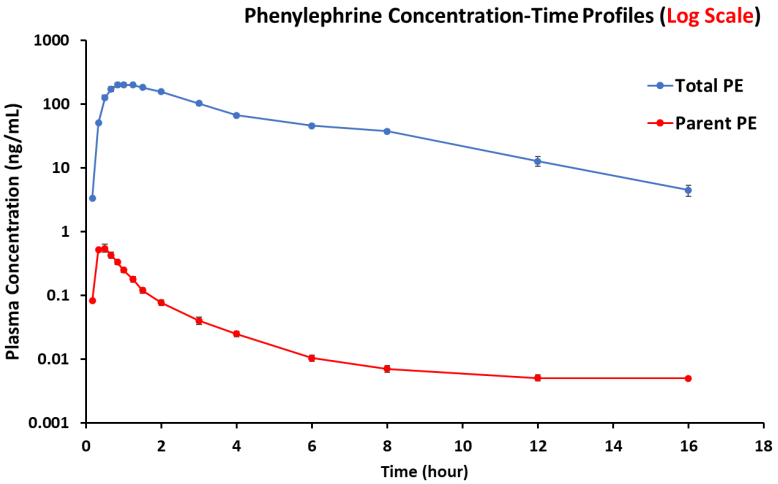
* As measured by cell-based calcium flux response

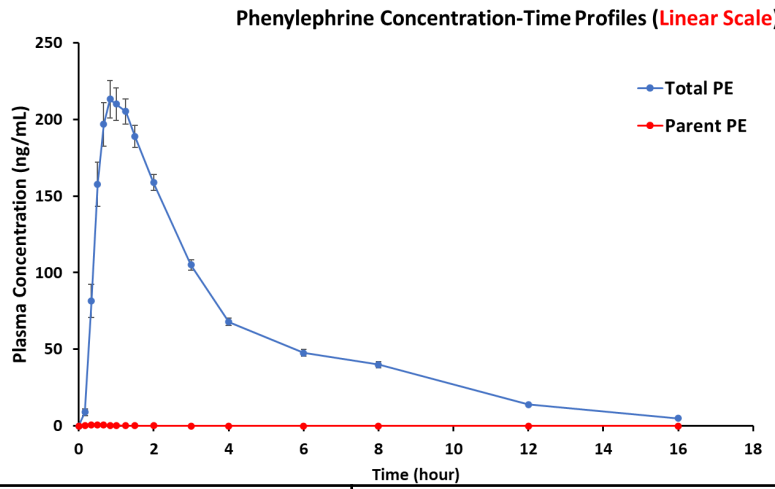
As measured by [^{35}S]-GTPγS binding exchange assay

Source: Schering-Plough 2007 Nonprescription Drugs AC meeting presentation

- *In vivo* **C_{max}** (~**0.65** ng/mL) of parent PE following a 10 mg oral dose is lower than *in vitro* α1 agonistic EC_{50} value

NDA 022565: Phenylephrine PK Profiles Following 10 mg Single Oral Dose





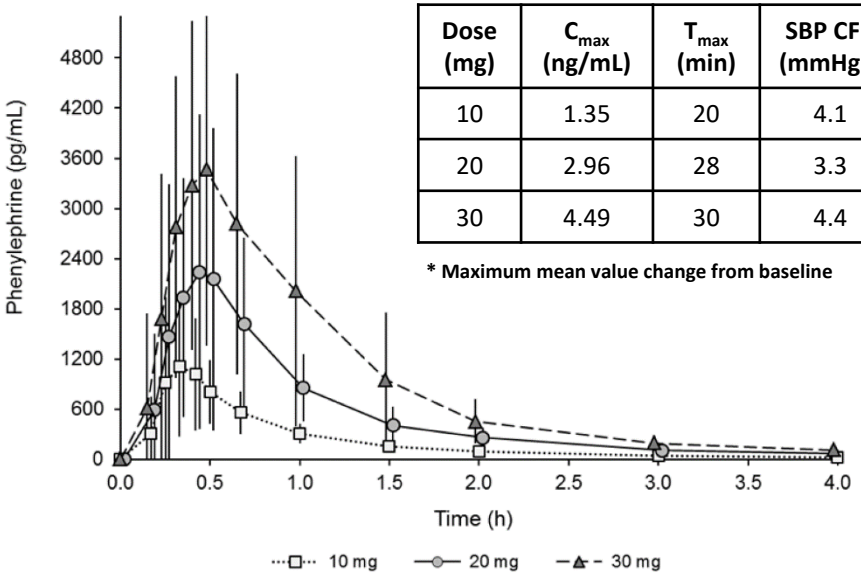
	Parent PE	Total PE	Mean Ratio (Parent/Total)
C_{max} (ng/mL)[1]	0.766 (49%)	225 (33%)	**0.34%**
$AUC_{0\text{-last}}$ (ng·hr/mL)[1]	0.692 (26%)	864 (22%)	**0.08%**
$AUC_{0\text{-inf}}$ (ng·hr/mL)[1]	0.730 (26%)	885 (22%)	**0.08%**
T_{max} (hour)[2]	0.33 (0.17, 0.83)	0.92 (0.5, 2)	N/A
$t_{1/2}$ (hour)[1]	1.55 (59%)	2.68 (21%)	N/A

[1] Geometric mean (CV%)
[2] Median (minimum, maximum)

Source: NDA 022565 Study 0813 (N=42) following single dose administration of 10 mg oral phenylephrine (Sudafed PE®)

Phenylephrine *in Vivo* PK-PD (Systemic α1-Adrenergic Activity) Relationship Following Oral Administration Route (N=28)

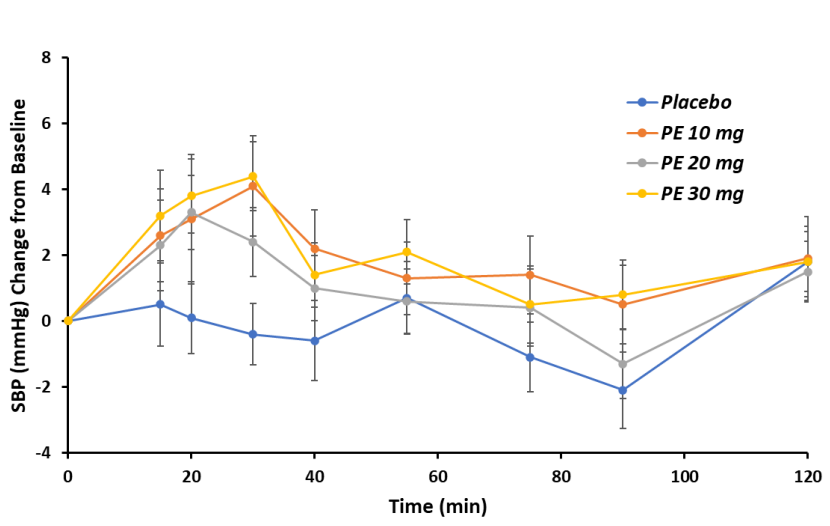
Mean Parent Phenylephrine Plasma Concentration Time Profile



Dose (mg)	C_{max} (ng/mL)	T_{max} (min)	SBP CFB (mmHg)*
10	1.35	20	4.1
20	2.96	28	3.3
30	4.49	30	4.4

* Maximum mean value change from baseline

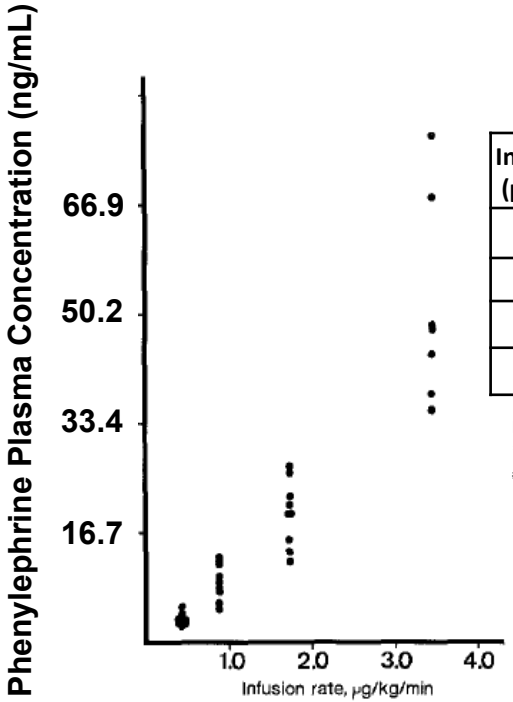
Mean Systolic Blood Pressure Change from Baseline Time Profiles



Source: Adapted from Gelotte CK. Et al. Clin Drug Investig. 2015 Sep;35(9):547-58

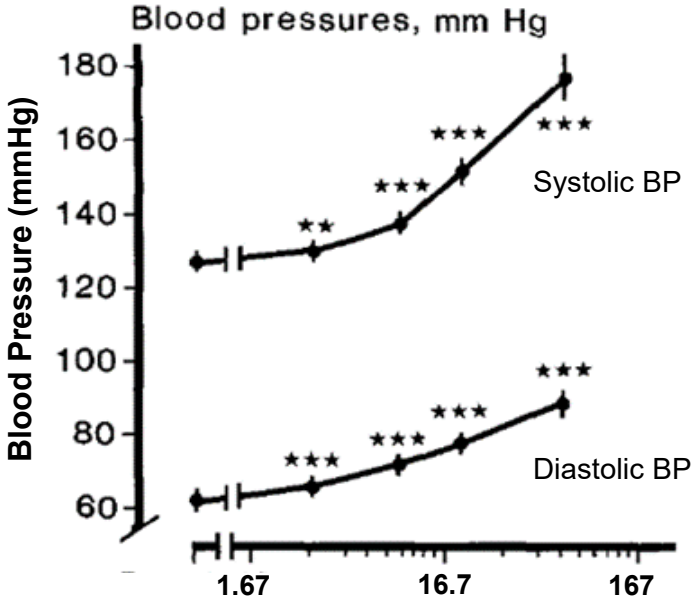
Phenylephrine *in Vivo* PK-PD (Systemic α1-Adrenergic Activity) Relationship Following IV Administration Route (N=9)

6-min Continuous Intravenous (IV) Infusion



Infusion Rate (μg/kg/min)	Dose (mg as 70kg BW for 6 min)	Css* (ng/mL)	SBP CFB (mmHg)#
0.5	0.21	3.3	3
1	0.42	9.4	11
2	0.84	19.7	26
4	1.68	51.5	53

BW: body weight
* Steady state concentration
# Maximum mean value change from baseline

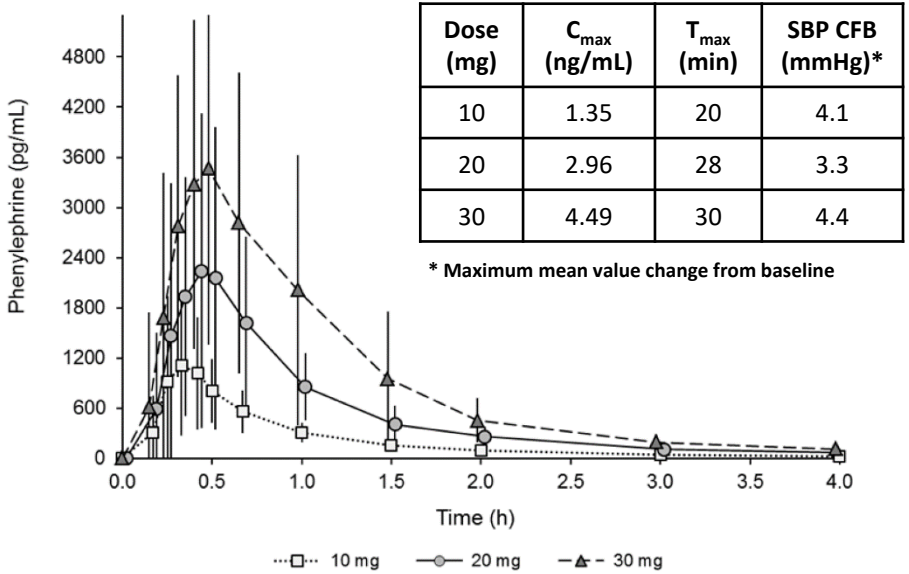


** p < 0.01
*** p < 0.001

Source: Martinsson A. et al. Eur J Clin Pharmacol. 1986;30(4):427-431

Phenylephrine *in Vivo* PK-PD (Systemic α1-Adrenergic Activity) Relationship Following Oral Administration Route (N=28)

Mean Parent Phenylephrine Plasma Concentration Time Profile



Dose (mg)	C_{max} (ng/mL)	T_{max} (min)	SBP CFB (mmHg)*
10	1.35	20	4.1
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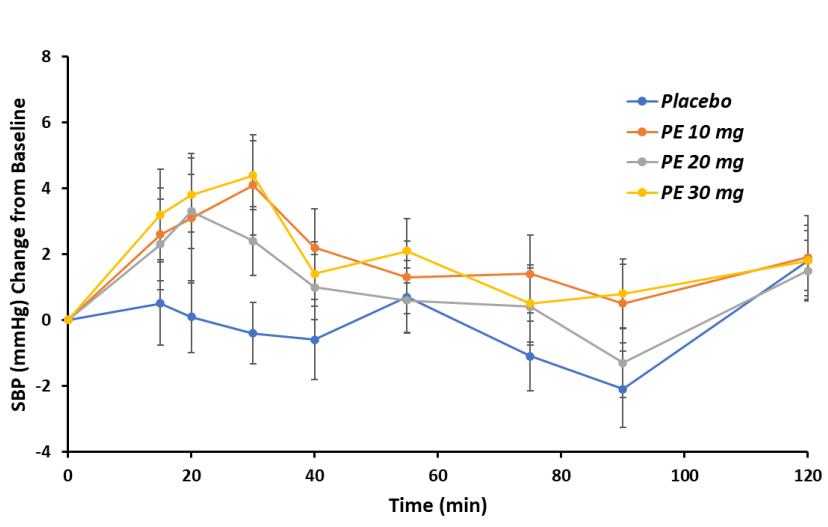
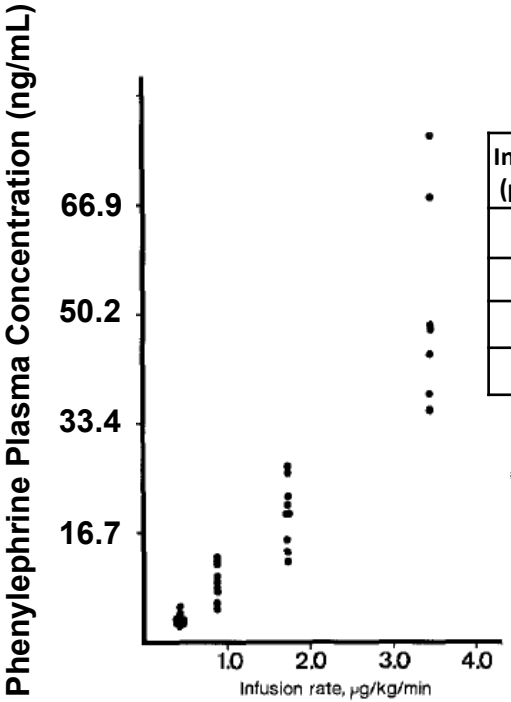
Mean Systolic Blood Pressure Change from Baseline Time Profiles



