TAB 7

MEMORANDUM OF MEETING
Monday, November 9, 1992
2:30 PM-4:00 PM
Maryland Conference Room

Between: Nonprescription Drug Manufacturers Association Members and Guests:

Daniel Abraham, Thompson Medical Company, Inc.
George L. Blackburn, M.D., Ph.D., Chief, Nutrition/ Metabolism Laboratory, New England Deaconess Hospital
Lawrence M. Brass, M.D., Associate Professor of Neurobiology, Director, Yale Stroke Program, Yale University School of Medicine
Timothy R. Dring, Assistant Director of Drug Regulatory Affairs, CIBA-GEIGY Corporation
Linda Ballai Fischer, Director, Regulatory Affairs, CIBA Consumer Pharmaceuticals
Ralph I. Horwitz, M.D., Harold H. Hines Professor of Medicine and Epidemiology, Yale University School of Medicine
Andrew Krulwich, Esq., Wiley, Rein and Fielding
Dan Rodgers, President, Thompson Medical Company, Inc.
Dana Rothacker, Ph.D., Clinical Research Director, Thompson Medical Company, Inc.
Harold I. Silverman, D.Sc., Senior Vice President, Scientific Director, The Bascomb Foundation
R. William Soller, Ph.D., Senior Vice President and Director of Science and Technology, Nonprescription Drug Manufacturers Association
Edward L. Steinberg, M.Sc., O.D., Thompson Medical Company, Inc.
Lorna C. Totman, Ph.D., Director, Pharmacology and Toxicology, Nonprescription Drug Manufacturers Association
Barbara Waitman, Esq., General Counsel, Thompson Medical Company, Inc.
Patrice B. Wright, Ph.D., Nonprescription Drug Manufacturers Association

and FDA Representatives:

Robert Temple, M.D., Director, Office of Drug Evaluation I (HFD-100)
Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products (HFD-110)
Philip Dern, M.D., Division of Cardio-Renal Drug Products (HFD-110)
Gary Buehler, Division of Cardio-Renal Drug Products (HFD-110)
Charles Anello, Sc.D., Acting Director, Office of Epidemiology and Biostatistics (HFD-700)

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Joel Freiman, M.D., Acting Chief, Epidemiology Branch (HFD-733)
William Gilbertson, Pharm. D., Director, Monograph Review Staff, Office of OTC Drug Evaluation (HFD-810)
Helen Cothran, Chief, Gastrointestinal and Contraceptive Drug Monographs Section (HFD-814)
Robert Sherman, Gastrointestinal and Contraceptive Drug Monographs Section (HFD-814)

Also Present:

Bruce DeMark, The Procter & Gamble Company
Mary Skelly, The Procter & Gamble Company
Emily Morley, A.H. Robins Company
Bonnie Lee, (HF-43)
Eli Embley, F-D-C Reports
Dianne Bach, NDMA

Subject: Proposal For an Epidemiologic Study of the Relationship Between Phenylpropanolamine (PPA) and Stroke and Interim Labeling

The meeting was held at the request of the Nonprescription Drug Manufacturers Association (NDMA) to present their proposal for a large-scale epidemiologic study of the relationship between the ingestion of PPA-containing weight control drug products and the incidence of cerebrovascular accidents, especially stroke and intracranial hemorrhage, and to discuss changes in package labeling, advertising, and promotion designed to insure the use of PPA at recommended doses. NDMA presented these proposals in response to safety concerns regarding PPA's association with increases in blood pressure and cerebrovascular accidents which have arisen during FDA's review of PPA as an over-the-counter (OTC) weight control drug product.

Dr. Gilbertson opened the meeting with a reminder that the meeting was a public feedback meeting and that minutes of the meeting would be available upon request.

Dr. Soller presented an overview of NDMA's two-part proposal which consists of post-marketing epidemiologic research and voluntary changes by the industry in the labeling, advertising, and promotion of PPA-containing weight control products to insure safe and responsible use at the recommended dose. Dr. Soller stated that the changes include stronger warning statements that would convey to the consumer that exceeding the recommended dose of one capsule per day has not been shown to result in any additional weight loss and may cause serious health problems. In addition, new language will be included to stress that PPA is intended for use only by adults as an adjunct to diet and

exercise for modest weight loss in motivated consumers (see attachment).

Dr. Soller stated that these concepts would also be incorporated on a rotational basis in print and video advertisements by including such statements as "Do not exceed the recommended dose", "For adult use only", and "For best results, do not take more than one capsule each day". Dr. Soller also stated that advertising and promotion of PPA products would be directed to nonteen adults. Dan Rodgers of Thompson Medical Company stated that labeling and package insert changes in his company's products would be in effect in approximately six weeks and that new print and video advertisements would be in effect in approximately three months. Dr. Temple expressed concern that statements such as "For best results, do not take more than one capsule each day" do not convey to the consumer that exceeding the recommended dose is dangerous, and suggested that stronger warning statements be used.

Dr. Soller reviewed NDMA's contention that at recommended doses, PPA does not cause clinically meaningful changes in blood pressure, and that available data do not demonstrate that the incidence of cerebrovascular accidents allegedly associated with the ingestion of PPA weight control products is greater than the spontaneous rate of those events. Dr. Blackburn presented some of the data from his study on PPA's effect on blood pressure. Dr. Horwitz cautioned that the agency should not necessarily associate blood pressure effects with stroke because such an association has not been demonstrated. Dr. Brass agreed that there is no evidence that elevation in blood pressure is associated with stroke.

