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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 9 1993

R. William Soller, Ph.D.
Senior Vice President and Director
of Science and Technology
Nonprescription Drug Manufacturers Association
1150 Connecticut Avenue, N.W.
Washington, D.C. 20036

Re: Docket No. 81N-0022
Comment No. PR7

Dear Dr. Soller:

This letter relates to your March 4, 1993 submission of a final draft protocol for a population-based, case-control study of the relationship between the use of over-the-counter (OTC) weight control drug products containing phenylpropanolamine hydrochloride (PPA) and the risk of hemorrhagic stroke. At the time we received your submission, we were in the final stages of preparing this letter to you. We have determined that it is still important to issue this letter at this time and convey our views on PPA to all parties interested in this drug.

Numerous comments on the safety of PPA have been submitted to FDA in the rulemakings for OTC weight control and OTC nasal decongestant drug products. Because the PPA safety issues in each of these OTC drug classes are closely related, the agency did not categorize or discuss PPA in the tentative final monograph for OTC nasal decongestant drug products, published in the Federal Register of January 15, 1985 (50 FR 2220), or in the notice of proposed rulemaking for OTC weight control drug products, published in the Federal Register of October 30, 1990 (55 FR 45788). Although this letter focuses primarily on one safety issue, the agency plans to discuss other safety considerations in a notice of proposed rulemaking for OTC weight control drug products which will be published in a future issue of the Federal Register. The agency's position regarding effectiveness will also be addressed at a later date.

As you are aware, the principal concern that still remains is the possibility that PPA might increase the risk of stroke. That possibility is raised by a relatively small number of spontaneous (published and unpublished) reports of intracranial bleeding associated with the use of PPA weight control drug products. Given the apparent rapid tolerance that develops to any hypertensive response to PPA, the adverse reaction reports that most plausibly represent an effect of PPA are those occurring after the first dose, or at least during the first day of PPA therapy, or upon resumption of PPA after a pause in therapy. However, only a few of the reported cases clearly meet this

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description. In some other reports, precise time and dose information are not available. The relatively few first dose/first day cases, combined with the short duration and seemingly modest size of the PPA hypertensive response at recommended or slightly excessive doses, tend to argue against PPA being the cause of these serious reactions. Also supporting that view is the relatively low rate of reported cases in people using PPA-containing cough-cold drug products, which are extensively marketed and widely used. On the other hand, one would expect very few stroke events in a healthy young population (from 1977-1987, mean age = 30.6 years in FDA adverse reaction reports associated with PPA weight control drug products). However, the observation that most reports of serious reactions involve single doses of at least 150 mg (two 75 mg controlled release dosage forms), higher than the recommended dose and presumably not the most commonly used dose, could suggest a dose-response and, thus, a causal relationship.

Moreover, a number of early case reports of hypertensive episodes and hemorrhagic stroke implicated a weight control drug product called Trimolets, which was marketed in Australia. In placebo-controlled clinical trials, a single dose of this preparation caused a significant increase in blood pressure in normal, healthy volunteers. It is now known that the Australian product contained 85 mg of an immediate-release nonracemate of norephedrine. In contrast, the maximum dosage immediate-release OTC drug product currently available in the United States contains 37.5 mg of the racemic mixture d-,l-norephedrine (PPA). The most commonly used product for weight control is a 75 mg sustained-release capsule. Thus, 85 mg of the Australian PPA-related preparation may have had the same hypertensive potency as two or more typical U.S. immediate-release weight control capsules or tablets. This again suggests that drugs with PPA-like properties may, at some dose, raise blood pressure substantially and cause strokes.

One difficulty in assessing PPA safety is evaluating often incomplete, isolated reports, of relatively rare events. The problems are magnified in the OTC drug-use setting, where information is sparse and, more importantly, little is known about adverse reaction reporting practices. Without specific knowledge of use patterns (ages of users, underlying diseases), and a reasonable estimate of the extent of under-reporting, the agency has found it impossible to determine whether the reported instances of intracranial bleeding are more than the expected background rate. To address this, we sought to compare the rate of reports we have of intracranial bleeding (based on estimates of use of PPA-containing weight control drug products), with available estimates of the rate of intracranial bleeding in young women 15-44 years old. We found that an evaluation of whether the rate was excessive depended heavily on what the extent of

under-reporting of adverse events was thought to be. If the available reports represent, e.g., 10% of actual occurrences, that would suggest a rate of intracranial bleeding that was not elevated compared to the background rate. Lower reporting rates would, on the other hand, suggest a relationship between hemorrhagic stroke and PPA use.

