

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Summary Minutes of the Nonprescription Drugs Advisory Committee Meeting  
December 14, 2007**

*Topic: The committee discussed the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as OTC oral nasal decongestants.*

These summary minutes for the December 14, 2007 meeting of the Nonprescription Drugs Advisory Committee were approved on December 31, 2007.

I certify that I attended the December 14, 2007 meeting of the Nonprescription Drugs Advisory Committee and that these minutes accurately reflect what transpired.

\_\_\_\_\_/s/\_\_\_\_\_  
Diem-Kieu H. Ngo, Pharm.D.

\_\_\_\_\_/s/\_\_\_\_\_  
Mary E. Tinetti, M.D.  
(Chair)

**Summary Minutes of the Nonprescription Drugs Advisory Committee Meeting  
December 14, 2007**

The following is the final report of the Nonprescription Drugs Advisory Committee meeting held on December 14, 2007. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at <http://www.fda.gov/ohrms/dockets/ac/cder07.htm>

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information office.

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The Nonprescription Drugs Advisory Committee of the Food and Drug Administration met on December 14, 2007 at the Hilton Washington DC/Silver Spring, 8727 Colesville Road, Silver Spring, Maryland. Mary Tinetti M.D., chaired the meeting. There were approximately 150 in attendance.

**Attendance:**

**Nonprescription Drugs Advisory Committee Members present (voting):**

Mary E. Tinetti, M.D.; Ruth M. Parker, M.D.; Robert E. Taylor, M.D., Ph.D., F.A.C.P.; William H. Shrank, M.D., M.S.H.S.; Garret A. FitzGerald, M.D.; Ralph B. D'Agostino, Ph.D.; Marie R. Griffin, M.D.

**Nonprescription Drugs Advisory Committee Members absent:**

Ernest B. Clyburn, M.D.; Jan L. Hewett, J.D., B.S.N.

**Temporary Voting Members:**

Ruth Hoffman, M.P.H. (Patient Representative); Arthur A. Levin, M.P.H. (Consumer Representative); Dean A. Follmann, Ph.D.; Dennis R. Ownby, M.D.; Richard W. Honsinger, M.D.

**Industry Representative (non-voting):**

Edward B. Nelson, M.D., Ph.D. (NDAC)

**FDA Participants (non-voting):**

Susan Johnson, Pharm.D., Ph.D.; Debbie Lumpkins; Michael Koenig, Ph.D.

**Open Public Hearing Speakers:**

None.

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On December 14, 2007, the committee met to discuss the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as OTC oral nasal decongestants.

On December 14, 2007, Mary Tinetti, M.D., (NDAC Chair) called the meeting to order at 8:00 a.m. The Committee members and the FDA participants introduced themselves. The conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., Designated Federal Official (DFO). The agenda for the meeting was as follows:

- 8:00 a.m. Call to Order and Opening Remarks **Mary E. Tinetti, M.D.**  
Chair, Nonprescription Drugs Advisory Committee
- Introduction of Committee
- Conflict of Interest Statement **Diem-Kieu H. Ngo, Pharm.D.**  
Designated Federal Official
- 8:15 a.m. FDA Introductory Remarks **Susan Johnson, Pharm.D., Ph.D.**  
Associate Director,  
Office of Nonprescription Products, CDER, FDA

**FDA PRESENTATION**

- 8:25 a.m. History of the OTC Drug Review as it  
Relates to Phenylephrine **Mary S. Robinson, M.S.**  
Regulatory Review Chemist,  
Division of Nonprescription Regulation  
Development  
Office of Nonprescription Products, CDER, FDA
- 8:35 a.m. Effectiveness and Safety of Phenylephrine  
as an OTC Oral Nasal Decongestant **Michael L. Koenig, Ph.D.**  
Interdisciplinary Scientist,  
Division of Nonprescription Regulation  
Development  
Office of Nonprescription Products, CDER, FDA
- 9:05 a.m. Statistical Evaluation of Effectiveness  
Submissions **Stan Lin, Ph.D.**  
Mathematical Statistician,  
Division of Biometrics 4  
Office of Biostatistics, OTS, CDER, FDA
- 9:25 a.m. Clinical Endpoints for Nasal Decongestants **Xu Wang, M.D., Ph.D.**  
Medical Officer  
Division of Pulmonary and Allergy Products  
Office of New Drugs, CDER, FDA
- 9:40 a.m. Questions/Clarifications

