DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
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Dear Dr. Kittner:

During your recent conversation with Dr. Bruce Stadel, you agreed to participate in FDA's review of phenylpropanolamine (PPA). I want to thank you for assisting the Agency by commenting on our evaluation and risk assessment of PPA used in over-the-counter (OTC) weight control drug products. Resolution of the complex scientific issues related to PPA is a very high Agency priority.

PPA for OTC weight control use was reviewed by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) as part of FDA's OTC drug review evaluating all OTC drugs. The Panel placed PPA in Category I (generally recognized as safe and effective) in its report that was published in the Federal Register of February 26, 1982 (copy attached). In September, 1990, concern about the safety of PPA was expressed in hearings before the House of Representatives Subcommittee on Regulation, Business Opportunities, and Energy. In response to these concerns, FDA held a public meeting in May, 1991 to discuss safety and effectiveness issues related to PPA. (See safety discussion on pages 13296-13297 of April 1, 1991 Federal Register notice attached.)

While a variety of possible consequences of PPA use for weight loss have been suggested, the most persistent suggestion, and the one of greatest concern to FDA, is the possibility that PPA used in OTC weight control drug products might increase the risk of stroke. The possibility is raised by a relatively small number of spontaneous (published and unpublished) reports of intracranial bleeding associated with use of PPA, in young, mainly female users of PPA weight loss products, and by the known ability of PPA to increase blood pressure. In an effort to help decide whether the spontaneous reports represent an increased risk due to PPA, our Epidemiology Branch has attempted to compare the number of strokes that have been reported as occurring during use of PPA weight control drug products with the number expected to be reported from a simple coincidence between the use of PPA weight control drug products and the background incidence of stroke in the user population. This effort is described in the following reports on the subject (copies and references attached):

1. "Epidemiologic Review of Phenylpropanolamine Safety Issues" (April 30, 1991)

2. "Additional Analysis of Phenylpropanolamine and Cerebral Hemorrhage" (August 6, 1991)

3. "Safety of Phenylpropanolamine Hydrochloride as an OTC Weight Control Drug Product" (December 26, 1991)

Because the analyses used are novel, and the issue important, we are seeking external review of what we have done. We would appreciate your evaluation of our reports and our risk assessment of these products in the OTC drug-use setting. Please include a response to the following questions in your review and recommendations:

1. Do the Epidemiology Branch reports of April 30, August 6, and December 26, 1991, adequately describe the data and methods used to evaluate the occurrence of cerebrovascular accidents (CVAs) and hypertensive episodes related to the use of PPA for weight control? Do the data and methods support the conclusions reached?

Please comment specifically on the following issues:

a. Introduction to the April 30 and August 6 reports - Are the reasons clear and valid for focusing on adverse drug experience (ADE) reports to FDA's Spontaneous Reporting System (SRS) and in the medical literature, and for not using data from Poison Control Centers and the Drug Abuse Warning Network?

b. Methods - Is the approach described in parts 1-5 of the April 30 report reasonable? Please consider specifically the following points:

1) One analysis of the Spontaneous Reporting System data for women 10-59 years of age compares the SRS proportion of CVA reports among all ADE reports for PPA weight control drug products with the proportion of CVA reports among all ADE reports for PPA cough-cold products, and with the proportion for all other drugs. This technique is often applied to drugs of the same class that are used for the same indication, presuming that in the presence of similar usage (similar patients, physicians, concomitant therapies, concomitant illnesses), an excess of a particular ADE would suggest that the ADE is caused by the drug. In the present case, however, comparisons are atypical. Both the all-patients group and the cough-cold group represent patient populations entirely different from the weight control patients. Most of the cough-cold group use PPA with combination products with several components that could generate their own ADEs, possibly adding to the background rate.

2) Perhaps the most critical analysis is the comparison of the number of reported CVA's in PPA weight control drug product users with the number expected by chance. The initial estimate of the number expected by chance on the first day of PPA use was calculated as 10,000,000 users x 1/10,000 x 1/365, or 2.7 per year (April 30 report); the August 6 report described several alternative analyses. Please comment on the critical numbers used in the various scenarios cited, and the estimated incidence rate of hemorrhagic stroke in young women of 1/10,000.

The focus on day one (April 30 report) is based on the reported stroke cases (9/17 cases with diet products where duration was specified occurred with the first dose) and the fact that the hypertensive effect of PPA is very much attenuated after the first dose. If the day one focus were changed, and all days considered days at risk, the expected annual number of strokes would be 2.7 x 16 (days of treatment) or 44.

