



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

October 24, 2000

Sydney M Wolfe, MD
Public Citizen's Health Research Group
1600 20th Street NW
Washington, DC 20009-1001

Dear Dr. Wolfe;

Your petition requesting the Food and Drug Administration to ban the use of phenylpropanolamine (PPA) in OTC Nasal Decongestants and OTC Weight Control Drug Products for Human Use was received by this office on 10/23/00. It was assigned docket number 76N-052N/CP 17 and 81N-0022/CP 19 respectively and it was filed on 10/23/00. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

A handwritten signature in cursive script, reading "Jennie C. Butler", is written over the typed name.

Jennie C. Butler
Dockets Management Branch

76N-052N

ACK-3

copy
#1/3

*Producers of Quality
Nonprescription Medicines and
Dietary Supplements for Self-Care*

8871 '00 OCT 23 A9:51

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Formerly Nonprescription Drug Manufacturers Association

October 2, 2000

Robert DeLap, M.D.
Director, Office of Drug Evaluation V
Center for Drug Evaluation & Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. DeLap

Further to our conversation on the matter of the nature of materials sent to FDA advisory committees prior to an advisory committee meeting, I enclose pages 1 and 2 from the FDA Background document that has been sent to the advisory committee members addressing the safety of PPA in advance of the October 19th meeting.

Please note that, while the FDA epidemiologic report provides a commentary dealing with scientific aspects of the strength of the Yale study, it also surprisingly provides a public health conclusion as to the availability of PPA (page 1, bottom paragraph and page 2, first paragraph, last sentence, attached). It is our understanding that information from FDA to advisory committee members, who are to provide their own public health recommendations based on the available data, should provide a scientific review of the available information and data and not the subsequent recommendation about a product's availability. On its face, FDA's epidemiologic report seems to prejudge the issue before the advisory committee meeting has happened, and we are aware of a number of highly credentialed epidemiologists who view the Yale study findings with considerable skepticism and would like their views to have a fair hearing.

Assuming that it is not FDA's intent to imply that the epidemiologic report is the FDA position on the matter of PPA's availability, we hope that FDA can provide a corrective interpretation of the two paragraphs in question to the advisory committee members.

Sincerely yours,

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

Attachments: As stated

cc: Charles Ganley, M.D.
Linda Katz, M.D.
Murray Lumpkin, M.D.

81N-0022/C/1/6
✓76N-052N/C 234

Attachment to CHPA October 2,2000 letter
to Robert DeLap, M.D.

MEMORANDUM

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

DATE: September 27, 2000

FROM: Lois La Grenade, M.D., M.P.H., Epidemiologist
Parivash Nourjah, Ph.D., Epidemiologist
Division of Drug Risk Assessment I, HFD-430
Office of Post-Marketing Drug Risk Assessment (OPDRA)

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Assessment I, HFD-430
Office of Post-Marketing Drug Risk Assessment (OPDRA)

SUBJECT: Review of study protocol, final study report and raw data regarding the
incidence of hemorrhagic stroke associated with the use of
phenylpropanolamine.

TO: Charles Ganley, M.D., Director,
Division of OTC Drug Products, HFD-560

PID # D 000487

Executive Summary

This consult is in response to a request from the Division of OTC Drug Products, HFD-560, to review the study report entitled "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of the Hemorrhagic Stroke Project", the study protocol and raw data submitted by Yale University. It was designed to test the association between hemorrhagic stroke in young people and use of phenylpropanolamine-containing products, a signal generated from studying case reports in our spontaneous reporting system. Our overall conclusion is that this study was well designed and executed. The case-control design was best suited for this study since the outcome under investigation was rare. All reasonable steps were taken to minimize bias and confounding. The study demonstrated a statistically significant increased risk of hemorrhagic stroke among both appetite suppressant users and first time users of PPA as a cough/cold remedy.

OPDRA concludes that the study provides compelling evidence of increased risk of hemorrhagic stroke in young people who use PPA-containing appetite suppressants. This finding, taken in association with evidence provided by spontaneous reports and case reports published in the medical literature, leads us to recommend that these products should no longer be available for over-the-counter use.

The Yale investigators also found a statistically significant association between first time PPA use in cough/cold remedies and hemorrhagic stroke. OPDRA considers this association to be as important as that for use of PPA as an appetite suppressant. FDA continues to receive spontaneous reports of hemorrhagic stroke with high-dose cough/cold remedies. Some reports indicate that only one dose was administered. The doses of PPA delivered in cough/cold preparations overlap those delivered in appetite suppressants, and there is evidence to suggest that the risk of hemorrhagic stroke may be higher with PPA doses at or above 75 mg/day. OPDRA concludes that high-dose PPA cough/cold remedies are associated with an increased risk of hemorrhagic stroke. These high doses may be achieved by exceeding the recommended labeled dose of the low-dose products. OPDRA therefore recommends that PPA-containing cough/cold remedies should no longer be available as over-the-counter products.

Introduction

This consult is in response to a request from the Division of OTC Drug Products, HFD-560, to review the study report entitled "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of the Hemorrhagic Stroke Project", the study protocol and raw data submitted by Yale University, as well as comments on the Hemorrhagic Stroke Project Report, May 24, 2000, provided by the CHPA Phenylpropanolamine Working Group. We were also requested to provide an update of cases of hemorrhagic stroke associated with phenylpropanolamine (PPA) use, reported to the Agency's Adverse Event Reporting System (AERS) since the end of January 1991, the date of the last review.

The body of this memorandum contains the review of the study protocol and final report. Appendix A contains an update of cases of hemorrhagic stroke in AERS along with information on background incidence rates of hemorrhagic stroke. Appendix B contains a response to CHPA's comments, in the form of a consult to OPDRA prepared by Dr. Yi Tsong from the Office of Biostatistics.

Review of Study Protocol and Report

The Yale study demonstrated an increased risk of hemorrhagic stroke associated with PPA use. The investigators found the increase in risk of hemorrhagic stroke to be statistically significant among appetite suppressant users and first time users of PPA as a cough/cold remedy. Observational studies, particularly case-control studies, are potentially subject to a number of biases, and this case-control study is no exception. However, the hallmark of a good case-control study is that these biases are anticipated and measures instituted in the design and analysis stages to minimize them to the greatest extent possible. In reviewing the design and analysis of this study we will attempt to examine potential biases and the measures taken to minimize them. We will also report on additional analyses undertaken by us to test the consistency of the data and the results.

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: Oct. 18, 2000

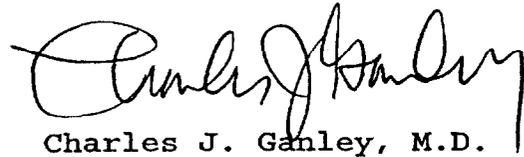
FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 81N-0022

TO: Dockets Management Branch, HFA-305

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

This material should be cross-referenced to Comment No. 76N-052N


Charles J. Ganley, M.D.

Attachment