Because of the difficulties of the analysis and the somewhat unconventional use of several databases by others to estimate the spontaneous rate of hemorrhagic stroke in young women, FDA asked three epidemiologists from outside the agency to review our assessment of the stroke data. Although the epidemiologists agreed that the agency's analysis was reasonable based on the available data, they also believe that interpretation of the data depends critically on the estimated reporting rate of PPA-associated adverse drug reactions in the OTC setting and that the reporting rate is unknown. Because this rate is unknown, they stated that the database could not support a conclusion that PPA increased the rate of strokes. However, they also did not believe the available information could rule out the possibility of an increase in the stroke rate.

Other analyses and data also are unable to yield a clear conclusion. The observation of a higher first day incidence and a possible dose-response relationship could reflect a recognition bias as well as a causal relationship. It is notable that the majority of strokes reported are associated with PPA-containing weight control drug products, although we estimate that 80 percent of PPA-containing drug products sold are cough-cold products. The relative lack of reports with cough-cold products could perhaps be explained by a greater tendency of users of OTC weight control drug products to exceed the recommended dose, or possibly ingest PPA on an empty stomach, affecting its rate of bioavailability; however, we do not know this to be true. The relative absence of reports from cough-cold drug product use could also suggest that the reports associated with weight loss drug products may be attributable to other factors. Whatever the explanation, a serious attempt to discourage use of more than the recommended dose is clearly in order.

It should also be noted that the reported stroke rate in young women (15-44 years old) in Canada, where PPA is not available as a weight control drug product either OTC or by prescription, but is marketed in OTC cough-cold drug products, does not differ significantly from the rate in the United States where PPA is widely available. This seems to indicate that PPA is unlikely to be a major contributor to stroke rates in the U.S. or Canada, even if it can sometimes cause them.

At the FDA-industry feedback meeting on November 9, 1992, you presented a proposal for a large-scale, population-based

epidemiologic study of the relationship between PPA-containing weight control drug products and the incidence of hemorrhagic stroke. Both we and our epidemiology consultants believe that a case-control study of the relationship of PPA and stroke can be carried out and can help determine whether PPA increases the rate of stroke. We appreciate your prompt submission of a draft protocol for this study. The agency will carefully review the protocol and will respond as soon as possible to your request for a meeting to discuss the conduct of the study.

In addition to the proposed study, you discussed voluntary changes in package labeling, advertising, and promotion of PPA weight control drug products to help insure that their use is confined to adults and that the recommended dose is not exceeded. We view this voluntary initiative as a reasonable precaution and believe it should be implemented as soon as possible. The agency will propose specific labeling recommendations for OTC weight control drug products in the notice of proposed rulemaking, to be published in a future issue of the Federal Register.

CONCLUSION:

Although we cannot rule out PPA as a rare cause of strokes, the agency does not believe, based on information currently available, that PPA used in OTC weight control drug products represents a major public health risk. In addition, while FDA is aware of specific instances of misuse, the agency lacks substantive, broad-based epidemiologic evidence of widespread misuse of PPA. Thus, the agency does not believe that it is necessary to remove PPA weight control drug products from the OTC market while additional data are being obtained.

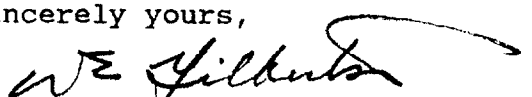
However, it is critical that the proposed case-control study be carried out promptly. The agency believes that a case-control study of PPA and stroke would provide a large enough database to determine if the incidence of stroke associated with ingestion of PPA is greater than the spontaneous rate of stroke, i.e., the rate that would be expected to occur in a similar population not using the drug. We will be looking at your proposed protocol to see if it will achieve this objective.

Based on the above discussion, in the notice of proposed rulemaking for OTC weight control drug products, the agency will be placing PPA in Category III for safety (insufficient data available to permit final classification). This status will be transient and not prolonged. Although FDA's decision is based on the data and information now in the administrative record, the final resolution of PPA's status will be influenced by the outcome of the proposed study concerning hemorrhagic stroke.

Any comment you wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,



William E. Gilbertson, Pharm.D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 9, 1993

FROM: Director
Monograph Review Staff (HFD-810)

SUBJECT: Material for Docket No. 81N-0022

TO: Dockets Management Branch (HFA-305)

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DOCKETS MANAGEMENT BRANCH

[X] The attached material should be placed on public display under the above referenced Docket No.

[X] This material should be cross-referenced to Comment(s) No. PR7.

William E. Gilbertson, Pharm. D.

Attachment