Source: Adapted from Gelotte CK. Et al. Clin Drug Investig. 2015 Sep;35(9):547-58

Phenylephrine *in Vivo* PK-PD (Systemic α1-Adrenergic Activity) Relationship Following IV Administration Route (N=9)

6-min Continuous IV Infusion



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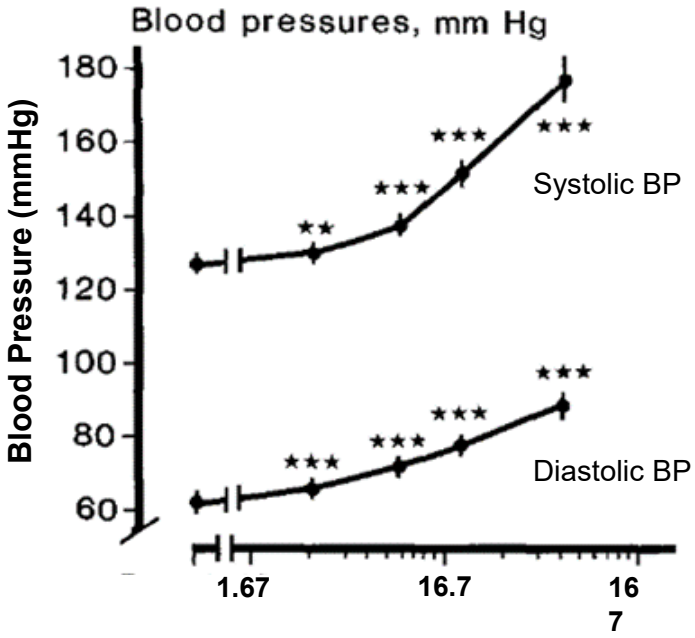

Source: Martinsson A. et al. Eur J Clin Pharmacol. 1986;30(4):427-431

Phenylephrine HCl Concentrations in Intranasal Products

- Intranasal PE products are listed in Nasal Decongestant Final Monograph since 1994.
- Monographed doses (21CFR 341.80)
  - 0.5% and 1% (5 and 10 mg/mL*) aqueous solution — Adults and children 12 years of age and over: 2 or 3 drops or sprays in each nostril (1.08 and 2.16 mg/dose assuming the same drop/spray volume in children 2 to <6 yo).
  - 0.25% (2.5 mg/mL) aqeous solution — Adults and children 6 to under 12 years of age: 2 or 3 drops or sprays in each nostril (0.54 mg/dose assuming the same drop/spray volume in children 2 to <6 yo).
  - 0.125% (1.25 mg/mL) aqeous solution — no more than 0.135 mg per three drops or three sprays, children 2 to under 6 years of age: 2 to 3 drops or sprays in each nostril (0.27 mg/dose).

* 1 mg/mL = 1,000,000 ng/mL; parent PE Cmax following 10 mg oral dose ~ 1 ng/mL

Concentration Comparisons

Scenario	Concentration	Note
Parent PE C_{max} value following 10 mg oral dose	~ 1 ng/mL	Increase systolic blood pressure by ~ 4 mmHg
Parent PE in vitro α1 adrenergic EC_{50} value	2.3 to 16.9 ng/mL	
Parent PE steady state concentration following continuous IV infusion (1 µg/kg/min)[1]	~ 10 ng/mL	Increase systolic blood pressure by ~ 10 mmHg
PE concentration for intranasal PE products (~ 0.135 mg per nasal spray dose)	1.25 mg/mL[2] (1,250,000 ng/mL)	Monograph dose/concentration[3] for PE intranasal products

[1] Approved PE IV dose for treating hypotension: 10 to 35 µg/min, titrating to effect, not to exceed 200 µg/min
[2] 0.125% or 0.125 g/100mL, 2 to 3 drops in each nostril, not more often than every 4 hours (previous 21 CFR 341.80)
[3] 0.125% is the lowest monographed concentration for intranasal PE products (0.125% to 0.5%)

Clinical Pharmacology Conclusions

- Oral relative bioavailability of parent phenylephrine is very low (<1%).
- Parent phenylephrine is a selective α1-adrenergic receptor agonist. None of phenylephrine major metabolites have detectable α1-adrenergic agonistic activity.
- The low systemic exposure of parent phenylephrine following the monographed 10 mg oral dose results in a relatively small and transient systemic α1-adrenergic activity (~ 4 mmHg↑).
- The optimal dosing frequency for oral phenylephrine to treat nasal congestion has not been sufficiently explored.


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Clinical Safety and Efficacy of Oral Phenylephrine as a Nasal Decongestant

Peter Starke, MD, FAAP
Medical Officer / Lead Clinical Reviewer
Division of Nonprescription Drugs I
Office of Nonprescription Drugs

Outline: Clinical Safety and Efficacy

- Current Data on the Efficacy of Oral PE
  - Scope of the new database
  - 2007 NDAC meeting
    - Historical context
    - Schering-Plough/Merck data
  - New clinical trials: 2011-2018
- Re-evaluation of the Pre-2007 (1970's) Monograph Data
  - 2007 meta-analyses
  - FDA re-assessment of the original studies
- Summary and Conclusion

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New Trial Database

Study	Results* (1°: Nasal Congestion Scores)
EEU	
Merck EEU (Horak 2009)	No significant difference from placebo
Merck EEU (Day 2009)	No significant difference from placebo
Clinical Trials	
Merck 10-40 mg Dose-Ranging (Meltzer 2015)	No significant difference from placebo
Merck 30 mg ER (Meltzer 2016)	No significant difference from placebo
J&J 30 mg ER (NCT03339726)	No significant difference from placebo

* Results for comparison between phenylephrine and placebo
Abbreviations: EEU = environmental exposure unit; ER = extended release

New Clinical Trial Database: Doses and Number Subjects Randomized

Trial	IR PE (mg)					ER PE 30mg	Placebo	PSE	Other
	10	12	20	30	40				
Merck EEU (Horak 2009)		38					38	39	
Merck EEU (Day 2009)	126						126		127
Merck Dose-Ranging (Meltzer 2015)	109		108	107	112		103		
Merck 30 mg ER (Meltzer 2016)						287	288		
J&J 30 mg ER (NCT03339726)		66				63	64		

Abbreviations: IR, immediate-release; PE, phenylephrine; PSE, pseudoephedrine PE 12mg is the European dose

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2007 NDAC Meeting*

- NDAC meeting addressed scientific issues raised by a 2007 Citizen Petition**
  - Amend the dosage(s) of both oral PE salts by increasing the maximum dosage for patients ≥12 years of age
  - Withdraw approval for use in children <12 years of age

* NDAC meeting held on December 14, 2007, information available at: https://wayback.archive-it.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs

** 2007 Citizen Petition – Phenylephrine, submitted by Leslie Hendeles, Pharm D; Randy C. Hatton, PharmD; and Almut Winterstein, PhD, the University of Florida on February 1, 2007. Docket ID: FDA-2007-P-108 (formerly FDA-2007-P-0047/CP1), available at: https://www.regulations.gov/docket/FDA-2007-P-0108

2007 Advisory Committee Meeting

- Original Studies
  - Petitioner's meta-analysis
  - Industry meta-analysis
  - FDA Statistical review - focused on the two meta-analyses
- **New** information
  - Schering-Plough: Clinical pharmacology and oral bioavailability data
  - Schering-Plough Merck: 2 environmental exposure unit (EEU) studies
- AC Recommendations
  - Obtain more clinical data to evaluate higher doses (≥12y)
  - Use clinical symptom scores as primary endpoint in future trials (per FDA Guidance for Industry. Allergic Rhinitis: Developing Drug Products for Treatment)

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Schering-Plough Merck Development Programs Pre- and Post- 2007 NDAC

- Two programs – IR and ER products
  - Receptor binding and PK studies
  - EEU studies
  - Safety – identified 40 mg dose as safe
  - Bioequivalence study – 30 mg ER not bioequivalent to 3 x 10 mg IR tabs dosed every 4 hours
  - 2 large CTs, one each for IR & ER products

Source

2007 NDAC

clinicaltrials.gov and/or publications

New Trial Database

Study	Results* (1°: Nasal Congestion Scores)
EEU	
Merck EEU (Horak 2009)	No significant difference from placebo
Merck EEU (Day 2009)	No significant difference from placebo
Clinical Trials	
Merck 10-40 mg Dose-Ranging (Meltzer 2015)	No significant difference from placebo
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J&J 30 mg ER (NCT03339726)	No significant difference from placebo

* Results for comparison between phenylephrine and placebo
Abbreviations: EEU = environmental exposure unit; ER = extended release

Environmental Exposure Unit (EEU) Studies

Presented by Schering-Plough Merck at 2007 NDAC Meeting

EEU Studies

- EEU studies
  - Proof-of-concept, pharmacodynamic (early Phase 2) studies
  - Subjects with Seasonal Allergic Rhinitis (SAR) are 'primed' by multiple exposures to pollen in the EEU chamber
  - When symptoms are sufficient, they are treated and observed for the response to treatment (crossover design with washout period OR a parallel group design)
  - SAR includes the symptom of nasal congestion
- Two Merck* studies
  - PE vs pseudoephedrine (PSE, 60 mg) vs placebo (Horak 2009)
  - PE vs test combination (loratadine-montelukast) vs placebo (Day 2009)
  - Primary efficacy assessment: Change from baseline in average nasal congestion score over 6 hours**
  - PE was no more effective than placebo

*Co-developed with Schering-Plough

**Follows FDA Guidance for Industry; Allergic Rhinitis: Developing Drug Products for Treatment. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/allergic-rhinitis-developing-drug-products-treatment-guidance-industry

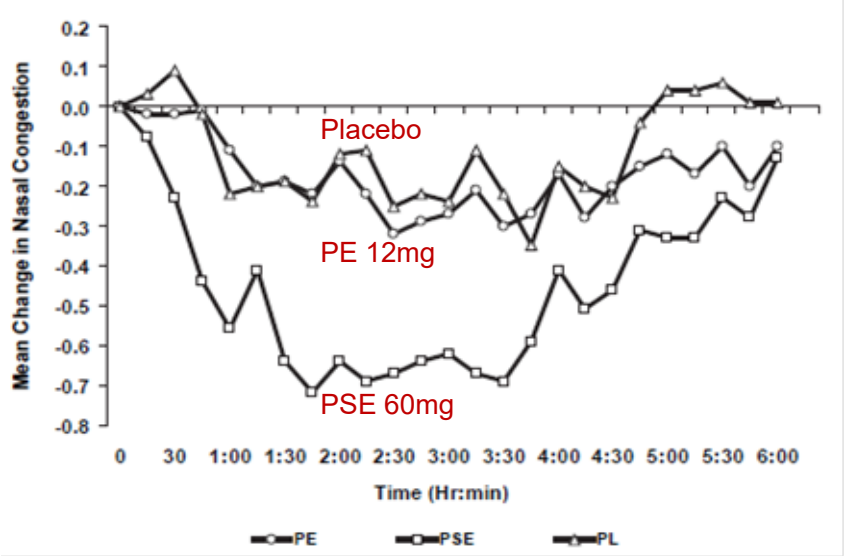
EEU Study P04579 (Horak 2009)*

- Randomized, investigator-blind, single-dose, 3-way crossover study in 39 patients with seasonal allergic rhinitis (SAR) to grass pollens
- Conducted January 2006 at the Vienna EEU chamber; funded by Schering-Plough Research Institute
- Patients who met minimum symptom scores during a 120-minute pre-dose challenge were treated with immediate-release (IR)
  - Phenylephrine (PE) 12 mg (EU-approved product)
  - Pseudoephedrine (PSE) 60 mg
  - Placebo (PLA)
- Symptom scores, rhinometry, peak nasal inspiratory flow (PNIF), and nasal secretions for weight were collected at 30-minute intervals
- Primary efficacy assessment: Change from baseline in average nasal congestion score over 6 hours

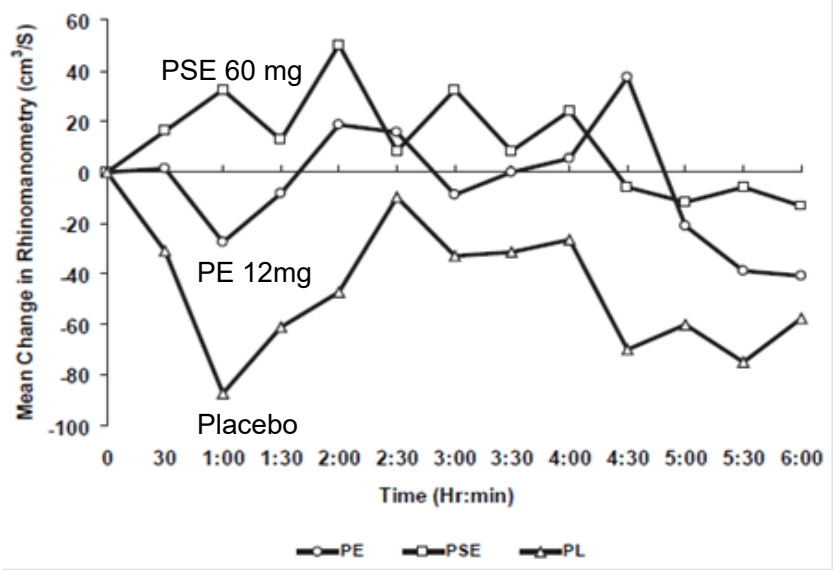
* Horak et al. A placebo-controlled study of the nasal decongestant effect of phenylephrine and pseudoephedrine in the Vienna Challenge Chamber. Ann Allergy Asthma Immunol 2009;102:116-120

