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Nonprescription Medicines and
Dietary Supplements for Self-Care

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Formerly Nonprescription Drug Manufacturers Association

May 24, 2000

By Messenger

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Dockets No. 81N-0022 and 76N-052N

To Whom It May Concern:

The Consumer Healthcare Products Association (CHPA) Phenylpropanolamine Working Group submits the enclosed comments on the report recently submitted by Yale University investigators to FDA Docket No. 81N-0022 (RPT 14). These comments were prepared upon our initial review of that Yale final report on the Hemorrhagic Stroke Project. We urge that these CHPA comments be treated as a companion to the Yale study report, as they highlight important issues to be considered in interpreting the study results.

The Hemorrhagic Stroke Project report must be considered in the context of the large existing safety database on phenylpropanolamine (PPA). This evidence from clinical trial and adverse-event tracking, when taken together, overwhelmingly supports the safety and effectiveness of PPA when used as directed on product labeling.

On behalf of the CHPA Phenylpropanolamine Working Group,

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

Lorna C. Totman, Ph.D., DABT
Director of Scientific Affairs

Enclosures: Comments on the Hemorrhagic Stroke Project Report
(six print copies and an electronic copy on disk)

cc: Charles J. Ganley, M.D., Director, Division of Over-the-Counter Drug Products
Robert DeLap, M.D., Director, Office of Drug Evaluation V

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CHPA Phenylpropanolamine Working Group

Comments on the Hemorrhagic Stroke Project Report

May 24, 2000

Introduction

In 1994, members of the Consumer Healthcare Products Association (CHPA) marketing phenylpropanolamine (PPA)-containing appetite suppressants contracted with investigators at Yale University to conduct an epidemiologic study on hemorrhagic stroke.¹ The final report of this study has been provided to the sponsoring companies and the Food and Drug Administration. This document provides commentary on the recently submitted report of the Hemorrhagic Stroke Project.

While even the best-designed and executed epidemiology studies have limitations for reaching definitive conclusions, the nature and complexity of the Yale study make drawing any meaningful conclusions particularly difficult, primarily due to inadequate controlling for bias and confounding. Also of particular concern are the scientific limitations of interpreting results from small numbers of cases and controls who were exposed to PPA. Important confounders and biases, which are likely to have had a profound impact on the study results and conclusions, have been overlooked in the study report.

Our core concern relates to the overall strength of the study, and we believe the study data do not support a serious challenge to the safety of phenylpropanolamine in over-the-counter medicines. We strongly disagree with any broad-sweeping statements and conclusions about the results of the Yale study that explicitly state or imply it represents strong epidemiologic evidence applicable to the general population. Numerous factors limit the ability of this study to support these conclusions.

These comments summarize our overall conclusions and specific concerns about the Yale study report. Important methodological and analytical issues of relevance in interpreting the study results are identified in the Attachment, which is entitled "Points to Consider in Review of The Hemorrhagic Stroke Project: Case-Control Study of Phenylpropanolamine (PPA) and Hemorrhagic Stroke."

¹ The five-year case-control study began in 1994 and involved interviews of 702 patients between the ages of 18 and 49 who had been hospitalized with hemorrhagic strokes and a total of 1,376 controls matched to cases on the basis of age, gender, race and geographic location. The cases were identified from a network of 20 hospitals in Connecticut and from participating hospitals in Providence, Rhode Island; Cincinnati, Ohio; and Houston, Texas.