10:00 a.m. **BREAK**

**PETITIONER PRESENTATION**

- 10:15 a.m. Background on Decongestants and  
Citizens Petition **Leslie Hendeles, Pharm.D.**  
Professor, Pharmacy and Pediatrics  
University of Florida
- 10:35 a.m. Efficacy and Safety of Oral  
Phenylephrine: Systematic Review  
and Meta-Analysis **Randy Hatton, Pharm.D.**  
Co-Director, Drug Information and Pharmacy  
Resource Center, Shands Hospital at the  
University of Florida; Clinical Professor,  
College of Pharmacy, University of Florida

10:45 a.m. Evaluation of the Statistical Methods  
Used in the CHPA Meta-Analysis

**Jonathan J. Shuster, Ph.D.**  
Research Professor, Division of Biostatistics,  
Department of Epidemiology and Health Policy;  
Research Biostatistician, General Clinical  
Research Center, College of Medicine,  
University of Florida

**INDUSTRY PRESENTATION**

11:05 a.m. Introduction

**Linda A. Suydam, D.P.A.**  
President, Consumer Healthcare Products Association

11:10 a.m. Clinical Overview of Two Allergy  
Chamber Studies with Phenylephrine

**Melvyn Danzig, Ph.D.**  
Project Director  
Clinical Research - Allergy/Respiratory  
Schering-Plough/Merck Pharmaceuticals

11:25 a.m. Understanding Phenylephrine Metabolism,  
Pharmacokinetics, Bioavailability, and  
Development Activity

**John O'Mullane, Ph.D.**  
Group Vice President, Research and  
Schering-Plough Corporation

11:40 a.m. Safety Data

**Edwin K. Kuffner, M.D.**  
Senior Director, Medical Affairs  
McNeil Consumer Healthcare

11:50 a.m. PE Pharmacology/Pharmacokinetics

**Cathy K. Gelotte, Ph.D.**  
Senior Director, Clinical Pharmacology  
McNeil Consumer Healthcare

12:00 p.m. Efficacy of Phenylephrine 10 mg

**Kenneth Dretchen, Ph.D.**  
Professor and Chairman,  
Department of Pharmacology  
Georgetown University Medical Center

12:20 p.m. Closing Remarks

**Linda A. Suydam, D.P.A.**  
President, Consumer Healthcare Products Association

12:25 p.m. **LUNCH**

1:25 p.m. Open Public Hearing

2:25 p.m. Questions/Clarifications

3:00 p.m. **BREAK**

3:15 p.m. Panel Discussion/Questions

5:00 p.m. **ADJOURNMENT**

### Questions to the Committee:

1. The many studies discussed today, in which the efficacy of oral phenylephrine hydrochloride (PEH) as a nasal decongestant was assessed, differ in many ways. For example:

- Patient inclusion criteria (healthy subjects or subjects with common cold, upper respiratory tract infection, acute rhinitis, or seasonal allergic rhinitis)
- Congestion model (naturally occurring, induced by exposure to pollen in an environmental exposure unit)
- Endpoints (objective reduction in nasal airway resistant (NAR), subjective improvement in symptom scores)
- Dose (10 mg, 25 mg), dosing interval, and endpoint assessment interval

In addition, the studies have been considered in several different groupings (studies evaluated by the Advisory Panel and discussed in the ANPR, CP meta-analysis, CHPA meta-analysis).