EEU Study P04579 (Horak 2009)*

1°: Nasal Congestion Scores



2°: Nasal Rhinometry (NAR)



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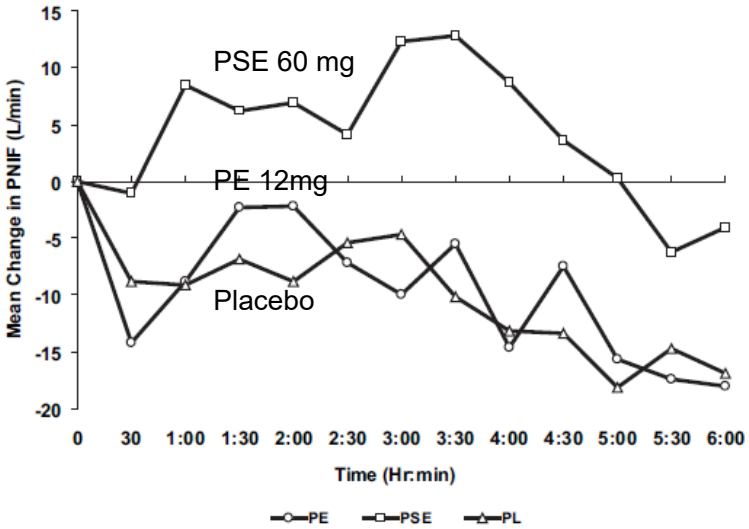
EEU Study P04579 (Horak 2009)*

2°: Peak Nasal Inspiratory Airflow (PNIF)



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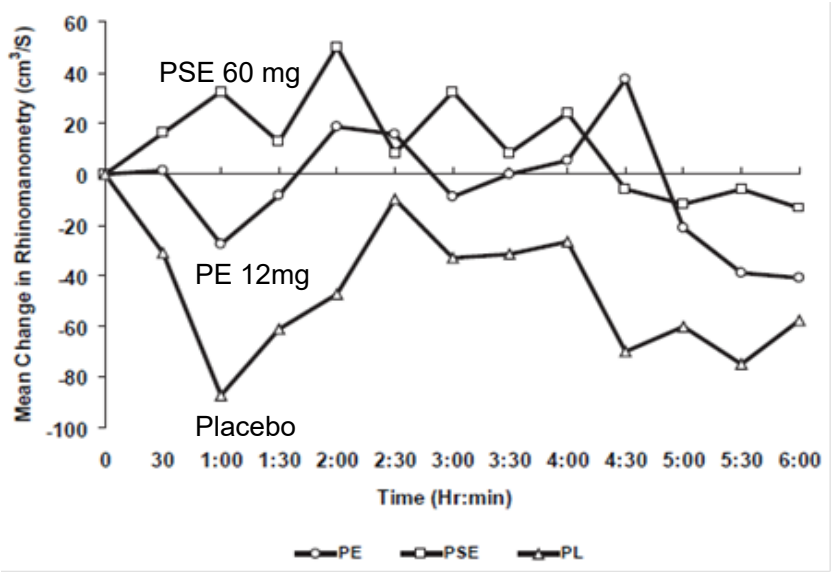

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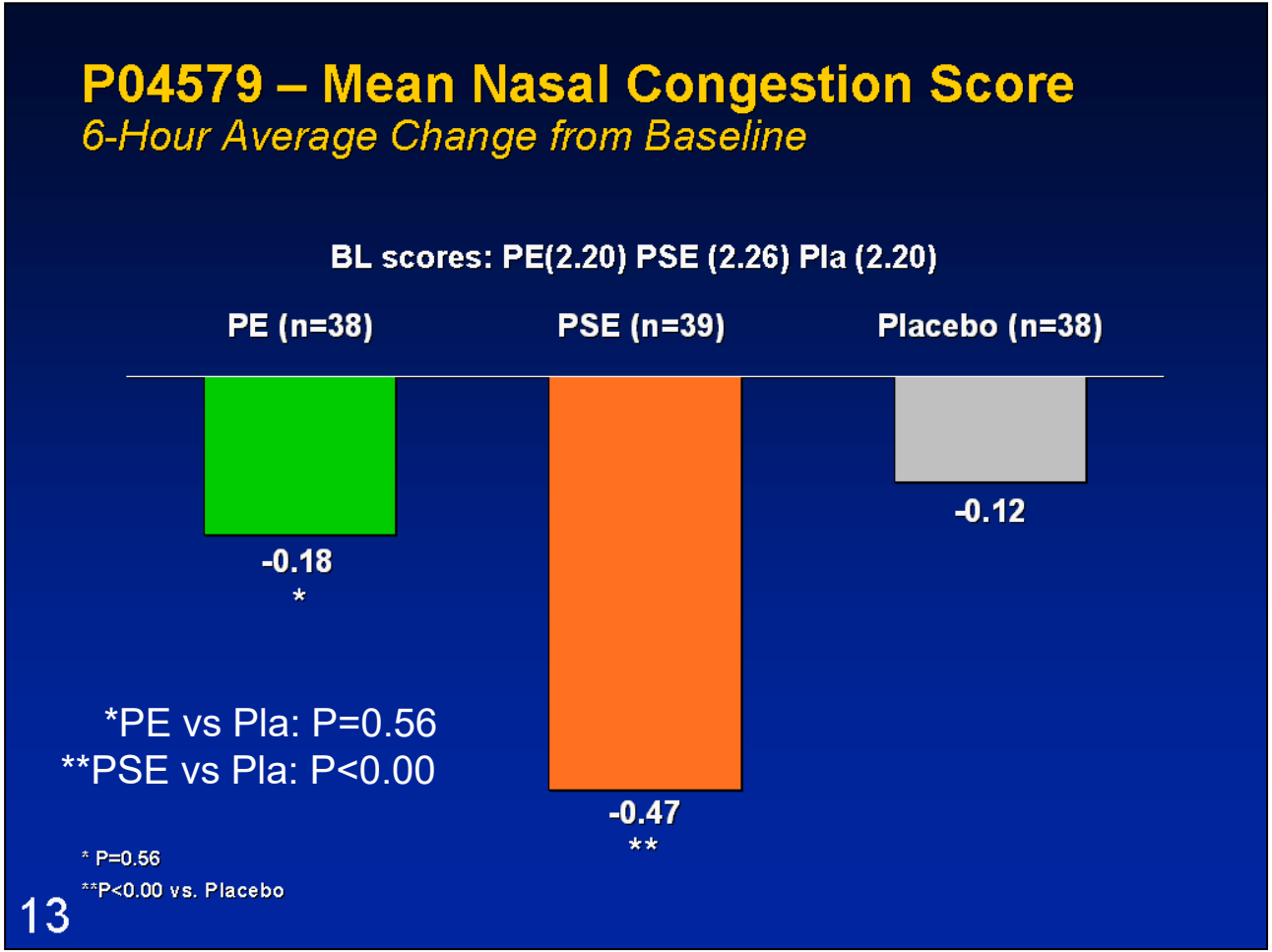
P04579 – Mean Nasal Congestion Score

6-Hour Average Change from Baseline



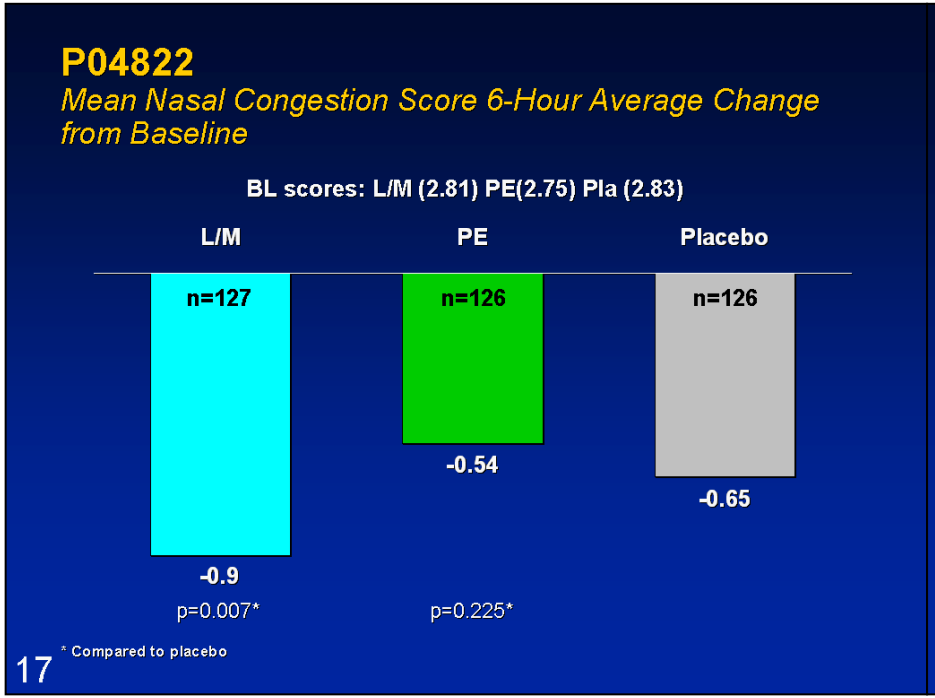
Source: Schering-Plough presentation at December 14, 2007 NDAC

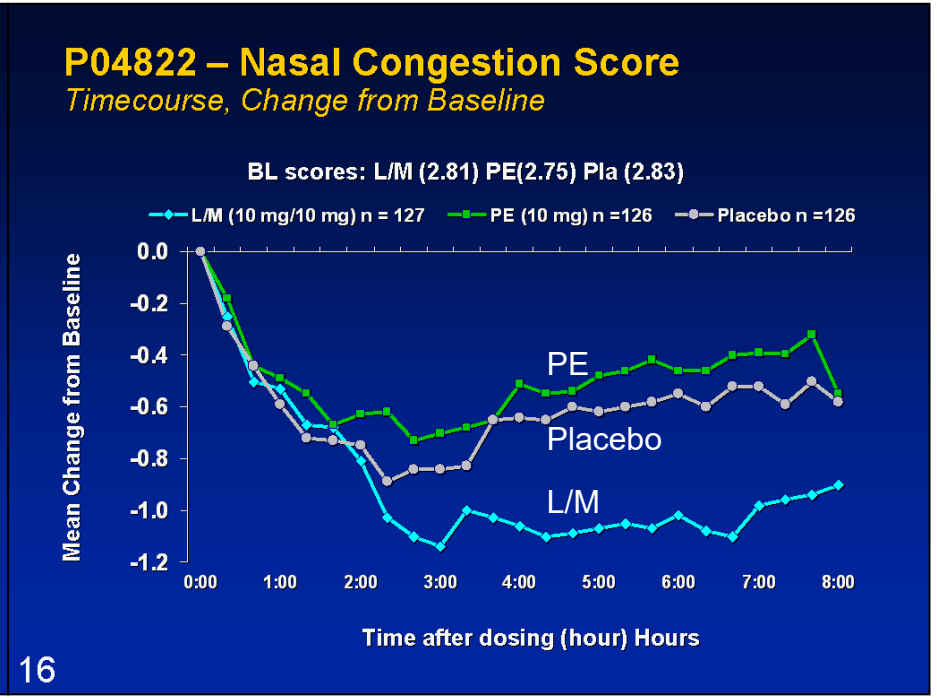
EEU Study P04822 (Day 2009)*

- Randomized, double-blind, double-dummy, placebo-controlled, 3-arm, parallel group, single-dose study in 379 patients with SAR to ragweed
- Kingston Ontario EEU chamber, funded by Schering-Plough Merck
- After priming, patients who met minimum symptom scores during a pre-dose challenge were treated with immediate-release
  - Test: Loratadine/montelukast (10mg/10mg) (n=127)
  - PE 10mg (n=126)
  - Placebo (n=126)
- Symptom scores and PNIF were collected at 20-minute intervals
- Primary efficacy assessment: Change from baseline in average nasal congestion score over 6 hours (Primary comparison: L/M vs placebo)

* Day et al. Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit. Ann Allergy Asthma Immunol 2009;102:328–338

EEU Study P04822 (Day 2009)*





Source: Schering-Plough presentation at December 14, 2007 NDAC

Industry Conclusions EEU Study P04822*

- "A single dose of [oral] pseudoephedrine (60 mg) showed the expected decongestant response (symptoms, nasal airflow) compared to placebo
- A single dose of [oral] phenylephrine (10 mg or 12 mg), overall, showed no decongestant response compared to placebo
  - Replicated in two studies"

*Source: Schering-Plough presentation at December 14, 2007, NDAC meeting

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* Results for comparison between phenylephrine and placebo
Abbreviations: EEU = environmental exposure unit; ER = extended release

Merck Clinical Trials

Post 2007 NDAC Meeting: Merck Clinical Trials (Conducted in 2011)

- Two large clinical trials in subjects with Seasonal Allergic Rhinitis (SAR)
  - Dose-ranging: 10, 20, 30, 40 mg IR vs placebo (NCT01330017 – Meltzer 2015)
  - 30 mg ER versus placebo (with an ER formulation that provides higher systemic exposure than 3 x 10mg IR Q4h) (NCT01413958 – Meltzer 2016)
- Both published in a peer-reviewed journals and at clinicaltrials.gov
- Size and primary endpoint similar to Phase 3 pivotal trials for drug registration of antihistamines and intranasal products for allergic rhinitis
  - SAR provides a more stable environment than upper respiratory infections (URIs)
  - Nasal congestion rated twice daily on a 4-point 0-3 scale, per FDA Allergic Rhinitis Guidance
  - Primary efficacy endpoint: Change in reflective nasal symptom scores over 1-week of treatment
- Results
  - Neither trial showed efficacy of any dose of PE compared with placebo
  - No meaningful safety issues

Merck 7-Day Safety Study
(CL2007-07, P07529; NCT00874120*)

- Randomized, double-blind, placebo-controlled, multiple-dose cross-over, ambulatory blood pressure safety study conducted in 2009
- Compared 7 days of treatment with a 30 mg ER oral PE product and placebo, with a 6-8 day washout between treatment arms
- 116 subjects randomized, 58 per arm, 106 completed the study
- Mean (SD) age: 29 (10.5) years; 52.6% were males
- Primary outcome: Average systolic BP readings for a 5-hour range around the time of maximal concentration (T_{max})
- No meaningful differences in mean (SD) systolic blood pressure (SBP) were noted
  - 30 mg ER: 118.3 (9.24)
  - Placebo: 118.6 (9.38)

