August 23, 2006

Andrew C. von Eschenbach, M.D.
Acting Commissioner
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
5600 Fishers Lane, Room 15-47
Rockville, MD 20857

Dear Dr. von Eschenbach:

In response to provisions in the 2006 reauthorization of the Patriot Act[1] setting a September 30, 2006, deadline for moving all pseudoephedrine products behind the counter, pharmaceutical companies have begun to offer reformulated oral nasal decongestants that eliminate pseudoephedrine. These alternative products contain the active ingredient phenylephrine, which permits them to be sold over-the-counter without any restrictions. However, the enclosed Letter to Editor, recently published in the Journal of Allergy and Clinical Immunology, concludes that phenylephrine oral nasal decongestants are not effective at the FDA-monograph dose of 10 mg.[2] The authors of the letter, Dr. Leslie Hendeles and Dr. Randy Hatton of University of Florida's College of Pharmacy, reviewed several studies on the safety and effectiveness of phenylephrine — including the studies on which an FDA advisory based its 1976 conclusion that the drug was safe and effective for OTC use — and concluded that there is virtually no evidence showing that phenylephrine is any more effective than placebo at the maximum FDA-approved dose.

I am extremely concerned about this recent switch to phenylephrine and urge you to promptly investigate this issue. American consumers deserve to have confidence that the

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[1] USA PATRIOT Improvement and Reauthorization Act of 2005, Pub. L. No. 109-177, enacted March 9, 2006. The Combat Methamphetamine Epidemic Act of 2005 (H.R. 3889) was passed as Title VII of the Patriot Act.

[2] Leslie Hendeles, PharmD, and Randy Hatton, PharmD, *Letter To the Editor — Oral Phenylephrine: An Ineffective Replacement for Pseudoephedrine?*, J. Allergy and Clin Immunology, Vol. 118, No. 1 (July 2006).

cold/allergy remedies on which they spend their hard-earned income will actually reduce their symptoms.

Until recently, almost all oral nasal decongestants have contained pseudoephedrine — not phenylephrine. Charles Ganley, M.D., director of FDA's Office of Nonprescription Products, recently confirmed that "[t]here are very few decongestants on the market that don't contain pseudoephedrine."[3] It was only in response to the recent legislative efforts to curb illegal methamphetamine production that manufacturers began to replace pseudoephedrine with phenylephrine.

Manufacturers are able to switch to phenylephrine without any review by the FDA because of an FDA regulation that is based on a 30-year old review of data on the ingredient. In 1976, FDA's Advisory Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products concluded that phenylephrine was safe and effective for use as an ingredient in non-prescription nasal decongestants.[4]

However, the attached letter to the editor calls into question whether, at that time, the advisory panel had an adequate basis for recommending phenylephrine for that indication. According to Drs. Hendeles and Hatton, the panel relied exclusively on "unpublished, manufacturer-sponsored studies conducted by commercial testing laboratories."[5] Within that group, only four studies showed any evidence of efficacy, compared to seven studies demonstrating that a 10 mg dose was no better than placebo.[6] Drs. Hendeles and Hatton conclude that the panel "reached a specious conclusion that was not based on a systematic review of the available data."[7]

Other studies cited in the attached letter have shown that phenylephrine is much less well-absorbed than pseudoephedrine and does not effectively reduce symptoms of nasal congestion. A 1982 study, published after the OTC Advisory Panel reached its conclusion on phenylephrine, showed that phenylephrine's bioavailability is only 38%, compared to a 90% bioavailability rate for pseudoephedrine. In other words, because it is highly susceptible to being broken down in the gut and liver, not enough phenylephrine reaches the nasal tissues; only 38%

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[3] Linda Bren, *Some Cold Medicines Move Behind Counter*, FDA Consumer Magazine (July-Aug. 2006) (online at http://www.fda.gov/fdac/features/2006/406_meth.html).

[4] Food and Drug Administration, *Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products*, 41 Fed. Reg. 38312, 38399 (Sept. 9, 1976) (online at http://www.fda.gov/ohrms/dockets/98fr/76-22710.pdf)

[5] Hendeles, *supra* note 2.