The agency would like the NDAC to discuss which aspects of the data, if any, that it finds supportive of the effectiveness of PEH for the symptomatic treatment of nasal congestion due to the common cold or upper respiratory allergies.

### Committee Discussion:

*It was noted by the committee that the standard to support “effectiveness” was not clearly defined. The committee noted that individual studies show some benefit of the 10 mg strength, but the results are not consistent across studies for NAR and are even murkier for symptom measures. The committee agreed that symptoms are the essential primary endpoint. While one half the studies were positive and one half negative, in none of the studies was the placebo superior to PEH, adding support to the effectiveness of PEH. The committee felt that efficacy may not be generalizable to a wide population based on small studies. The committee noted that the available evidence consists primarily of studies conducted 40 years ago and included fewer than 200 people across all the studies. (See Transcript for Complete Discussion)*

2. The following four statements represent alternative summary assessments of the data presented for PEH. Please consider each statement and vote (yes or no) on whether it represents your conclusions about the data.

- a. PEH in a 10 mg immediate release formulation may be effective when dosed every 4 hours for the symptomatic treatment of nasal congestion. No additional studies are needed. (Vote: yes or no)

### Committee Discussion:

*(See Transcript for Complete Discussion)*

*The committee proposed to change the wording of the question to:*

PEH in a 10 mg immediate release formulation has been shown to be effective when dosed every 4 hours for the symptomatic treatment of nasal congestion and no additional studies are needed to support its effectiveness.

**Yes: 2      No: 10      Abstain: 0**

- b. PEH in a 10 mg immediate release formulation is effective. Additional study is needed to identify an appropriate dosing interval for this dose. (Vote: yes or no)

### Committee Discussion:

*(See Transcript for Complete Discussion)*

*The committee proposed to change the wording of the question to:*

Given the available data that exist, the evidence is supportive that the 10 mg immediate release formulation may be effective.

**Yes: 11      No: 1      Abstain: 0**

- c. PEH in a 10 mg immediate release formulation is at the lower end of the dose response range. Additional studies are needed to assess the efficacy of higher doses (e.g., 25 mg) and determine appropriate dosing intervals. (Vote: yes or no)

**Committee Discussion:**

*(See Transcript for Complete Discussion)*

*The committee proposed to change the wording of the question to:*

Additional studies are needed to assess the efficacy and safety of higher doses (e.g., 25 mg).

**Yes: 9      No: 3      Abstain: 0**

- d. There are no data to support the efficacy of PEH in a 10 mg immediate release formulation. Additional studies are needed to assess the efficacy of higher doses (e.g., 25 mg) and determine an appropriate dosing interval. (Vote: yes or no)

*The committee proposed to change the wording of the question to:*

What additional studies of the 10 mg and/or 25 mg dose needed?

**Committee Discussion:**

*The committee recommended additional trials be conducted as follows:*

- *A 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. The trials need to have sufficient sample size to evaluate efficacy and safety according to key characteristics such as age, gender, race, and severity of symptoms;*
- *Characterization of the PEH dose response and the effect of dosing interval, formulation, type of delivery system, and potentially, genetic factors, on safety and efficacy endpoints;*
- *Comparison of the pharmacokinetics of single-ingredient products versus multiple-ingredient products;*
- *Safety evaluation of the effects of PEH on blood pressure and cardiovascular use of PEH in patients with important comorbidities such as BPH, hypertension, or diabetes mellitus.*

*(See Transcript for Complete Discussion)*

3. Based on the data presented, do you recommend that there be additional study of the effects that formulation (e.g., extended release) may have on the bioavailability and performance of phenylephrine? (Vote: yes or no)

**Committee Discussion:**

*This question was not voted on since discussions that transpired during the above questions already addressed this question. (See Transcript for Complete Discussion)*

The meeting was adjourned at approximately 3:20 p.m. on December 14, 2007.