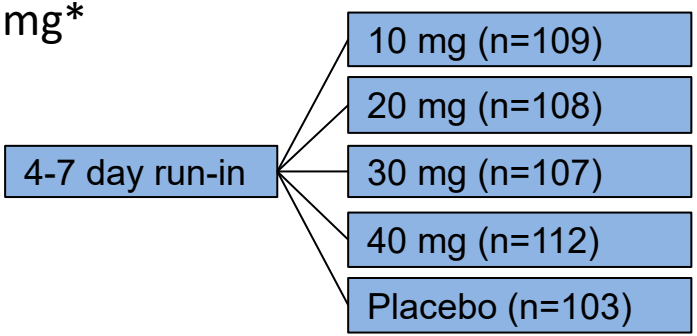
*Results available at clinicaltrials.gov: https://clinicaltrials.gov/ct2/show/NCT00874120

Merck Dose-Ranging Trial (2011)

Dose-Ranging Trial

(Merck Protocol CL2010-06; NCT01330017; Meltzer 2015)*

- Multicenter, randomized, dummied but only partially-blinded, placebo-controlled, 5-arm, parallel-group trial in healthy adults with SAR caused by spring allergens
- Background treatment: loratadine 10 mg*



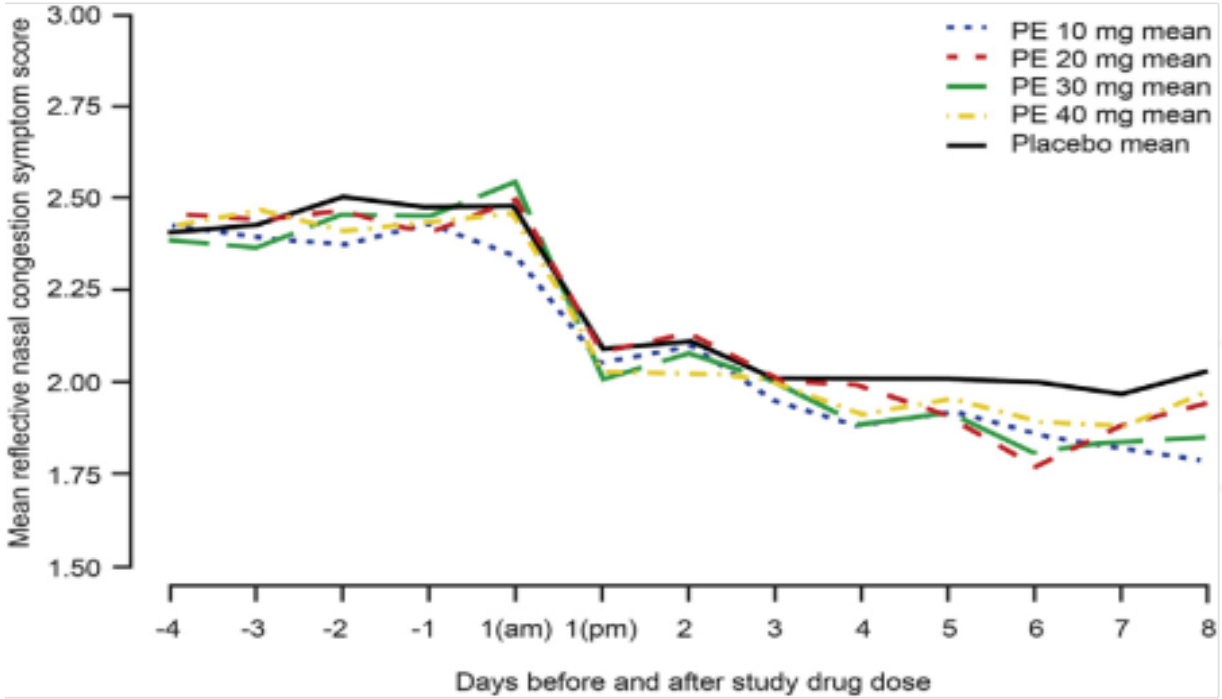
- IR dosing every 4 hours for 1 week
- Similar but not identical placebo
- Primary endpoint: Mean change from baseline in daily reflective nasal congestion scores over the treatment period
- 539 randomized, 519 (95.9%) completed
- Treatment groups comparable

*Prior studies have shown that this dose of loratadine has no effect on congestion.
Meltzer et al. J Allergy Clin Immunol Pract. 2015;3(5):702-8
Results available at: https://clinicaltrials.gov/ct2/show/results/NCT01330017

Dose-Ranging Trial – Results

(Protocol CL2010-06; NCT01330017; Meltzer 2015)*

Mean Reflective Nasal Congestion Scores by Treatment and Study Day



539 randomized
- 10 mg = 109
- 20 mg = 108
- 30 mg = 107
- 40 mg = 112
- placebo = 103

- No statistically significant differences between any PE dose and placebo
- No meaningful difference between PE doses

* Meltzer et al. J Allergy Clin Immunol Pract. 2015;3(5):702-8

Merck 30 mg Extended-Release Trial (2011)

Extended-Release Trial

(Merck Protocol CL2011-06; NCT01413958; Meltzer 2016)

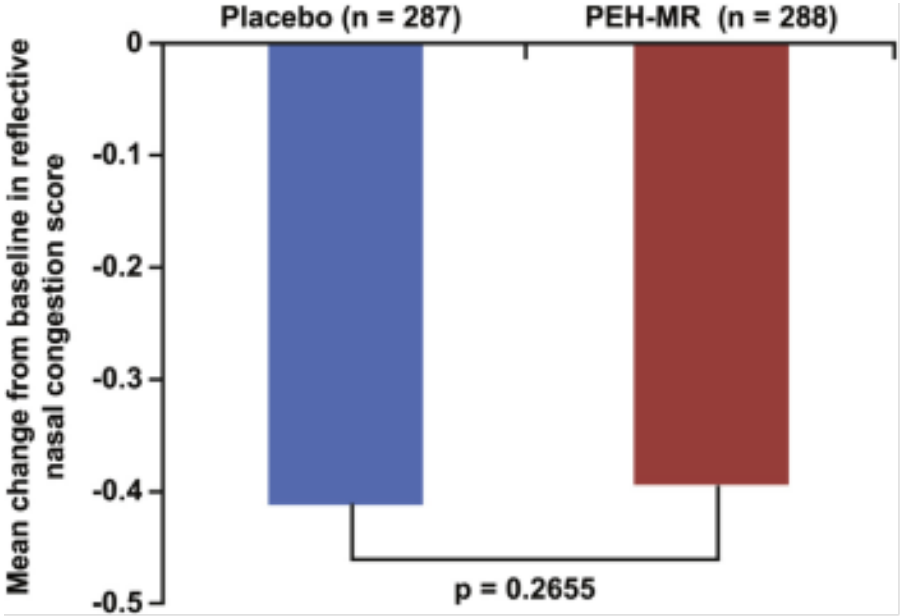
- Performed after a bioavailability (BA) study failed to show bioequivalence to, and with higher systemic exposure than, 3 x 10 mg IR PE tabs
- Multicenter, randomized, double-blind, double-dummy, placebo-controlled, 2-arm, parallel-group trial
  - 30 mg modified-release PE (n=287)
  - Placebo (n=288)
- BID treatment for 7 days
- No background treatment except loratadine 10 mg rescue prn
- Primary endpoint: Mean change from baseline in daily reflective nasal congestion scores over the treatment period
- 575 randomized, 574 (99.8%) completed
- Treatment groups comparable, 61% female, 83% White, mean 40.1 yrs.

Meltzer et al. Ann Allergy Asthma Immunol 2016 Jan;116(1):66-71. Results available at: https://clinicaltrials.gov/ct2/show/results/NCT01413958

Extended-Release Trial – Results

(Study CL2011-06; NCT01413958; Meltzer 2016)

Primary Endpoint: Mean Change From Baseline in Reflective Nasal Congestion Score (ITT Pop)*



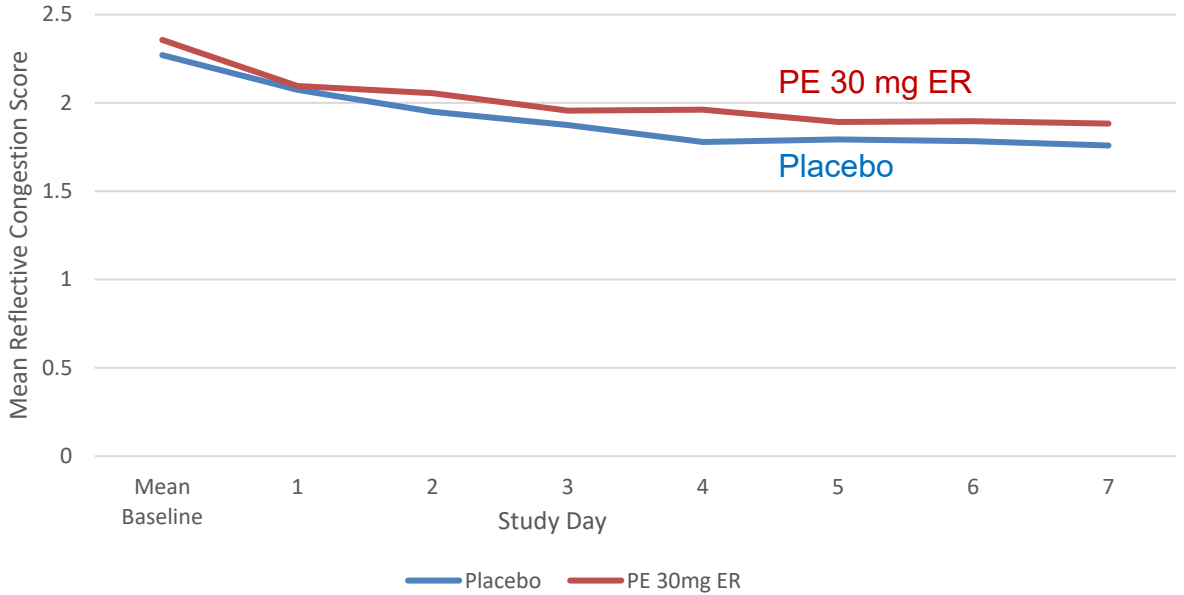
	Placebo N=287	PEH-MR 30 mg N=288
Baseline (SD)	2.271 (0.5586)	2.357 (0.5203)
Primary Endpoint: Mean change Over Treatment (SD)	-0.412 (0.5383)	-0.394 (0.4880)

*Meltzer et al. Ann Allergy Asthma Immunol 2016 Jan;116(1):66-71 and https://clinicaltrials.gov/ct2/show/NCT01413958

Extended-Release Trial – Results

(Study CL2011-06; NCT01413958; Meltzer 2016)

Mean Daily Reflective Nasal Congestion Scores at Baseline and by Study Day (ITT Pop)



Adapted from results published at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01413958)

Johnson & Johnson* Trial (NCT03339726) (2017-18)

*Performed by Johnson & Johnson Consumer Inc. (J&JCI)

Johnson & Johnson Cold Trial*

- Conducted in Canada during the 2017-2018 cold season
- Randomized, double-blind, double-dummy, placebo-controlled, parallel-group in adults with nasal congestion due to the common cold (~72 hours into symptoms)
- Treatments
  - 30 mg PE ER tablet taken twice daily (2 doses 12 hours apart)
  - 12 mg PEH IR capsule taken four times daily (4 doses 4 hours apart)
  - Placebo
- Assessments
  - Reflective Nasal Congestion Severity Score (NCSS), assessed on an 8-point (0-7) scale, where 0 = none and 7 = severe
  - Baseline, and at 2, 4, 6, 8, 10, 12, 24 hours after first dose

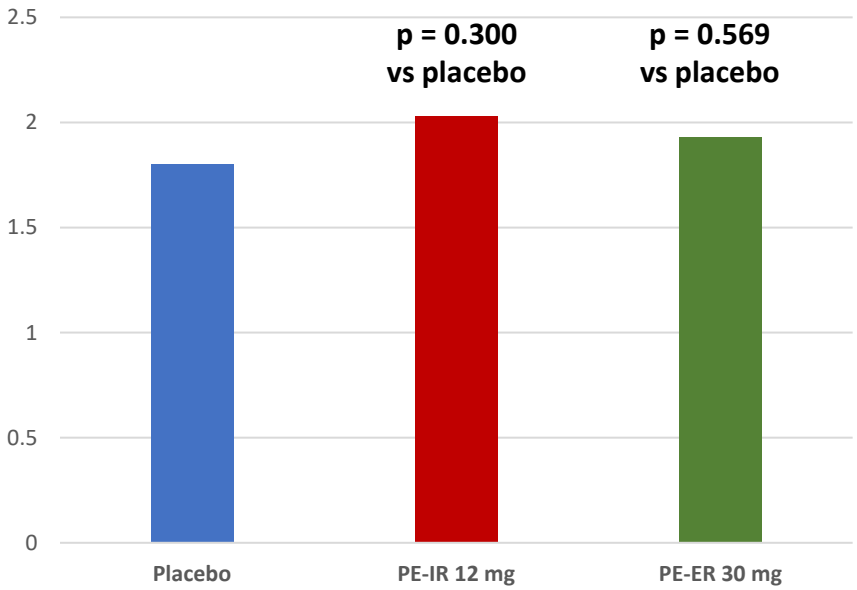
* Source: clinicaltrials.gov, NCT03339726. Available at: https://clinicaltrials.gov/ct2/show/NCT03339726

Johnson & Johnson Cold Trial*

- Primary endpoint
  - Mean change from baseline in NCSS over 0-12 hours after the first dose
  - Analyzed for the intent-to-treat (ITT) population using an analysis of variance (ANOVA) model with treatment group, study center, and baseline nasal scores as factors
- Planned 450 subjects
- Enrolled 193 subjects prior to the end of the cold season (terminated early)
- Demographics
  - Similar between the three arms
  - 63.2% female, 78.2% White, 13.9% Asian
- Safety: No adverse events reported

* Source: clinicaltrials.gov, NCT03339726. Available at: https://clinicaltrials.gov/ct2/show/NCT03339726