Note also that the annual number of expected cases would double if one presumes two 16 day courses of treatment per year, which some have suggested as the likely rate of use.

c. Results - Are the findings described in parts 1-4 of the April 30 report clear?

d. Discussion - Please comment on all critical aspects of the discussion in the three reports and particularly the conclusions (page 9 of the April 30 report) that "This analysis of reports to the SRS and in the literature suggests that PPA diet pills increase the risk of CVA," that "it is not feasible to test the hypothesis of an association between PPA weight control products and cerebral hemorrhage by clinical trials or cohort studies," and that "a case-control study of cerebral hemorrhage in young women is a possible approach."

In addition, please specifically consider the following questions:

1) What is the implication of the observation that excess dose was associated with CVA reports? On its face, the observation suggests a drug relationship (a minority of use, presumably, is at an excessive dose, yet this use is associated with the majority of reports) and is plausible in light of the dose related blood pressure elevation of PPA. Note also that this blood pressure relationship is present for the cough-cold products, which the SRS data do not suggest as increasing the risk of strokes.

2) What is the implication of the observation that most CVA cases follow the first dose? Does the compatibility of this observation with the known rapidly developed tolerance to the

pressor effect of PPA argue drug relatedness? Could this merely be a consequence of reporting bias (you notice the early response)? Note that the relationship is present for both weight control and cough-cold cases. To what extent do you believe this suggests a drug relationship versus reporting bias?

3) To what extent do you believe that the comparison of stroke/total ADE ratios for PPA weight control products vs PPA-cough/cold products controls for possible reporting bias?

4) Possible explanations for a difference between CVA reporting rates for weight control preparations and cough/cold products with similar doses of PPA are given on page 8 of the April 30 report. Please identify those (if any) you consider plausible, suggest others, or provide other comment on this issue.

5) The analysis of expected vs observed cases of stroke in the weight control drug product user population is sketched briefly in the April 30, 1991 report and in much more detail in the August 6, 1991 report. This aspect of the report, we believe, requires your closest attention, specifically to:

a) The cases included in each analysis. For example, the first day analysis in scenario A includes cases specifically noted as occurring on the first day (14) or not otherwise specified (8). If, given that of the 36 cases with time specified, only 14 (39%) were first day, should all 8 not otherwise specified be attributed to the first day? Note also the discussion in the December 26, 1991 report of the differences between Dr. Jolsen's included cases and those of the Nonprescription Drug Manufacturers Association (NDMA).

b) Should gross overdoses (as opposed to just taking 2 instead of 1) be included? (Eight cases took at least 5).

c) Which scenario (A-D, August 6 report) do you find most persuasive? The agency's focus has been on C, mainly because of the pharmacologic observation of rapid development of tolerance to the pressor effect of PPA, but little is known about recovery from tolerance; e.g., would a full pressor response occur after skipping one day.

d) Perhaps most important, what do you consider to be the most reasonable estimate of reporting rate? It is apparent that for any scenario, the 1% estimated reporting rate gives observed/expected (O/E) ratios that strongly suggest a drug effect, but the 10% estimate gives O/E ratios that are far less impressive.

In particular, as the December 26, 1991 report shows, if the 10% estimate is used, various analyses using first day cases cluster in the area of O/E ratios of 1-4.

Feel free to discuss any other aspects you think are important.

The method of payment to you will be based on your submission of completed Timekeepers Payroll Record forms. Several copies of these forms are enclosed. Let us know if additional forms are required. It is important that you mail a completed form to us within a few days of the close of each pay period, if you have worked within that period. Each form should be mailed no later than Tuesday of the last week in a pay period. We have also enclosed self-addressed envelopes for your convenience in sending these forms to us. It is a good idea for you to make a photocopy of each completed form for your records.

In order to expedite handling of your communications on this assignment, please include the following identifying number, OTC Trac No. 206-12, on the first page of your letter. We would appreciate receiving your response by August 3, 1992, or sooner if possible. If you have any questions or need any additional information, please contact Robert Sherman of my staff at (301) 295-8897.

We appreciate your help in our evaluation of this important public health matter.

Sincerely,

Paula Botstein MD

Paula Botstein, M.D.
Acting Director
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

and

Deputy Director
Office of Drug Evaluation I

Enclosures

cc: HFD-100(Temple)
HFD-110(Lipicky/Dern/Fenichel)
HFD-700(Johnson/Anello)
HFD-733(Stadel)
HFD-800(Botstein/Weintraub)

HFD-810:DDC-980.3/ING-40.33/Reading/Lessing
HFD-811(Rachanow)
HFD-813(Mustafa)
HFD-814:Weight Control/PPA/Cothran/Sherman/Robinson
HFD-820(Doyle)
R/D-RSherman/3/10/92
Revised:RTemple/4/24/92
Addendum:Botstein/Stadel/6/5/92
DOC ID:CONSULT.LET Disk (40 B)