

# Menley & James Laboratories

A SMITHKLINE BECKMAN COMPANY

May 15, 1985

Docket No. 76N-052N

Dockets Management Branch  
HFA-305 Room 4-62  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Gentlemen:

In response to the notice of proposed rulemaking concerning Over-the-Counter Nasal Decongestant Drug Products (Federal Register 50: 2219-2241, Jan. 15, 1985), Menley & James Laboratories, a SmithKline Beckman Company, submits the following comments:

Active Ingredients. We regret that FDA did not recommend category I status for phenylpropanolamine as an oral nasal decongestant in concurrence with the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antihistamine Drug Products (CCABA). We support the Panel's recommendations as to both the safety and effectiveness of phenylpropanolamine as an oral nasal decongestant. After thoroughly reviewing the literature and numerous data submissions, and hearing testimony from interested parties, that advisory review panel concluded that as an ingredient in OTC oral nasal decongestant products, phenylpropanolamine and its salts are safe in adult doses of 25 mg every 4 hours or 50 mg every 8 hours (Federal Register 41: 38400-38402, September 9, 1976).

In addition, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Weight Control Panel) concluded that phenylpropanolamine is safe and effective as an ingredient in diet aid products at adult doses of 25 to 50 mg not exceeding 150 mg daily (Federal Register 47: 8474-8476, February 26, 1982). However, the FDA, in its preamble to the Panel's report, raised specific safety questions in regard to phenylpropanolamine weight control products and requested further information on blood pressure effects of phenylpropanolamine and its interaction with drugs which inhibit prostaglandin synthesis. The agency cited more recent published literature in support of its position.

We believe the safety reports referred to in the preamble, which were made available after the Weight Control Panel's report was submitted, should not alter either panel's conclusion that phenylpropanolamine is safe at the recommended doses.

76N-052N



C  
C00204

Nine reports were cited in the preamble as having been made available after the Weight Control Panel's report was submitted. Two of these re-confirmed the results of studies considered by the Panel which showed that phenylpropanolamine does not induce hypertension in normotensive patients. These two positive reports are the study by Silverman et al and the studies of 50 mg immediate and sustained release dosages by Cuthbert, Greenberg and Morley. Of the remaining seven reports cited in the preamble, six included isolated cases of individual adverse reactions. These were the case reports of Horowitz et al; Frewin, Leonello and Frewin; King; Peterson and Vasquez; Lee, Beilin and Vandongen; and Deitz. In none of these cases was there any possibility of verification of the actual dose of phenylpropanolamine taken since the dose was reported by the patient and not taken under controlled conditions. In at least two of the cases overdoses were stated to have been taken. In five of the seven cases, "Trimolets", an immediate-release 85 mg anorexiant marketed only in Australia, was used. In only two of the seven cases was there any follow-up to determine whether the symptoms reported were repeated under the same or different circumstances. Six of the cases were simply anecdotal in nature. Clearly, any drug, OTC or prescription, has the capacity to cause idiosyncratic reactions in a small number of individual patients, especially when taken at higher than recommended doses.

Only two of the seven adverse reports cited in the preamble were purportedly of controlled clinical studies, both conducted by Horowitz et al. To the first of these the agency attributes "the most striking new finding" regarding elevation of blood pressure (Federal Register 47: 8466, February 26, 1982). Both of these studies are inappropriate to the agency's safety evaluation of the recommended dose in the United States because the adverse reactions reported by Dr. Horowitz were the result of testing the 85 mg Australian product "Trimolets". This product was labeled as timed-release, but it is open to question whether it did in fact contain a time-release mechanism. H.I. Silverman, whose study was cited in the preamble, received and analyzed a small number of "Trimolets". As he has since reported to FDA, Silverman found that the phenylpropanolamine in the product was immediately soluble in water and was not in a sustained release form. In addition, there is the possibility that "Trimolets" contained only d-phenylpropanolamine, not the racemic form that is used in the U.S.

Silverman's analysis indicates that "Trimolets", which had been used in most of the instances of reported adverse blood pressure effects, delivered in a bolus dose approximately three-and-a-half times the maximum recommended oral nasal decongestant immediate release dose (25 mg). The reported adverse reactions, therefore, were due to overdose.

The safety of phenylpropanolamine has been examined by the Boston Collaborative Drug Surveillance Program, and the complete reports have previously been submitted to the FDA. Jick et al. examined the relative risk of certain serious diseases for persons enrolled in the Group Health Cooperative (GHC) of Puget Sound who received a prescription cough or cold product containing phenylpropanolamine (Jick, H., Aselton, P. and Hunter, J.R.: "Phenylpropanolamine and Cerebral Hemorrhage", Lancet 1: 1017, May 5, 1984; Aselton, P., Jick, H. and Hunter, J.R.: "Phenylpropanolamine Exposure and Subsequent Hospitalization", J. Am. Med. Assoc. 253: 977, Feb 15, 1985).