Johnson & Johnson Cold Trial - Primary Endpoint



	Placebo N=64	PE-IR 12 mg N=66	PE-ER 30 mg N=63
Mean Change (SD)	1.80 (0.156)	2.03 (0.1540)	1.93 (0.158)
Mean difference vs placebo (95% CI)		0.23 (-0.205 to 0.662)	0.13 (-0.311 to 0.564)

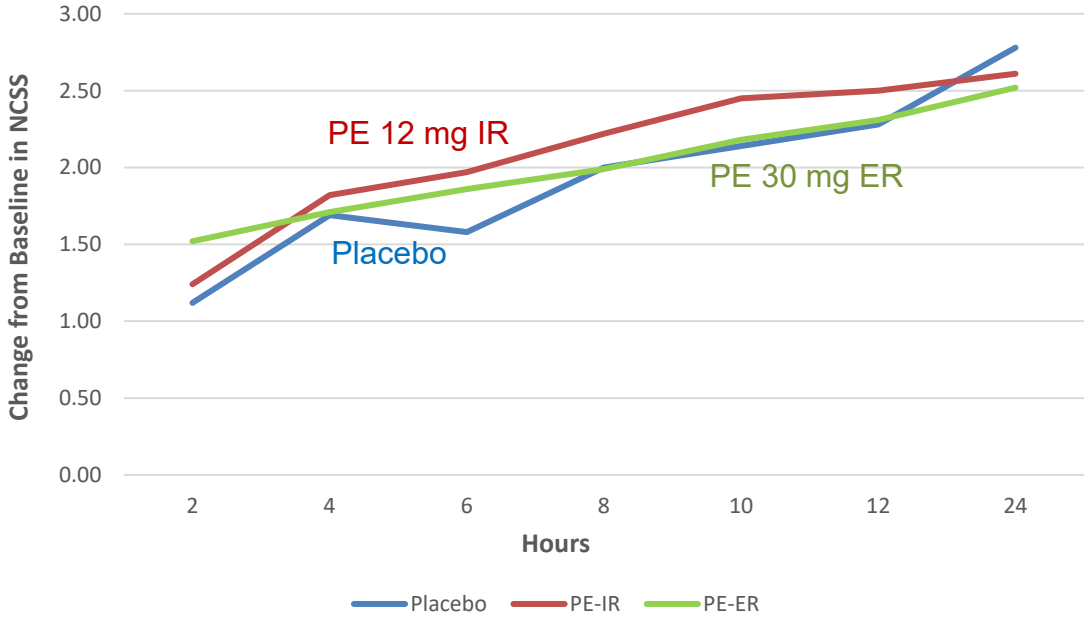
Note: All results expressed as positive numbers, suggesting that either the results were expressed as Absolute Change from Baseline OR, everyone got worse (with placebo the least)

Y Axis: Zero value = Baseline NCSS

Source: Adapted from data available at: https://clinicaltrials.gov/ct2/show/NCT03339726

Johnson & Johnson Cold Trial – Change Over Time

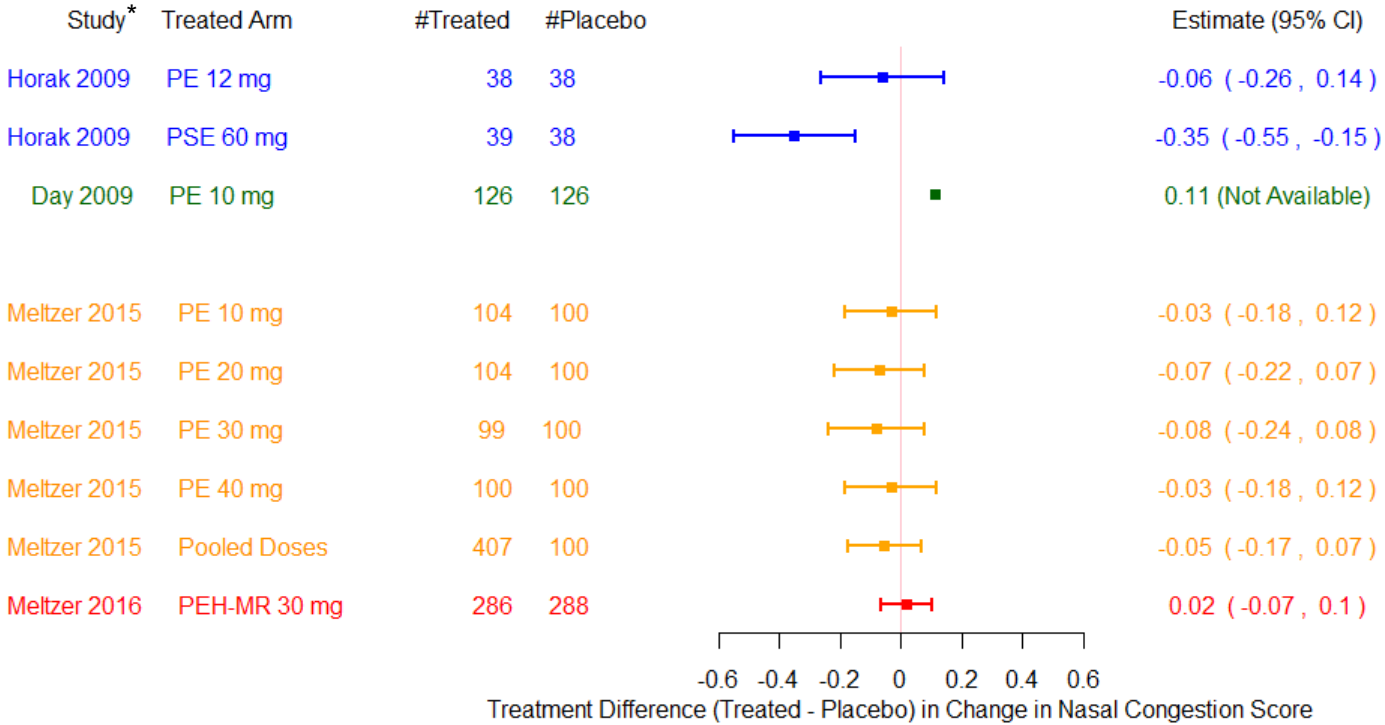
Change From Baseline in Nasal Congestion Severity Scores (NCSS) Over 24 Hours
[Presumed Absolute Change]



Source: Adapted from data available at: https://clinicaltrials.gov/ct2/show/NCT03339726

Summary of Treatment Difference in New Trials

PSE



* Change from baseline was averaged over 6 hours in the two 2009 studies and 7 days in the 2015 and 2016 studies.
# The number of treated and placebo refer to subjects who completed the study. There were very few subjects who did not complete the study in general.

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2007 NDAC Meeting: Meta-Analyses

Meta-Analyses of Original Panel Studies

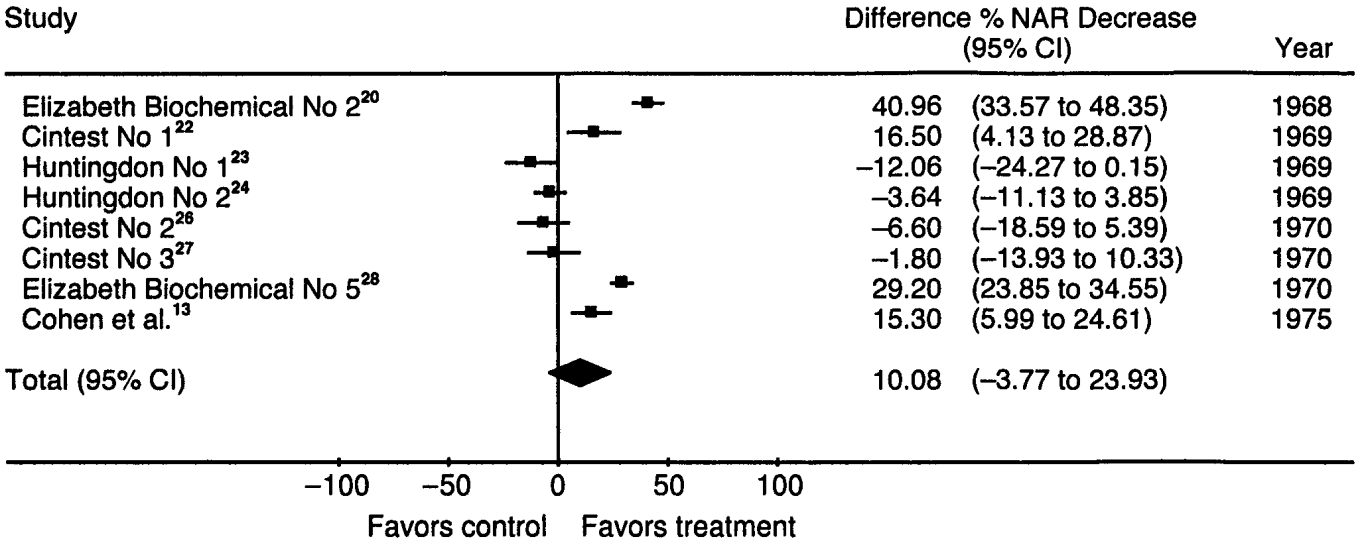
- Petitioners Meta-Analysis*
  - Used 8 of the 14 original efficacy studies
  - Did not confirm the Original Panel's findings
- Industry Meta-Analysis**
  - Used 7 crossover studies
  - Appeared to confirm the Original Panel's findings

*Hatton et al. Efficacy and Safety of Oral Phenylephrine: Systematic Review and Meta-Analysis. Annals of Pharmacotherapy, 2007;41:381

**Kollar et al. Meta-analysis of the efficacy of a single dose of phenylephrine 10 mg compared with placebo in adults with acute nasal congestion due to the common cold, Clin Ther, 2007;29(6):1057-1070

2007 CP – Petitioner's Meta-Analysis

Pooled Random Effects Mean Maximum Difference in Percentage NAR Decrease over 120 Min Between Phenylephrine and Placebo



Source: Hatton et. al. 2007 Efficacy and safety of oral phenylephrine: systematic review and meta-analysis, *Ann Pharmacother*, 41(3):381-390. *Note*: Cohen et al. is also BEI Whitehall study.

FDA Statistical Analysis (Dr Lin)

- Petitioners and industry meta-analyses
  - Included different studies
  - Used analyses of nasal airway resistance (NAR) endpoints that were different than how the original studies were analyzed (i.e., new endpoints)
- Looked at data from all available studies
  - Found evidence of treatment-by-study-site interaction, which "indicates heterogeneity and limits poolability"
- Assessment: Neither meta-analysis conclusive

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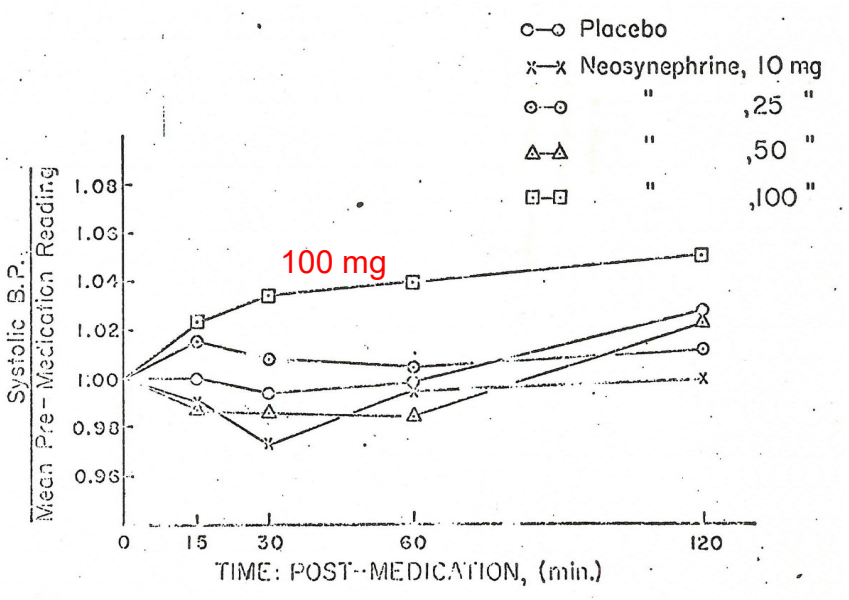
Original Studies
Reviewed by the DESI Panel

Original DESI Panel Review: Safety

- 16 studies - oral doses mostly between 5-60 mg, several up to 100 mg
- Cardiovascular effects of 10 mg "approximate placebo"
- No side effects at 10 mg - mild central nervous system (CNS) stimulation at 15-25 mg
- Pharmacodynamic (PD) effects (↑BP) inconsistent until ~100 mg

Systolic BP*



*41 FR 38312 (9/9/1976) at 38400, Ref 3: Standler to Ludena. Analysis of blood pressure and pulse results for subjects given placebo and Neo-Synephrine orally. Unpublished report from Sterling-Winthrop Lab, dated January 6, 1967

Original DESI Panel Review: Efficacy

- 14 studies - oral doses up to 40 mg
  - All but one were in subjects with colds
  - 1° Endpoint: Nasal airway resistance (NAR) as measured by rhinometry*
  - 2° Endpoint: Symptoms
  - Most evaluated PD parameters: BP and heart rate (HR)

* The Agency now recommends use of clinical symptom scores as a primary endpoint, as recommended in the Guidance for Industry: Allergic rhinitis: Developing drug products for treatment (FDA, 2018). Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/allergic-rhinitis-developing-drug-products-treatment-guidance-industry

Original DESI Efficacy Studies

N = 14	Study	Results (1°: NAR)
Parallel design		
1	BEI 1025 (Whitehall)	“Positive”
Crossover design		
1	Univ of Maryland	No data
1	Sterling-Winthrop – preliminary	No usable data
10	Sterling-Winthrop	6 "Positive”, 4 “Negative”
1	Columbia Univ*	“Negative”

*See Rogers. Also, see Bickerman 1971, which is an earlier publication of the same study from the same authors