[6] *Id.*

[7] *Id.*

of a 10 mg dose of phenylephrine actually reaches the bloodstream where it can be delivered to the nose, as opposed to 90% of a dose of pseudoephedrine.[8] Other randomized, double blind, placebo-controlled studies also showed that phenylephrine was no more effective than placebo at reducing nasal congestion.[9]

A review of these studies makes it quite clear why manufacturers have traditionally relied upon pseudoephedrine-based oral nasal decongestants: phenylephrine apparently does not work when used as an oral nasal decongestant.

In light of the concerns raised in the attached letter to the editor, I request that you explain why FDA continues to believe that phenylephrine is effective when used as the active ingredient in oral nasal decongestants at a maximum dose of 10 mg. I also request that you promptly convene a meeting of the Nonprescription Drugs Advisory Committee to assess whether phenylephrine should continue to maintain its status as a monograph-approved active ingredient in oral nasal decongestants at the current dose of 10 mg and whether additional dose-response studies are needed to determine whether a higher dose will provide efficacy and still be safe.

With the impending September 30 deadline for moving pseudoephedrine products behind the counter, it is critical that FDA act quickly to address this issue. FDA should not stand by and permit consumers to waste their money on medications that simply do not work.

Please provide a response to this letter by September 8, 2006.

Sincerely,

Henry A. Waxman
Ranking Minority Member

Enclosure

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[8] Isadore Kanfer, Ph.D., Roslind Dowse, Ph.D., and Vusumuzi Vuma, B.Pharm. *Pharmacokinetics of Oral Decongestants*, Pharmacotherapy, 13:116S-28S (1993).

[9] Hylan Bickerman, *Physiologic and Pharmacologic Studies on Nasal Airway Resistance.* Proceedings of a Conference Sponsored by the Scientific Development Committee of the Proprietary Association, Washington, D.C. (Dec. 8, 1971); JW McLaurin, et. al., *Oral Decongestants: A Double Blind Comparison Study Of The Effectiveness Of Four Sympathomimetic Drugs: Objective And Subjective.* Laryngoscope, 71: 54-67 (1961).

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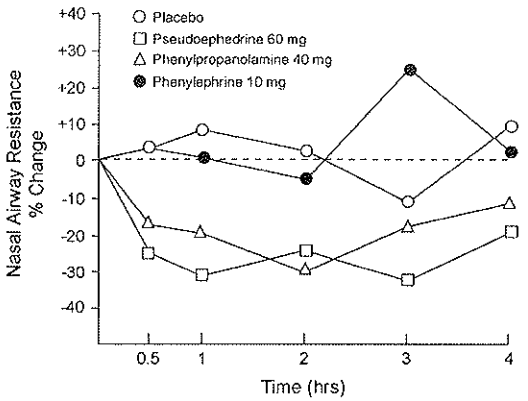

FIG 1. Percent change in nasal airway resistance in 20 patients with chronic nasal stuffiness after single doses of placebo and 3 oral decongestants administered in a randomized, double-blind, crossover manner on different days. Changes were significant at each time point after pseudoephrine and phenylpropanolamine but not after phenylephrine. Drawn from data presented by Bickerman.[5] This graph was previously published[11] and is reproduced with permission of *Pharmacotherapy*.