Summary Comments

1. The Hemorrhagic Stroke Project did not establish a causal relationship between PPA use and hemorrhagic stroke.
2. The findings of the Hemorrhagic Stroke Project must be considered in the context of existing safety data on PPA. This evidence overwhelmingly supports the safety and effectiveness of PPA when used according to label directions.²
3. The study findings of an apparent "association" between stroke and PPA exposure should not be relied upon as conclusive. Important biases and inadequate controlling for confounding factors (see below) could account for the reported association. A more appropriate conclusion is that the data are derived from too few cases and controls to allow an unbiased assessment about any relationship between exposure and stroke.
4. Conclusions from the study should be based on overall PPA exposure, which is the study's first objective (i.e., "Do PPA users have an increased risk?"). The overall analysis based on this endpoint resulted in an odds ratio that does not demonstrate increased risk [i.e., OR=1.49 (p=0.084)] of PPA use and hemorrhagic stroke. No meaningful conclusions can be derived from analyses of very small, selected subsets. There are too few cases and controls in the subgroups who reportedly took PPA to allow for effective controlling for confounding factors.
5. Confounding factors, which are independent risk factors that are associated with both PPA product use and the occurrence of stroke and include lifestyle habits and pre-existing medical conditions that could independently contribute to stroke, such as hypertension and cigarette smoking, were not controlled for in the study analyses. Cases and controls were not adequately matched for confounding factors, which is a deviation from the study protocol.
 - Some examples of confounders that were not adequately controlled for include the following:
 - Educational level and socioeconomic status were quite different between the cases and the controls, and cases were more likely to be black than were controls. Lower socioeconomic status and a lower educational level are known risk factors typically associated with greater morbidity and mortality in a number of diseases, including stroke. Those and several other risk factors for stroke are significantly more prevalent among cases than among controls. Cases were more likely to be current smokers, consume more alcoholic beverages, be illicit drug users, be reported to have hypertension, and/or have a family history of stroke.

² Submissions by CHPA [then named Nonprescription Drug Manufacturers Association] to FDA Docket No. 81N-0022: October 17, 1990, letter to William E. Gilbertson, Director, Division of OTC Drug Evaluation; September 6, 1991, "Overall Statement on the Safety and Effectiveness of Phenylpropanolamine as an OTC Appetite Suppressant"

- Hypertension is a risk factor for hemorrhagic stroke and for an increased risk of aneurysm formation and rupture, and is associated with obesity. Obese persons might be expected to be more likely to use PPA-containing appetite suppressants, but notably few persons in the study had taken PPA appetite suppressants. Although the use of antihypertensive medication and degree of blood pressure control are potentially important risk factors, they were not assessed nor, therefore, controlled for as confounders.
 - The reported apparent “association” of hemorrhagic stroke and PPA in this study could arise from the comparison of a high-risk group for hemorrhagic stroke (hypertension, cocaine and alcohol abuse, caffeine consumption, family history of hemorrhagic stroke, obesity) with controls drawn from the general population, with limited control of confounding.
6. Because of the small number of cases of hemorrhagic stroke reportedly associated with PPA use identified in this five-year study, errors in classification of exposure could easily and significantly skew the results of the study. This could be caused by errors in participant recall and/or product misclassification. The apparent association between PPA appetite suppressant use and stroke reported by the Yale investigators would not be apparent if only four controls were misclassified as unexposed to PPA.
- Since there are cough/cold products and appetite suppressants that do not contain PPA, a participant could incorrectly recall that they took product A (with PPA), when in fact they took product B (with no PPA).
 - Telephone interviews preclude the use of visual aids to assist subjects in their recall of exposure. More than twice as many controls as cases were interviewed over the telephone, suggesting it was more likely for an exposed control to be misclassified on reported product use.
 - Many other factors could also affect the accuracy of exposure classification. For example:
 - Study participants were asked to recall the specifics of medicine taken more than two weeks before, a substantial time between reported use and time of interview.
 - Forty percent of the interviewed cases had a degree of aphasia. (Aphasia is the loss of ability to speak or understand spoken or written language due to disease or injury of the brain.) The proportion of aphasic cases could have affected accurate identification and classification of cases reported to have used PPA products.
 - Interviewers knew which subjects were cases and which were controls, and could have inadvertently prompted specific answers and thereby skewed the results.
 - The difference in the severity of the event for cases versus controls and in the location of the interviews (hospital versus home) could also have contributed to skewing the results.