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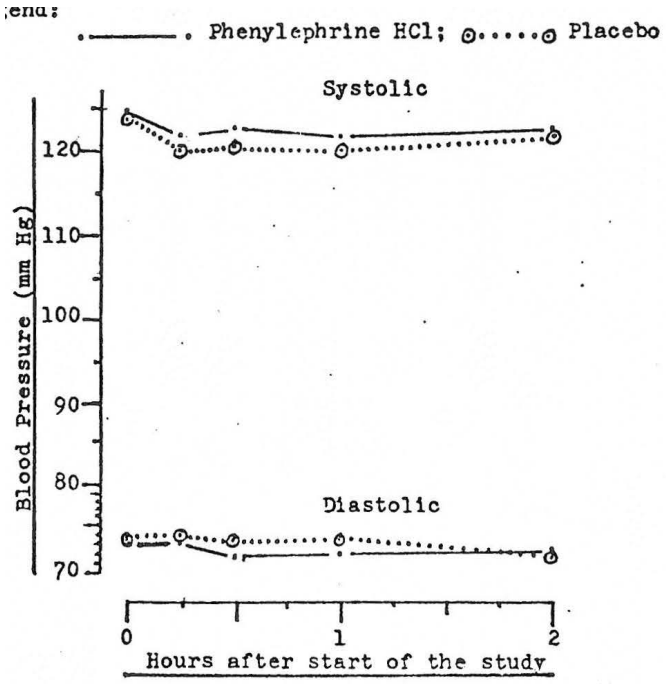
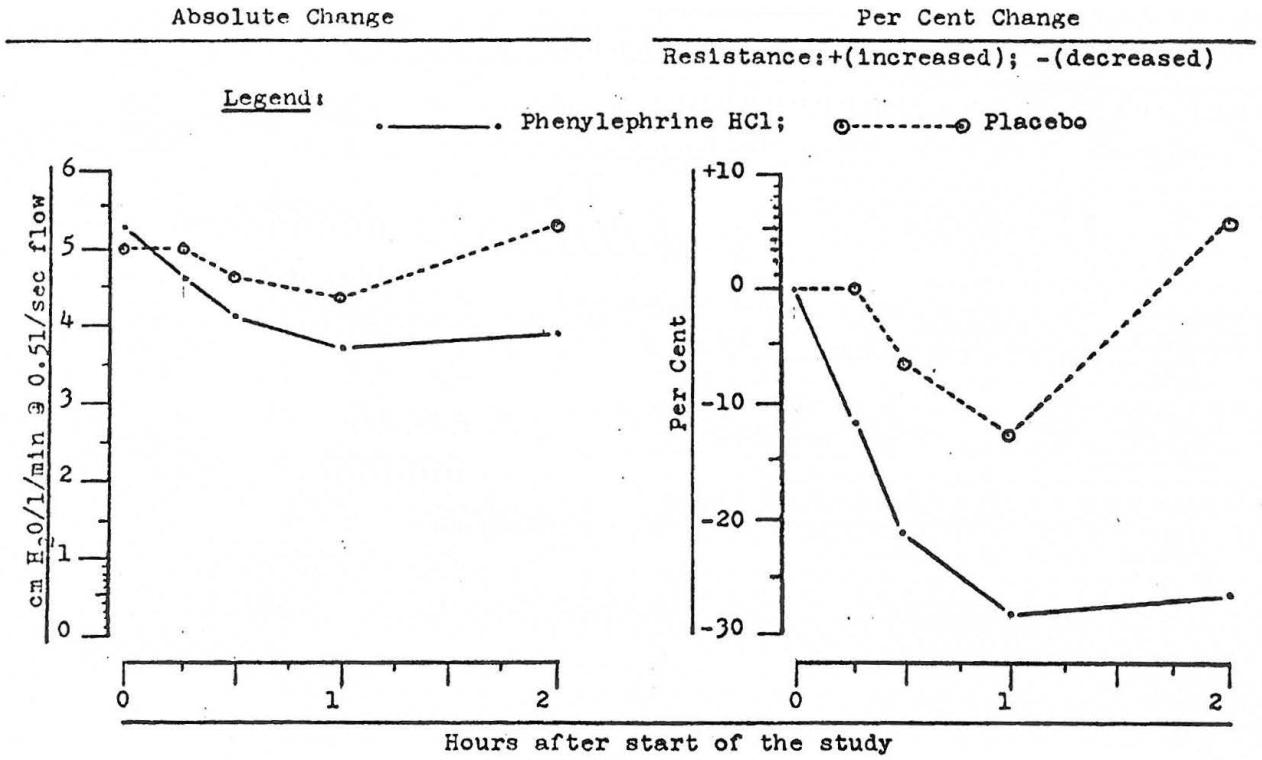
BEI 1025 Study (Whitehall Labs)*

- Double-blind, placebo-controlled, parallel group
- 200 subjects with “common cold”
- 4 doses of PEH 10 mg or placebo over 12 hours
- 1°: Rhinometry (N= 50; 25/arm), performed at 0, 15, 30, 60, 120 minutes after first dose
- 2°: Symptoms (N=200; 100/arm) over 12 hours
  - Improvements in nasal congestion, runny nose, and sneezing throughout the 12-hour observation period that was different for PE than placebo (scoring unspecified)
  - No improvement in cough or muscle ache
- No differences in SBP or diastolic blood pressure (DBP)



* 41 FR 38312 (September 9, 1976) at 38399, Ref 26. Study report from Burton Cohen at Bio-Evaluation, Inc., for Study BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.

BEI 1025: Absolute and Percent Changes in NAR Over 2h (n=50)*



% NAR reduction

15 min	11%
30 min	21%
60 min	28%
120 min	26%

* 41 FR 38312 (September 9, 1976) at 38399, Ref 26. Study report from Burton Cohen at Bio-Evaluation, Inc., for Study BEI 1025 and 1025a, conducted for Whitehall Laboratories, June 1975.

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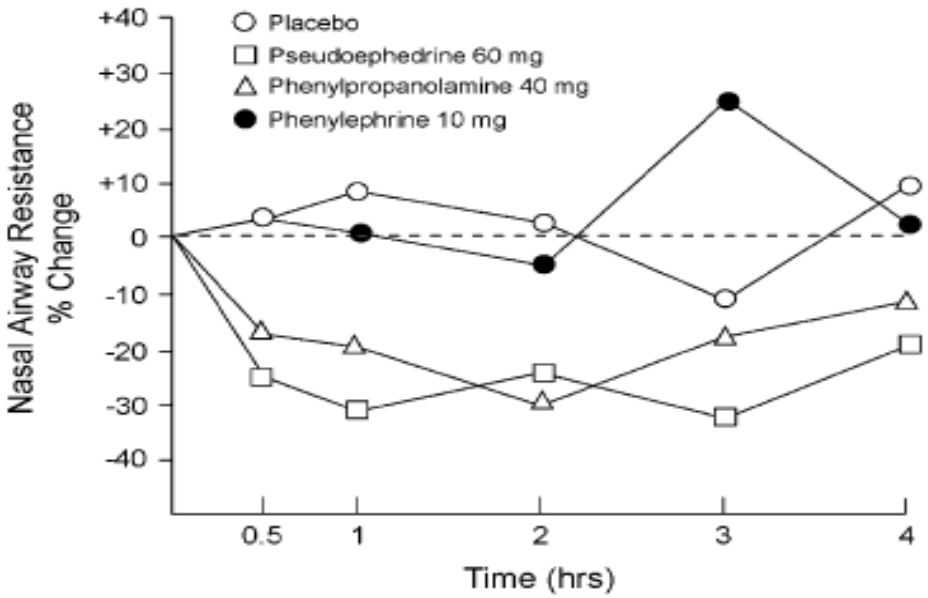
Bickerman et al. (Rogers) – Columbia University

- R, DB, PC, crossover
- 57 patients with reversible, non-atopic nasal congestion
- Treatments
  - ○ Placebo
  - ❑ PSE 60 mg*
  - Δ PPA 40 mg**
  - ● PE 10 mg*
  - ● NOT shown: PE 20, 40 mg***
- Endpoint: Nasal airway resistance

* Monographed doses of PE and PSE
** Proposed dose of PPA was 25 mg
*** Rogers 1973, 41 FR 38312 (9/9/1976), Ref 25

Comparison of the Effect of Phenylephrine, Phenylpropanolamine, and Pseudoephedrine on Nasal Airway Resistance over 4 Hours Post Dosing*



Graphic published by Hendeles, L. Selecting a decongestant. *Pharmacotherapy*, 1993;13(6 Pt 2), 129S-134S; discussion 143S-146S. Adapted with permission from Bickerman HA. Physiologic and Pharmacologic Studies on Airway Resistance. JACI, 1971. Appears under a citation attributed to Rogers (ref 25) in the 1976 ANPR.

Original DESI Efficacy Studies

N = 14	Study	Results (1°: NAR)
Parallel design		
1	BEI 1025 (Whitehall)	"Positive"
Crossover design		
~~1~~	~~Univ of Maryland~~	~~No data~~
~~1~~	~~Sterling-Winthrop – preliminary~~	~~No usable data~~
10	Sterling-Winthrop	6 "Positive", 4 "Negative"
1	Columbia Univ*	"Negative"

*See Rogers. Also, see Bickerman 1971, which is an earlier publication of the same study from the same authors

10 Sterling-Winthrop Studies

- 3 sites (Elizabeth, Huntingdon, Cintest)
- R, DB, PC, 2-way crossover
- Subjects with colds
- Similar design and Endpoints
- 1° Endpoint: Nasal airway resistance
- 2° Endpoint: Symptoms
  - Generally not considered if NAR was not positive
  - No clear delineation of how results were collected

Number of Completed Subjects*
10 Sterling-Winthrop Studies

Study / Dose	Phenylephrine				PPA	Ephedrine	
	10 mg	15 mg	20 mg	25 mg	50 mg	8 mg	50 mg
Elizabeth 1				12		13	
Elizabeth 2	16	10		6			6
Elizabeth 3		8		9	9		
Elizabeth 4		6	5	9			
Elizabeth 5	10	6		9			
Huntingdon 1	16			16	16		
Huntingdon 2	25		24				
Cintest 1	16		16		15		
Cintest 2	15	16	15				
Cintest 3	15	16		16			

*All subjects were crossed over with placebo. Numbers of completers shown. PPA = phenylpropanolamine.
Red font = Significance reported for NAR results.

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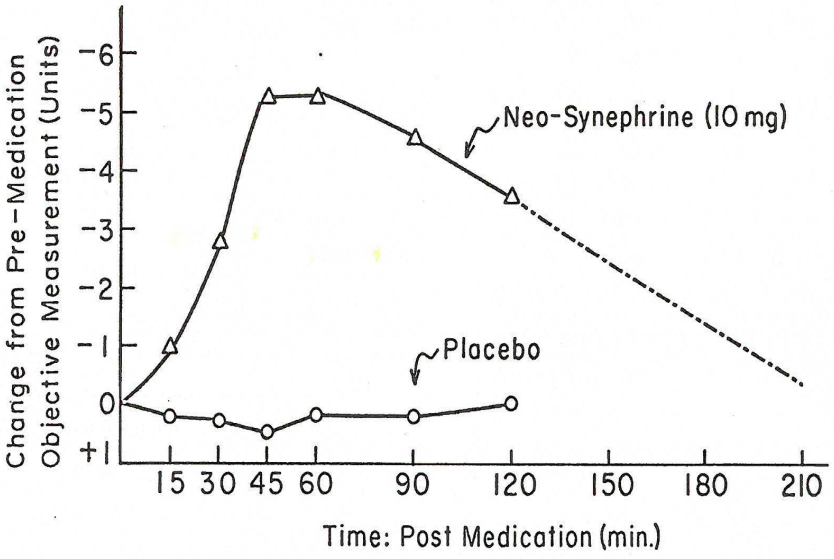
Elizabeth 3		8		9	9		
Elizabeth 4		6	5	9			
Elizabeth 5	10	6		9			
Huntingdon 1	16			16	16		
Huntingdon 2	25		24				
Cintest 1	16		16		15		
Cintest 2	15	16	15				
Cintest 3	15	16		16			

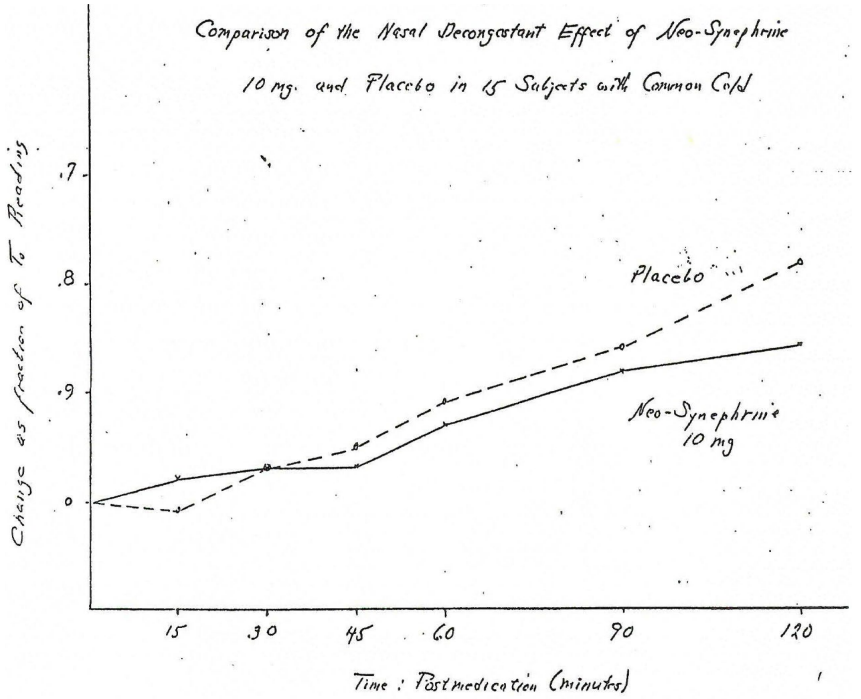
*All subjects were crossed over with placebo. Numbers of completers shown. PPA = phenylpropanolamine.
Red font = Significance reported for NAR results. Elizabeth studies 4 and 5 were terminated due to insufficient enrollment by the end of the cold season.