Persons were considered to be at risk of developing a serious illness for 30 days after receiving a phenylpropanolamine prescription (new or refill). The number of prescriptions was multiplied by 30 days and then subtracted from the total number of patient-days for GHC members under 65 years of age. Then, the incidence of serious illness in the number of days exposed was compared with the incidence in the number of days unexposed to develop an estimate of relative risk. None of the 20 persons hospitalized for malignant hypertension and none of the 313 patients with an arrhythmia had received phenylpropanolamine. Two of the 108 persons admitted for acute neuropsychiatric disorders had taken phenylpropanolamine within the past 30 days, for a relative risk of 1.29. Only one of the 276 persons admitted with a thrombotic or nonspecific cerebrovascular accident had taken phenylpropanolamine, for a relative risk of 0.25. The relative risk of cerebral hemorrhage for phenylpropanolamine users compared with nonusers was 0.58 (one of 114 admissions).

These data show that phenylpropanolamine-containing cough/cold products are safe and that the risk of hospitalization attributable to taking these products, if present at all, is very small.

In response to the FDA request in the preamble to the Proposed Monograph for OTC Weight Control Drug Products, the Proprietary Association submitted additional data to FDA on July 26, 1982 in the form of comments on the proposal. These new data reported results of studies in which more than 3,500 patients were treated with phenylpropanolamine as an oral nasal decongestant or as an anorectic. These data along with the data received by the two panels demonstrate that PPA does not induce hypertension either in normotensives or hypertensives or when it is in combination with aspirin. These data, together with almost 50 years of safe use of phenylpropanolamine in this country, clearly outweigh the handful of adverse reports referred to in the agency's Preamble. Therefore, we believe the agency should support the Category I recommendation for phenylpropanolamine made by the CCABA Advisory Review Panel.

Indications. If a product is marketed primarily for one indication (i.e., a common cold or hay fever), it should not be required to carry both indications in its labeling. Therefore, we suggest that proposed section 341.80 (b)(1) be changed from "...common cold (cold), hay fever..." to "...common cold (cold) and/or hay fever...". We support the agency's inclusion of "relieves sinus pressure" in proposed sections 341.80 (b)(2)(iv) and (v) as this is a term which is meaningful to consumers.

An additional indication, "helps (select one of the following: relieve, alleviate, decrease, reduce) post-nasal drip" should be added as an additional consumer term for this class of products.

The phrases "for the temporary relief of" (in the Nasal Decongestant TFM) and "temporarily relieves" (in the Antihistamine TFM) should be interchangeable in order to permit more concise labeling for combination products.

Warnings. We suggest that proposed sections 341.80 (c)(1)(i)(a) and (ii)(a), which currently state "Do not exceed recommended dosage because at higher doses, nervousness, dizziness, or sleeplessness may occur", be revised to state "Do not exceed recommended dosage. If nervousness, dizziness or sleeplessness occur, discontinue use and consult a physician." As the warning presently stands it might suggest to consumers that nervousness, dizziness and sleeplessness are the only consequences of exceeding the recommended dose, which is not necessarily so. We feel that nervousness, dizziness and sleeplessness are significant enough to be a separate warning as they may, on occasion, occur at the recommended dose.

Proposed sections 341.80 (c)(2)(vi) and (x) prescribe labeling which limits the duration of propylhexedrine use to not more than three days. The preamble to the tentative final monograph states that this limitation is intended to discourage prolonged use because of the agency's perception of a rebound congestion problem. One two-week study and a single dose study showed that rebound congestion is not a problem with propylhexedrine, and a third study was ambiguous and only "suggest(ed) a possible rebound congestion" (Federal Register 41: 38402, September 9, 1976). To our knowledge, no studies exist which show a definite association between use of propylhexedrine and the occurrence of rebound congestion. Further, there are no studies which conclude that three days is the duration of therapy which reduces any risk of rebound congestion. In other words, the three-day warning is arbitrary and unsubstantiated. We recommend that the agency revise proposed sections 341.80 (c)(2)(vi) and (x) to read "Not to be used for prolonged periods".

Directions. We strongly recommend that the several subsections under proposed section 341.80 (d), which presently provide doses for children 6 to under 12 years of age and, in some cases, for children 2 to under 6 years of age, be revised to include more precise

divisions of dosing for children. Specifically, we recommend that a dosing schedule be developed for children in the following age groups:

- 11 to under 12 years
- 9 to under 11 years
- 6 to under 9 years

and, where applicable:

- 4 to under 6 years
- 2 to under 4 years

Such a dosing schedule would be more valid and would prevent under or overdosing of children. Also, as a practical matter a dosing schedule identical to that in the Proposed Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products would enable proper labeling of combination products when the monographs are final. We also recommend that manufacturers be permitted to include a pediatric dosage schedule based on weight in the labeling, as this is a medically sound alternative.

We understand that a subcommittee established by the Proprietary Association is developing a pediatric dosing schedule with finer age breaks, and we strongly urge you to adopt its recommendations.

Sincerely,



Raymond Ragland, Jr., Ph.D.  
Director,  
Regulatory Affairs

RR/sas  
0948C