- Because such factors as those suggested above may have a significant and unpredictable impact on the odds ratio in either direction and virtually no information is provided to give a perspective on how such recall issues affect the study results, the scientific documentation supporting a putative exposure is, at best, inconclusive.
7. The study was based on prevalent cases. Cases who died before interview and those who were unable to communicate within 30 days (i.e., 34%) were excluded. Studies based only on prevalent cases could be misleading. A higher apparent risk of hemorrhagic stroke among PPA users might be due to a lengthening of their survival rather than an increase in disease incidence, and excluded cases may differ in their exposure to PPA and other risk factors for hemorrhagic stroke that would likely be confounders of the association of interest. Exclusion of the most severe patients could have affected the results, overestimating the risk associated with the use of PPA. This bias does not allow any posterior control for confounding factors associated with survival from hemorrhagic stroke.
 8. The study report fails to acknowledge that the findings cannot be entirely generalized to the U.S. population, as the enrolled cases and controls were not adequately population-based and differ in sociodemographic characteristics from typical U.S. consumers who use PPA drug products. Furthermore, the study's case population does not appear to be totally representative of the hemorrhagic stroke population among 18- to 49-year-olds in the United States (i.e., the study shows a different distribution by stroke type), as well as excluding fatal strokes.
 9. The large differential in participation rates between cases and controls could affect the findings and is not adequately explained in the report. Likewise, inadequate data are provided to allow independent verification of the findings or to verify that sensitivity analyses do not alter the confidence limits or p values for the findings.
 10. Choice of analytical methodology is also of concern. Inappropriate statistical methods were used, given the small numbers of exposed cases. Likewise, inappropriate and/or inadequate methods were used to control for confounding.
 - The number of subjects exposed to appetite suppressants is too few to meet the criterion for the use of asymptotic statistical methods. These methods require a minimum of five observations in each exposure-disease category. Seven exposed subjects divided between cases and controls does not satisfy this criterion. Therefore, analysis of exposure to appetite suppressants should use exact, rather than asymptotic, statistical methods.
 - The attempt to control for confounding by including confounders in the exact method of analysis was unsuccessful due to the few exposed subjects. Therefore, interpretation of the results of the exact analysis must include confounding as a very likely explanation for the observed association. Further, these confounders cannot be considered controlled in the asymptotic analysis, since the assumption for this analysis is violated.
 - A reflection of the inappropriateness of the asymptotic statistical analysis is the fact that the strength of the association between exposure and disease (i.e., the magnitude of the

odds ratio) increased when confounders were “controlled.” This is contrary to what is usually observed in control of confounding variables, where the adjusted odds ratio is expected to be smaller than the unadjusted odds ratio.

11. The study provided no insight on a biologically plausible mechanism for any relationship between use of PPA and hemorrhagic stroke. Although recommended doses of PPA have been shown to cause small, transient, but clinically insignificant, changes in blood pressure,³ these minor changes are within the range of usual increases associated with such daily activities as climbing stairs or mowing a lawn. Hence, alteration of blood pressure is not a clear underlying mechanism for a putative association between PPA and stroke, nor is any other biologically plausible mechanism known.

Concluding Points

The Hemorrhagic Stroke Project report must be considered in the context of the large existing safety database on PPA. This evidence from clinical trial and adverse-event tracking, when taken together, overwhelmingly supports the safety and effectiveness of PPA when used as directed on product labeling. PPA-containing products have been used by millions of consumers over the past 50 years with a very low incidence of reports of serious side effects.

The CHPA PPA Task Group and expert consultants continue to review the reported results and additional data from the study. The group expects to submit all of its findings to the Food and Drug Administration.

Attachment: Points to Consider in Review of The Hemorrhagic Stroke Project:
Case-Control Study of Phenylpropanolamine (PPA) and Hemorrhagic Stroke

WS/LT/ct/PPA/Comments to FDA:5-23-00

³ Blackburn et al. 1989. *Journal of the American Medical Association* 262(22):3267-72; Morgan and Funderbunk 1992. *American Journal of Clinical Nutrition* 55:2065-2105



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DATE: May 24, 2000

TO: Dockets Management Branch, FDA

FROM: Lorne C. Totman, Ph.D.

NUMBER OF PAGES: 1 (including this cover page)

MESSAGE: *The submission sent today for Dockets No. 81N-0022 and 76N-052N included an attachment which was inadvertently still marked "confidential." Nothing in the CHPA submission was intended to be kept confidential. Please let me know if there will be any problem in entering the documents you received into the docket.*

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