Elizabeth 2 vs Cintest 3

Elizabeth 2: PE 10 mg vs placebo (n=16)
Objective Change From Baseline



Cintest 3: PE 10 mg vs placebo (n=15)
Change From Baseline as a Fraction of the Reading



DESI Cough-Cold Panel's Conclusions/Recommendations

- Data "not strongly indicative of efficacy", but… in the absence of a safety issue they recommended that the 10 mg dose be GRASE*
  - There were multiple failed studies and weak positive data
  - Did not know metabolites were inactive
  - Oral bioavailability of total PE versus parent PE was uncharacterized
  - Considered intranasal PE to be effective

*Decongestant Tentative Final Monograph, 50 FR 2220, Jan 1, 1985, at 2226

FDA Re-Assessment of the Original Studies

Original Studies – Design/Methodological Issues

- Performed in a different era – before good clinical practice (GCP) guidelines*
- Mechanistic primary endpoint: Nasal airway resistance (NAR)
  - Highly variable and subject to numerous methodological issues
  - Not validated; No information to judge statistical significance or clinical relevance of results, including what difference in NAR translates to a clinical improvement in nasal congestion symptoms
  - No longer accepted by FDA

* International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use. Harmonized Guideline / Draft Guidance: E6(R3) Good Clinical Practice (GCP), Endorsed on 19 May 2023.

Original Studies – Design/Methodological/Statistical Issues

- Methodological/Statistical Issues
  - Blinded, but unclear what other steps were taken to prevent bias (other than placebo control) – no protocols submitted to docket
  - Single-center
  - VERY small Ns, no sample size calculations
  - No statistical analysis plans
  - No controls for multiplicity
- Enrollment Issues
  - Two of 5 positive studies (Elizabeth 4 and 5) ended early

* International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use. Harmonized Guideline / Draft Guidance: E6(R3) Good Clinical Practice (GCP), Endorsed on 19 May 2023.

Original Studies – Possible Data Integrity Issues

- Findings highly inconsistent between the 5 studies conducted at Elizabeth site and the 5 studies conducted at Huntingdon and Cintest
- Other study sites contemporaneously questioned the Elizabeth results
  - Cintest visited Elizabeth to observe the techniques they were using and ensure that they were doing the same – did not find any differences
  - Huntingdon performed a standard deviation analysis of results from all three sites, and found a marked difference between the Elizabeth results and the SDs from the other two sites (≥10x smaller at Elizabeth)
- Results from studies Elizabeth 2 & 5 are near textbook perfect, mimic the known PD curve, and show no change from baseline in placebo
- Forensic analysis* of the results at Elizabeth studies 2 & 5
  - Highly suspicious results at Elizabeth study 2

* Shuster, et.al. (2010) Reply to discussion of 'Empirical vs natural weighting in random effects meta-analysis'. *Statistics in Medicine* 29(12): 1272-1281. https://doi.org/10.1002/sim.3842

One Additional Study NOT Considered by the DESI Panel

Cohen (1972) – New Jersey College of Medicine

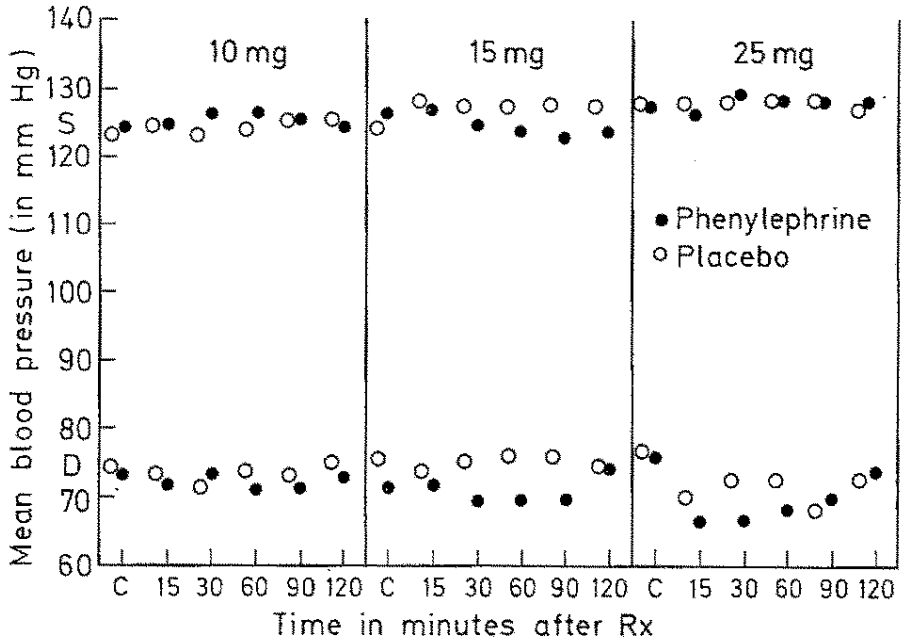
- R, DB, PC, single-dose, 2-way crossover
- 48 subjects with URI (16/arm)
  - PE 10 (n=16)
  - PE 15 mg (n=16)
  - PE 25 mg (n=16)
- 1° Endpoint: NAR
- 2° Endpoint: Congestion on 5-point scale

- Same author as Whitehall's BEI 1025 study, but appears to have been supported by Sterling-Winthrop
- Published, but not reviewed for ANPR or GRASE determination
- Methodological and statistical issues with this study are similar to all the other DESI studies (unvalidated mechanistic endpoint, small N, no SAP, no controls for multiplicity, no PD effect on systolic BP)

Source: Cohen, BM, Clinical and Physiologic "Significance" of Drug-Induced Changes in Nasal Flow/Resistance, Europ. J. Clin. Pharm. 5, 81--86 (1972). Sterling-Winthrop supplied Neo-Synephrine and matched placebo, along with randomization code.

Cohen (1972) – BP Results

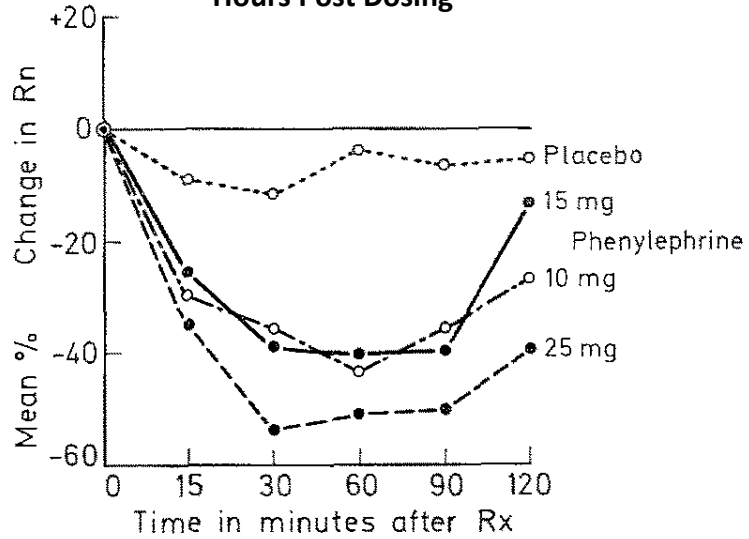
Systolic and Diastolic BP over 2 Hours Post Dosing



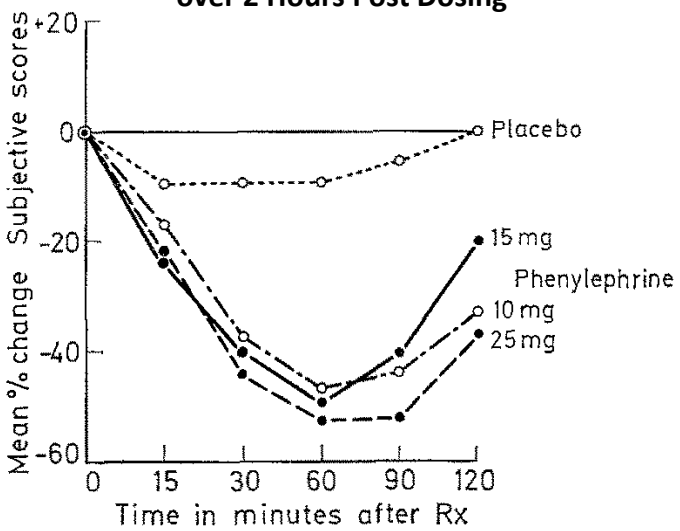
Source: Cohen, BM, Clinical and Physiologic "Significance" of Drug-Induced Changes in Nasal Flow/Resistance, Europ. J. Clin. Pharm. 5, 81--86 (1972). Sterling-Winthrop supplied Neo-Synephrine and matched placebo, along with randomization code.

Cohen (1972) – NAR & Congestion Results

Percent Change in Nasal Airway Resistance over 2 Hours Post Dosing



Percent Change in Congestion Scores over 2 Hours Post Dosing



Source: Cohen, BM, Clinical and Physiologic "Significance" of Drug-Induced Changes in Nasal Flow/Resistance, Europ. J. Clin. Pharm. 5, 81--86 (1972). Sterling-Winthrop supplied Neo-Synephrine and matched placebo, along with randomization code.

Summary and Conclusions

Clinical Pharmacology Summary

- Only parent PE, not its metabolites, has α1-adrenergic activity
- *In vivo* parent PE Cmax following monographed oral dose is lower than *in vitro* EC_{50} values
- <1% of an oral PE dose is systemically bioavailable as active parent PE
- Short half-life (~ 1.5 hours)

Clinical Summary

- Original efficacy studies (prior to 2007 NDAC)
  - Clinical and statistical methodology does not meet today's clinical trial design standards (e.g., NAR, generalizability)
  - Inconsistent results
- Two environmental exposure unit studies (presented at 2007 NDAC)
  - Single center proof of concept studies
  - Nasal congestion score results showed PE 10 mg was not significantly different from placebo
- More recent efficacy studies (post 2007 NDAC)
  - Three multi-center, parallel, randomized, double blind, placebo-controlled trials evaluating nasal congestion scores
  - Results showed PE 10 mg was not significantly different from placebo

Conclusions

1. The original studies had significant methodological and statistical issues and do not meet today's clinical design standards.
2. The new data do not provide evidence that, at monographed doses, oral phenylephrine is effective as a nasal decongestant.
3. Data suggest that IR doses up to 40 mg may not be effective, and that higher doses might present a safety issue.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Sales of OTC Oral Products Containing Phenylephrine or Pseudoephedrine in the United States

Tracy Pham, PharmD
Drug Utilization Analyst
Division of Epidemiology II (DEPI II)
Office of Surveillance and Epidemiology

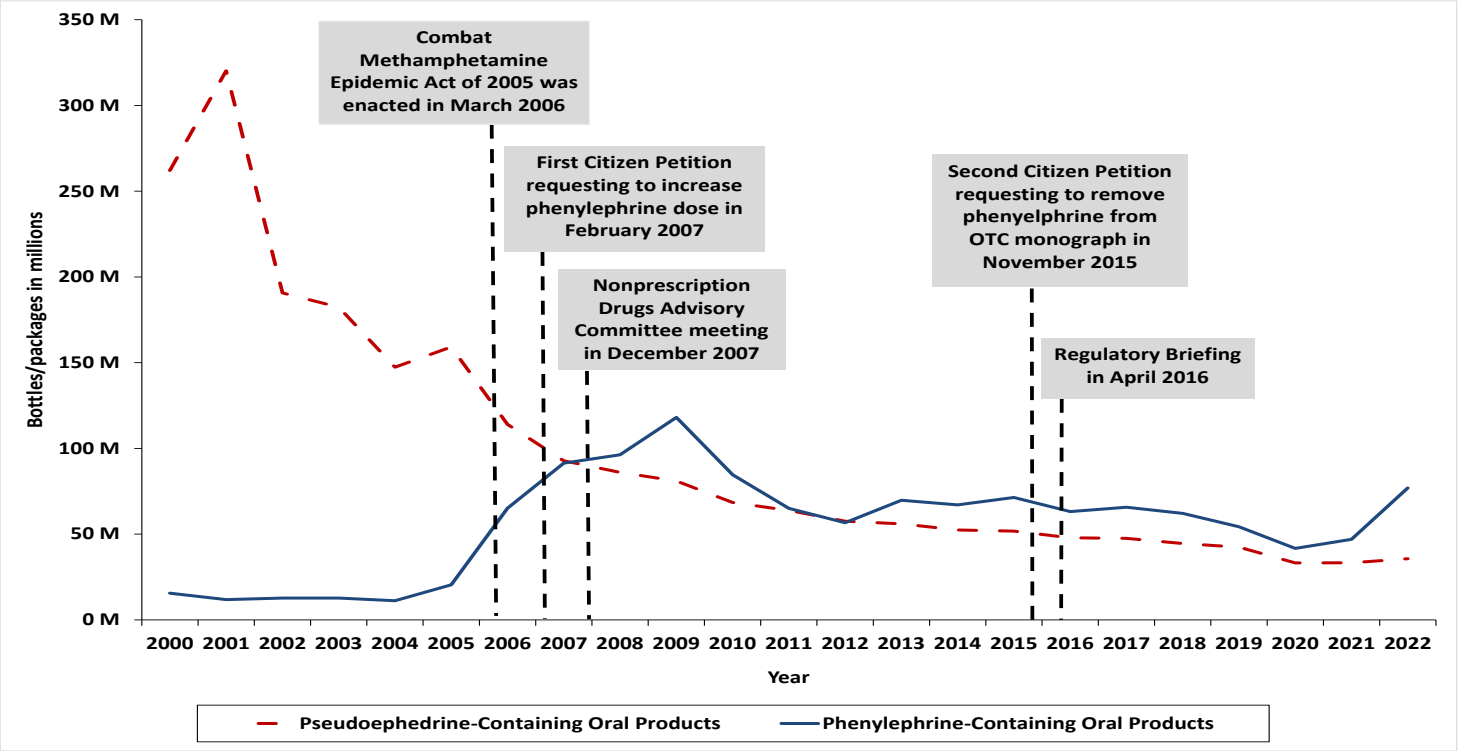
Outline

- Manufacturer sales data
- Retail sales data
- Database limitations
- Summary of findings

Manufacturer Sales Data – Database Description

- National Sales Perspective™ (NSP) measures volume of prescription and OTC drugs sold from manufacturers and wholesalers to various U.S. settings of care
  - Retail settings: chain drug stores, independent drug stores, food stores, and mail service
  - Institutional/Non-Retail settings: clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings
- Historical data are available back to 1992
- **Limitation: NSP captures <50% of sales of all OTC drug products. Therefore, OTC sales in NSP are significantly underestimated.**

Sales (Bottles/Packages) From Manufacturers, 2000-2022



Annual estimates of bottles/packages of over-the-counter (OTC) cough/cold/allergy oral products containing phenylephrine or pseudoephedrine sold from manufacturers to retail and non-retail settings, 2000-2022