REFERENCES

1. Athman R, Philpott D. Innate immunity via Toll-like receptors and Nod proteins. Curr Opin Microbiol 2004;7:25-32.
2. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol 2003;21:335-76.
3. Vandenbulcke L, Bachert C, Van Cauwenberge P, Claeys S. The innate immune system and its role in allergic disorders. Int Arch Allergy Immunol 2005;139:159-65.
4. Upham JW, Holt PG. Environment and development of atopy. Curr Opin Allergy Clin Immunol 2005;5:167-72.
5. Kollisch G, Kalali BN, Voelcker V, Wallich R, Behrendt H, Ring J, et al. Various members of the Toll-like receptor family contribute to the innate immune response of human epidermal keratinocytes. Immunology 2005; 114:531-41.
6. Miller SI, Ernst RK, Bader MW. LPS, TLR4 and infectious disease diversity. Nat Rev Microbiol 2005;3:36-46.
7. Eder W, Klimecki W, Yu L, von Mutius E, Riedler J, Braun-Fahrlander C, et al. ALEX Study Team. Toll-like receptor 2 as a major gene for asthma in children of European farmers. J Allergy Clin Immunol 2004; 113:482-8.
8. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, Klotz M, Werfel T, Herz U, et al. The toll-like receptor 2 R753Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. J Allergy Clin Immunol 2004;113:565-7.
9. Fageras Bottcher M, Hmani-Aifa M, Lindstrom A, Jenmalm MC, Mai XM, Nilsson L, et al. A TLR4 polymorphism is associated with asthma and reduced lipopolysaccharide-induced interleukin-12(p70) responses in Swedish children. J Allergy Clin Immunol 2004;114:561-7.
10. Werner M, Topp R, Wimmer K, Richter K, Bischof W, Wjst M, et al. TLR4 gene variants modify endotoxin effects on asthma. J Allergy Clin Immunol 2003;112:323-30.

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Oral phenylephrine: An ineffective replacement for pseudoephedrine?

To the Editor:

In 1976, a US Food and Drug Administration (FDA) review panel concluded that oral phenylpropanolamine, pseudoephedrine, and phenylephrine are safe and effective for nonprescription relief of nasal congestion caused by the common cold, allergic rhinitis, and sinusitis.[1] They are α-adrenergic agonists that decrease nasal mucosal swelling by vasoconstriction.

In 2000, phenylpropanolamine was voluntarily removed from all products because hemorrhagic strokes were associated with its use.[2] Recently, 34 states have enacted restrictions on the availability of pseudoephedrine because it is used to manufacture methamphetamine illegally. Some states require products containing this decongestant to be sold by a pharmacist or "behind the counter," whereas others restrict the quantity sold. Effective September 30, 2006, an amendment to the USA Patriot Act (HR 3889, Title VII) will require all stores to keep pseudoephedrine products behind the counter and purchasers will have to show a photo identification and sign a log book to obtain them.

Although these actions are unlikely to prevent patients from obtaining pseudoephedrine-containing products from pharmacists, it is increasingly difficult to obtain them from grocery, discount, and convenience stores. In response, Pfizer, Inc (Morris Plains, NJ), introduced a replacement product containing 10 mg phenylephrine (Sudafed-PE) that cannot be converted to methamphetamine and can be sold without restriction. Other manufacturers are following suit.

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.[3] Only 38% of the dose reaches the systemic circulation,[3] compared with 90% of a pseudoephedrine dose.[4] Moreover, in a randomized, double blind, placebo-controlled, crossover study of 3 oral decongestants in 20 patients with chronic nasal stuffiness, phenylephrine was no more effective than placebo in reducing nasal airway resistance[5] (Fig 1).

(Reference 5 is available in the Online Repository at www.jacionline.org.)

Two published reports indicate a correlation between decrease in objective measurement of nasal airway resistance and improvement in subjective symptom scores after oral decongestants.[6,7] McLaurin et al[6] compared single doses of 4 oral decongestants with placebo in a randomized, double-blind, crossover study in 88 patients with nasal congestion from a variety of causes. They concluded that 10 mg phenylephrine was no more effective than placebo in decreasing either nasal airway resistance or subjective symptom scores. In contrast, ephedrine 25 mg was effective for both endpoints, and objective improvement correlated with subjective relief.

In the second report,[7] 3 different panels of 16 patients with nasal stuffiness from a common cold were studied. Each panel took placebo and either 10 mg, 15 mg, or 25 mg phenylephrine in a randomized, double-blind, crossover manner on 2 consecutive mornings. Symptom scores were significantly reduced for all 3 doses compared with placebo, but there was no difference between doses. In contrast, there was a dose-response relationship for decrease in nasal airway resistance. It is noteworthy that in the cohort treated with 10 mg, baseline nasal airway resistance was significantly different on the 2 study days, making the results difficult to interpret.

