



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

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DATE : April 14, 2000

FROM : Robert J. DeLap, MD, PhD *RD 4/14/00*
Office of Drug Evaluation V
Charles Ganley, MD *CG 4/14/00*
Division of OTC Drug Products

SUBJECT: Yale PPA Study - Conversation with W. Soller and L. Totman of the Consumer Healthcare Products Association on April 12, 2000

TO: Office and Division Files

Following a periodic "Scientific Dialog" meeting with several representatives of the CHPA on the afternoon of April 12, 2000, Dr. Charles Ganley and I spoke briefly with Drs. W. Soller and L. Totman of the CHPA, regarding the status of the Case Control Study of PPA and Hemorrhagic Stroke, that has been conducted by investigators at Yale University with CHPA sponsorship.

We noted that we were aware that the study investigators were analyzing the study results, and that Dr. Kernan had previously noted some concern to us, based on preliminary analyses of the data, about the possibility of safety issues in some study subgroups. We noted our need to see the results very soon. Dr. Soller indicated that CHPA had seen the results only very recently, and had been given a period of only several days to comment on the Yale group's draft study report (their comments had just gone back to the Yale group, evidently in the last few days). We reminded Drs. Soller and Totman of CHPA's responsibility to promptly report to FDA any information from this study that might indicate significant safety concerns.

81N-0022

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On October 19, 1999 at 12:00, Drs. DeLap and Katz and Ms. Walling returned Dr. Walter Kernan's call (203-397-9481 h).

He had called to report that the Scientific Advisory Group recommend that additional analyses be done prior to sending the report of the findings of the study of PPA and the risk of hemorrhagic stroke.

He indicated that a letter was prepared with the findings but that there would be a delay of perhaps 2-3 days (Thursday of this week) in sending it. On the advice of their advisory group, one additional analysis would be done.

The sponsor (CHPA) had been notified. The Yale group would meet with the sponsor to discuss the results of the study as soon as was convenient.

A summary of the results thus far is as follows:

For the three coprimary endpoints-

1- any use 3 days prior to stroke (males and females)- the adjusted odds ratio (1.52) was not significant- 95% CI lower bound=0.94 and the p value= 0.078

2- use for cough/cold or appetite suppressant 3 days prior to stroke- male and female cough/cold adj. odds ratio= 1.23, CI lower bound = 0.75, and p= 0.246 AND for females as an appetite suppressant, the adj. odds ratio= 14.17, CI lower bound = 2.13 and the p= 0.011 (statistically sig)

3- females- first use stroke first day- (first use is defined as no use in prior 2 weeks and first dose is on index date or day before)- the adj. odds ratio= 3.53, CI lower bound = 1.19 and p= 0.028. They looked at males too but there were only 2. (statistically sig.)

The factors for adjustment were race, hypertension, cigarette smoking and cocaine use.

These analyses were drawn from 706 cases (which included 27 individuals exposed to PPA and 1383 matched controls (including 32 exposed to PPA).

The advisory group asked for a reanalysis based on using different definitions (consistent) of control groups (non-exposure was defined slightly differently in the three groups).

Dr. Kernan doesn't expect the results to change but he will send the letter with all of the information summarized when the reanalysis is done.

Dr. DeLap asked that he summarize in the letter who was studied, what were the findings, what was the statistical significance and what was the clinical significance. He also asked how the people that fell between more than 3 days post and less than 2 week exposure would be evaluated in the study, if they were counted neither as "exposed" or "not exposed".

MINUTES OF TELECONFERENCE
April 14, 2000
Corporate Building, Room S-219

Subject: Yale study regarding PPA and hemorrhagic stroke

FDA Participants:

Bob DeLap, M.D., Ph.D., Director, Office of Drug Evaluation V
Charles Ganley, M.D., Director, Division of OTC Drug Products
Linda Katz, M.D., M.P.H., Deputy Director, Division of OTC Drug Products
Mary Jane Walling, Associate Director, Office of Drug Evaluation V
Sandy Titus, Executive Secretary, Non-Prescription Drugs Advisory Committee
Tom Parmelee, Pharm.D., Regulatory Project Manager

External Participants:

Walter Kernan, M.D., Associate Professor of Medicine, Yale University School of Medicine

Objective:

To discuss the submission of a study report and data from a case-control study concerning the use of phenylpropanolamine (PPA) and the incidence of hemorrhagic stroke.

Discussion:

Dr. Kernan had questions for the Division of OTC Drug Products regarding the structure of the Yale study report to be submitted to the Agency. Dr. Kernan inquired about how detailed the methods and results sections should be, and how much interpretation regarding results is generally recommended. The Agency representatives responded that typical reports from sponsors of clinical studies generally provide significant interpretation. However, it is usually the decision of the sponsor or individual investigator as to the level of interpretation of the results of a study. The Agency will analyze the data internally and come to an independent conclusion. The sponsor or investigator should be comfortable with the content of the final study report. Certainly others may come to a different conclusion or interpretation of the study results and data compared to the sponsor or investigator. The study report should generally resemble a manuscript for publication in a medical or scientific journal.

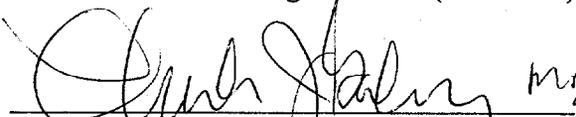
Dr. Kernan conveyed that CHPA had the opportunity to comment on the study report, but did not have any veto power. Dr. Kernan can inform CHPA regarding what he is planning to submit to the Agency for review. Dr. Kernan stated that the study and results had been presented to CHPA and to pharmaceutical sponsors.

The Agency representatives briefly explained some of the differences between the OTC monograph process and the New Drug Application review process. The Agency representatives agreed to fax some background information to Dr. Kernan including 21 CFR Part 330 for OTC drug products, and the Federal Register notice published February 14, 1996 discussing OTC Drug Products Containing Phenylpropanolamine; Labeling Requirements.

Action Items:

- 1) The Agency will fax a copy of 21 CFR Part 330 and the FR notice for OTC Drug Products Containing Phenylpropanolamine to Dr. Walter Kernan.
- 2) Dr. Walter Kernan will send a copy of the PPA study report directly to the Division of OTC Drug Products and to the appropriate dockets (#81N-0022 and #76N-052N).
- 3) Dr. Kernan will also provide the Agency with information needed for incorporation and analysis in the Agency's independent evaluation of the study results.


Tom Parmelee, Pharm.D., Project Manager
Minutes Preparer
Division of OTC Drug Products (HFD-560)


Charles Ganley, M.D., Chair Concurrence
Division of OTC Drug Products (HFD-560)

Electronic Mail Message

Date: 4/18/00 10:57:02 AM
From: Linda Katz (KATZL)
To: See Below
Subject: PPA

Dr. Kieman called this AM to say that he should be sending in the data by the end of the week. He will send a desk copy to the division and the original to dockets management as outlined in the letter signed by Charley.

Linda

To: Robert DeLap (DELAPR)
To: Charles Ganley (GANLEY)
To: Sandra Titus (TITUSS)
To: Thomas Parmelee (PARMELEET)
To: Mary Jane Walling (WALLINGMA)
To: Elizabeth Ryland (RYLAND)
To: Robert Sherman (SHERMANR)
Cc: Linda Katz (KATZL)
Cc: Rosemary Cook (COGKR)