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)
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:
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>8:00 a.m.</td>
<td>Call to Order and Opening Remarks</td>
<td>Mary E. Tinetti, M.D. Chair, Nonprescription Drugs Advisory Committee</td>
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<td></td>
<td>Introduction of Committee</td>
<td>Diem-Kieu H. Ngo, Pharm.D. Designated Federal Official</td>
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<td>Conflict of Interest Statement</td>
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<td>8:15 a.m.</td>
<td>FDA Introductory Remarks</td>
<td>Susan Johnson, Pharm.D., Ph.D. Associate Director, Office of Nonprescription Products, CDER, FDA</td>
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<td>8:25 a.m.</td>
<td>FDA Presentation</td>
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<td></td>
<td>History of the OTC Drug Review as it Relates to Phenylephrine</td>
<td>Mary S. Robinson, M.S. Regulatory Review Chemist, Division of Nonprescription Regulation Development Office of Nonprescription Products, CDER, FDA</td>
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<td>8:35 a.m.</td>
<td>Effectiveness and Safety of Phenylephrine as an OTC Oral Nasal Decongestant</td>
<td>Michael L. Koenig, Ph.D. Interdisciplinary Scientist, Division of Nonprescription Regulation Development Office of Nonprescription Products, CDER, FDA</td>
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<td>9:05 a.m.</td>
<td>Statistical Evaluation of Effectiveness Submissions</td>
<td>Stan Lin, Ph.D. Mathematical Statistician, Division of Biometrics 4 Office of Biostatistics, OTS, CDER, FDA</td>
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<td>9:25 a.m.</td>
<td>Clinical Endpoints for Nasal Decongestants</td>
<td>Xu Wang, M.D., Ph.D. Medical Officer Division of Pulmonary and Allergy Products Office of New Drugs, CDER, FDA</td>
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<td>9:40 a.m.</td>
<td>Questions/Clarifications</td>
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<td>10:00 a.m.</td>
<td>BREAK</td>
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<td>10:15 a.m.</td>
<td>Petitioner Presentation</td>
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<td>Background on Decongestants and Citizens Petition</td>
<td>Leslie Hendeles, Pharm.D. Professor, Pharmacy and Pediatrics University of Florida</td>
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<td>10:35 a.m.</td>
<td>Efficacy and Safety of Oral Phenylephrine: Systematic Review and Meta-Analysis</td>
<td>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</td>
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</table>
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 Development Activity, 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 cardiovasculature and 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.