As proof of efficacy, the FDA panel cited unpublished, manufacturer-sponsored studies conducted by commercial testing laboratories.[1] One study involved 2 immediate-release 5-mg tablets (Whitehall Laboratories, Inc, New York, NY). The remainder were studies of various doses (up to 25 mg phenylephrine) of immediate-release Neosynephrine tablets (Sterling-Winthrop, New York, NY). All of these studies evaluated both objective and subjective endpoints. Also, they cited studies conducted by other testing laboratories, as well as the 2 we have commented on,[5,6] that did not demonstrate a significant difference from placebo for either symptom relief and/or nasal airway resistance. In total, for the 10-mg dose, the panel cited only 4 studies demonstrating efficacy compared with 7 demonstrating no difference between this dose and placebo. Thus, in our view, the panel reached a specious conclusion that was not based on a systematic review of the available data.

It is possible that poor bioavailability can be overcome by increasing the dose of phenylephrine, but adequately powered dose-response studies are required to determine whether this will increase efficacy safely. In the meantime, healthcare providers can recommend that patients obtain pseudoephrine from a pharmacist if they require an oral decongestant for sinusitis or eustachian tube dysfunction. For patients with nasal stuffiness from a common cold, they can recommend a topical nasal decongestant, which is more effective than oral decongestants.[8] However, a topical decongestant should be avoided by patients with allergic rhinitis because of the risk of rhinitis medicamentosa.[9] For these patients, an intranasal corticosteroid is likely to provide the greatest relief[10] with low risk of systemic effects.

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REFERENCES

1. Food and Drug Administration. Establishment of a monograph for OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products. Federal Register 1976;41:38399-400. Available at: http://www.fda.gov/OHRMS/Dockets/98fr/76-22710.PDF. Accessed December 8, 2005.
2. Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826-32.
3. Hengstmann JH, Goronzy J. Pharmacokinetics of ^{3}H-phenylephrine in man. Eur J Clin Pharmacol 1982;21:335-41.
4. Kanfer I, Dowse R, Vuma V. Pharmacokinetics of oral decongestants. Pharmacotherapy 1993;13:116S-28S.
5. Bickerman HA. Physiologic and pharmacologic studies on nasal airway resistance (R_N). Presented at a conference sponsored by the Scientific Development Committee of the Proprietary Association. Washington, DC. December 8, 1971. (Available in the Online Repository at www.jacionline.org.)
6. McLaurin JW, Shipman WF, Rosedale R Jr. Oral decongestants: a double blind comparison study of the effectiveness of four sympathomimetic drugs: objective and subjective. Laryngoscope 1961;71:54-67.
7. Cohen BM. Clinical and physiologic "significance" in drug-induced changes in nasal flow/resistance. Eur J Clin Pharmacol 1972;5:81-6.
8. Dressler WE, Myers T, Rankell AS, London SJ, Poetsch CE. A system of rhinomanometry in the clinical evaluation of nasal decongestants. Ann Otol Rhinol Laryngol 1977;86:310-7.
9. Black MJ, Remsen KA. Rhinitis medicamentosa. CMAJ 1980;122:881-4.
10. Pullerits T, Praks L, Ristioja V, Lötvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109:949-55.
11. Hendeles L. Selecting a decongestant. Pharmacotherapy 1993;13:129S-34S.

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Normal lung function in children with mild to moderate persistent asthma well controlled by inhaled corticosteroids

To the Editor:

International guidelines on the diagnosis and management of childhood asthma emphasize the importance of assessing its severity with objective measures of lung function.[1] More specifically, FEV_1 and its reversibility after a bronchodilator are proposed as measures for the severity of childhood asthma, both at initial assessment and during follow-up.[1] Inclusion criteria for many clinical trials in asthma usually include a certain reduction of FEV_1% predicted, along with an improvement of >12% in FEV_1 after bronchodilator.[2,3] Several studies have shown that FEV_1 levels may improve considerably during treatment with inhaled corticosteroids (ICSs),[4] and that normal levels of lung function may be attained during ICS treatment.[5-7] We tested the hypothesis that children with mild to moderate persistent asthma well controlled on ICS therapy have normal FEV_1 levels and little or no bronchodilator response (BDR), unless they are experiencing a symptomatic episode at the moment of lung function testing, or when their adherence to treatment is poor.