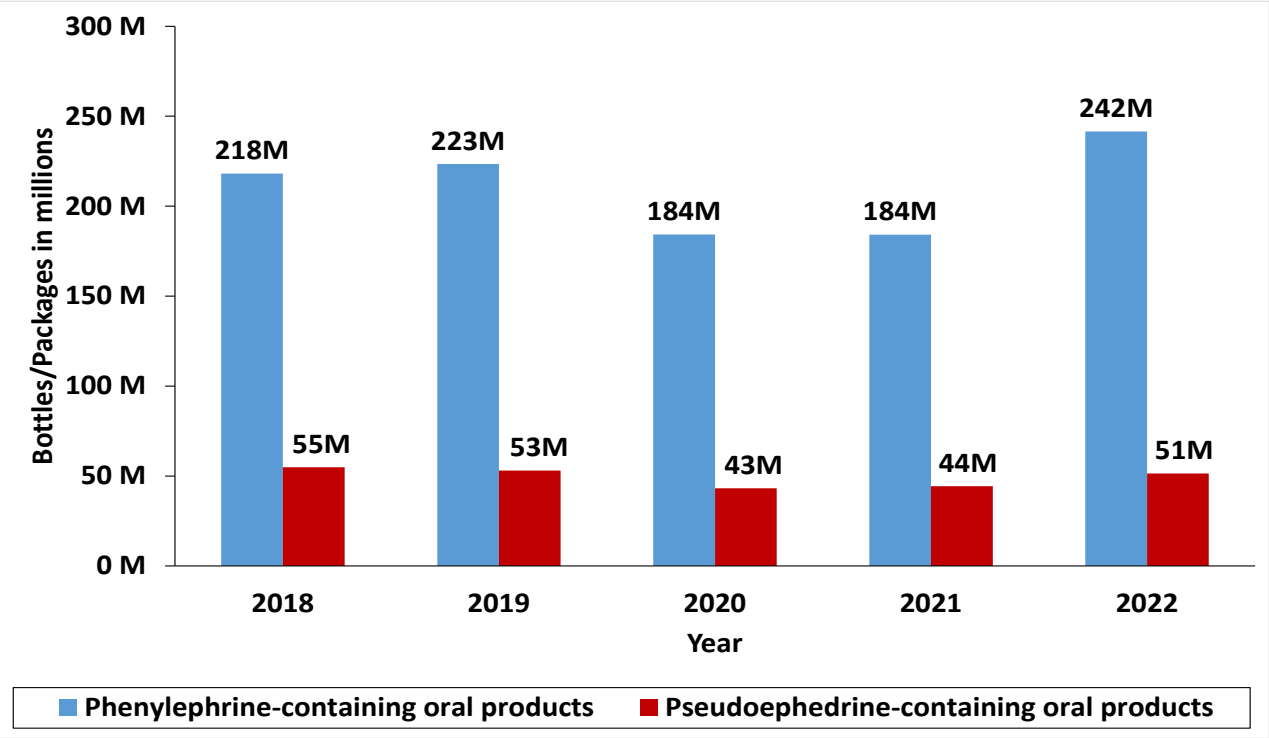
Source: National Sales Perspectives™, 2000-2022. Data extracted May 2022 and February 2023.

* Manufacturer sales data of OTC cough/cold/allergy oral products containing phenylephrine were 32% or less of the retail sales data of these products from 2018 to 2022 and should not be directly compared to the retail sales data because they were substantially underestimated.

Retail Sales Data – Database Description

- OTC International Market Tracking and Private Label Ingredient-Level Report capture point-of-sales of OTC drug products to consumers from a panel of ~63,000 retail stores
- Retail stores: grocery and drug stores, mass merchandisers, supercenters, Club stores, Dollar stores, and military commissaries
- Data are available only from 2018 and forward
- **Limitations: Panel of retail stores does not include Costco, Dollar Tree/99Cent stores, specialty stores, kiosks, internet sales, phone sales, and 7-Eleven**

Sales (Bottles/Packages) From U.S. Retail Stores, 2018-2022



From 2018 to 2021:

- PE sales declined 16%
- Pseudoephedrine (PSE) sales declined 19%

From 2021 to 2022:

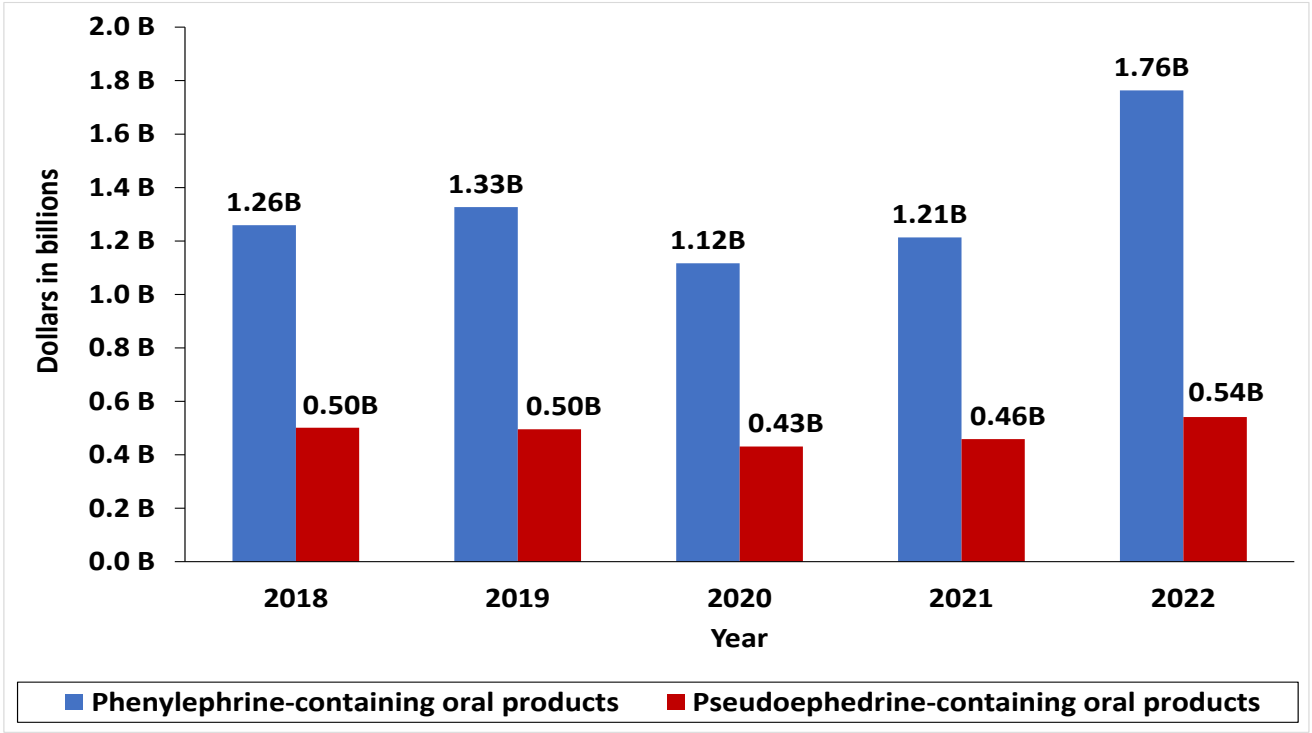
- PE sales increased 31%
- PSE sales increased 16%

PE – phenylephrine
PSE – pseudoephedrine

Annual estimates of bottles/packages of over-the-counter (OTC) cough/cold/allergy oral products containing phenylephrine or pseudoephedrine sold from U.S. retail stores* to consumers, 2018-2022

Source: OTC International Market Tracking and Private Label Ingredient Level Report, 2018-2022. Data extracted February 2023.
* Retail sales data do not capture sales activity from Costco, convenience stores, specialty stores, internet sales, phone sales or kiosks.

Sales (Dollars) From U.S. Retail Stores, 2018-2022



Phenylephrine had

- the majority of sales
- over 1 billion dollars in sales per year

Annual estimates of dollars* of over-the-counter (OTC) cough/cold/allergy products oral containing phenylephrine or pseudoephedrine sold from U.S. retail stores to consumers, 2018-2022**

Source: OTC International Market Tracking and Private Label Ingredient Level Report, 2018-2022. Data extracted February 2023.
* Sales in dollars represent the price of a manufacturer's pack before the wholesaler mark-up is applied.
** Retail sales data do not capture sales activity from Costco, convenience stores, specialty stores, internet sales, phone sales or kiosks.

Database Limitations

- Manufacturer sales database
  - Captures <50% of sales of all OTC drug products
  - Sales of OTC drug products are significantly underestimated.
- Retail sales database
  - Panel of retail stores does not include Costco, Dollar Tree/99Cent stores, specialty stores, kiosks, internet sales, phone sales, and 7-Eleven

Summary of Key Findings

- Phenylephrine had higher proportions of both manufacturer and retail sales than pseudoephedrine
  - Since 2018, phenylephrine accounted for most of retail sales in bottles/packages (80-82%) and in sale dollars (72-77%)
- Retail sales of phenylephrine and pseudoephedrine decreased from 2018 to 2021, before increasing in 2022
- In 2022, phenylephrine retail sales represented 1.8 billion dollars and pseudoephedrine retail sales represented 0.5 billion dollars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Summary and Introduction to Discussion

Martha Lenhart, MD, PhD
Deputy Director
Division of Nonprescription Drugs I
Office of Nonprescription Drugs

Phenylephrine (PE)

- One of two orally administered α1-adrenergic receptor agonists that are generally recognized as safe and effective (GRASE) in the CCABA OTC Monograph
- Indication: Temporary relief of nasal congestion
- Dose: 10 mg every 4 hours, not to exceed 60 mg in 24 hours (adult/adolescent)

OTC Drug Monograph Effectiveness Standard

- Procedure for classifying drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs

  21 CFR 330.10(a)(4)(ii)

  - Effectiveness means a reasonable expectation that, in a significant portion of the target population, the pharmacological effect of the drug… will provide clinically significant relief of the type claimed
  - Proof of effectiveness shall consist of controlled clinical investigations as defined in 21 CFR 314.126(b)
    - 314.126(b) is the definition of adequate and well controlled studies for New Drug Applications (NDAs)

2007 NDAC Meeting

- Discussed the safety and effectiveness of oral phenylephrine as a nasal decongestant
  - Results are not consistent across studies for nasal airway resistance (NAR); symptoms should be the essential primary endpoint
  - Evidence of efficacy consists primarily of studies conducted 40 years ago and included fewer than 200 people
  - NAR results may not be generalizable to a wide population based on small studies
- Committee recommended additional trials
  - Multi-center, parallel, randomized, double blind, placebo-controlled trials, preferably with an active control such as pseudoephedrine, to evaluate nasal congestion scores and symptom relief
  - Characterization of PE dose response and dosing interval
  - Comparison of PK of single-ingredient products versus multiple-ingredient products
  - Safety evaluation of the effects of PE on blood pressure

2007 NDAC materials available at: https://wayback.archiveit.org/7993/20170403222236/https://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs

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Charge to the Advisory Committee

Questions for the Committee

1. **Discussion:** Discuss the current scientific efficacy and pharmacokinetic data for phenylephrine.
2. **Voting:** Do the current scientific data that were presented support that the monograph dosage of orally administered phenylephrine is effective as a nasal decongestant?
   a. If yes, discuss what data you consider supportive.
   b. If no, discuss what additional data, if any, are needed to assess phenylephrine pharmacokinetics or efficacy.
3. **Discussion:** Discuss whether the current scientific data that were presented support that a dose of orally administered phenylephrine higher than the monograph dosage would be safe and effective.
4. **Discussion:** Discuss the implications for and communication strategies to consumers regarding the current oral phenylephrine data.

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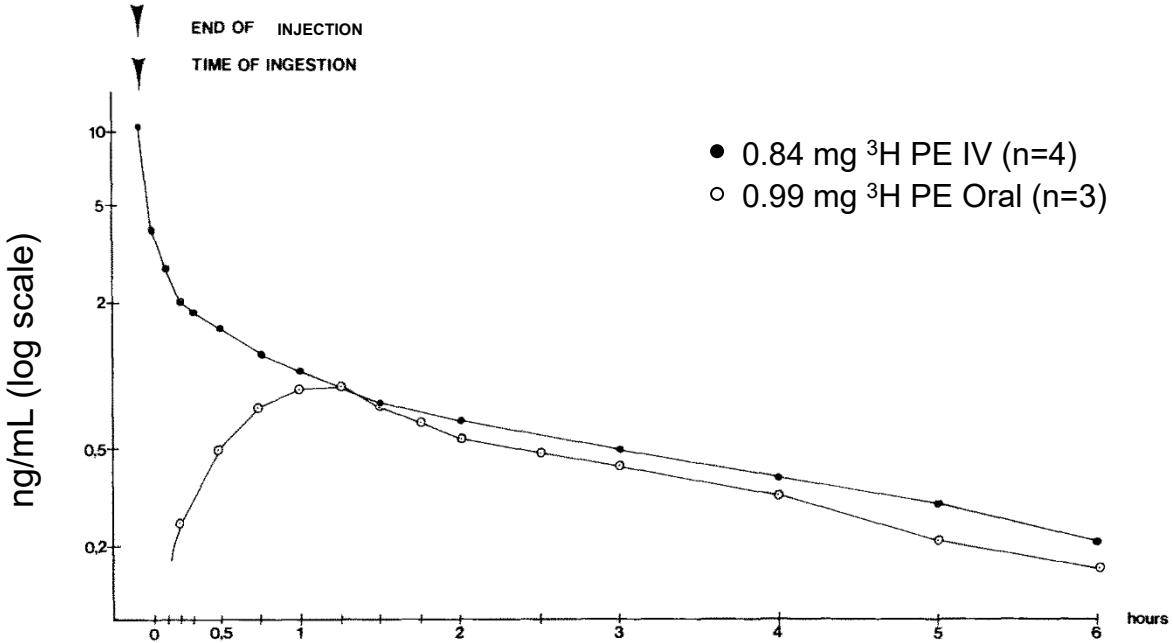
Backup Slides Shown

Hengstmann Paper



$AUC_{oral/IV}$ = 37.5% $C_{max\ oral/IV}$ ≤ 10% (parameter estimate: 2%)

Hengstmann JH, Goronzy J, Eur J Clin Pharmacol. 1982, 21 (4):335-41