Dr. Soller reported that the background rate of stroke in women 15-44 years of age is approximately 8/100,000 and that there has been no incidence of PPA-associated stroke at recommended doses in the last four years. Dr. Horwitz said that the agency should not place too much emphasis on the existing stroke data because the incidence of these adverse events is very small and the data unreliable.

Dr. Soller reviewed NDMA's proposed research program which includes an updated estimate of the background rate of stroke compared to the current reporting rate of these events, a case-assessment study in Connecticut, and a patient interview study.

Timothy Dring reviewed the current data on the background rate of stroke in women 15-44 years of age which consists of hospital discharge data and is estimated at 8.2/100,000. Mr. Dring stated that newer technologies such as the CAT scan can now detect hemorrhagic strokes which may have gone undetected several years ago, and that such advances may change the estimated background

rate. Mr. Dring also pointed out that the estimated background rate in Canada, where PPA is not available as an OTC drug product, is 8.8/100,000.

Dr. Brass reviewed the proposed population-based study in Connecticut which has a population of 2 million in the 15-44 age range. Dr. Brass stated that a reporting network of 36 general, acute care hospitals and 3 Veterans Administration hospitals would be employed to rapidly identify strokes as they occurred. He stated that the 20 largest hospitals in the state care for 80 percent of the stroke patients. He stated that there are 8,000 to 10,000 strokes per year in Connecticut with 20 to 25 percent being hemorrhagic and that the study duration would be from 6 to 12 months.

Dr. Horwitz stated that there is not enough information concerning the background rate of stroke and that such a study would improve the knowledge base regarding the occurrence rate of stroke for all individuals as well as providing information on patients separated by age and gender. He said that the study would also collect information on clinical characteristics, risk factors, and exposure to other medications.

Dr. Brass stated that, in addition to the Connecticut study, a New England Stroke Consortium would be formed to collect additional data if it was determined that the Connecticut database was not large enough.

There was a general discussion regarding the proposed methods of data collection and the estimated time required to collect a sufficient database. Dr. Horwitz stated that based on the relatively rare occurrence of stroke, the study could take as long as two years to gather enough data on an adequate number of subjects. Dr. Temple stated that the agency would need to have an accurate estimate of the exposure rate in order to interpret the data and expressed doubts about the presumed 10 to 15 percent exposure rate in 15 to 44 year olds. Mr. Abraham stated that approximately 200,000 packages of PPA-containing weight control drug products were sold per year. Dr. Freiman cited data from the Case-Control Surveillance Study of the Sloane Epidemiology Unit which suggested that the exposure rate was far less than 10 percent. Dr. Horwitz suggested that community based exposure data would be better than hospital based exposure rates to answer this question.

Dr. Soller reminded the group that the ability to carry out this study would depend on the continued availability of PPA as an OTC weight control product. Dr. Temple stated that he could not reveal FDA's decision regarding PPA's OTC status but noted that it would be difficult for the agency to make a determination within the next six months. Dr. Gilbertson stated that the

agency's decision would be based on the data and information currently in the administrative record and would not depend on the outcome of the proposed study. He noted, however, that it would be highly unlikely that PPA products would be removed from the OTC market within six months.

Dr. Blackburn stated that even the modest weight loss associated with PPA weight control products produces beneficial health effects without any health risk and urged the agency to allow the continued marketing of PPA as an OTC weight control drug product. Dr. Soller reiterated the need for the continued OTC availability of PPA weight control products so that the Connecticut case-control study could be conducted and asked for continued feedback from the agency regarding the study and the proposed labeling, advertising and promotional changes.

Robert Sherman

Robert Sherman

Attachment

Nonprescription Drug Manufacturers Association

PPA Working Party

Labeling Program for OTC Diet Aids Containing Sustained Release PPA
November 8, 1992

Issues:

1. The available data support the safety of PPA use as an OTC appetite suppressant at recommended doses. A point of discussion focuses on the data on PPA's safety at greater than OTC recommended doses.

2. The available data support the effectiveness of PPA at recommended OTC doses in terms of a modest weight loss over a 12 week period, which is the type of weight loss endorsed by the American Dietetic Association and the American Medical Association. A point of discussion focuses here on the effectiveness of PPA in the consumer setting, the need to recognize the fact that --like other OTCs (e.g., anticaries products, contraceptives, sunscreens, antifungals for prevention of athlete's foot, antidandruff products and contact lens products) -- it is the motivated consumer who will achieve the best anticipated results.

Strategy for Labeling Initiative:

The strategy to address the above mentioned issues is comprised of a multi-tiered approach to augment the labeling of PPA-containing OTC appetite suppressants in terms of additional new warnings and directions of use statements, all of which are not currently a part of the Proposed Monograph for these products. Here, labeling is construed in a broad context to include package labeling, advertising and promotion. Specifically with respect to helping to ensure use at recommended doses, the PPA Working Party is undertaking the following changes in labeling:

1. Addition to Blister Cards:

   "Do not take more than one tablet [or capsule] daily." or

   "Read label before using this product."

2. Additions to Front Label:

   a. Indication: "An aid to appetite control in conjunction with a sensible weight loss program."

. . . continued

b. Statement referring to warnings: E.g., "See Warnings and Tamper Resistant Features on back panel."

3. Additions to Back Panel:

a. Directions: "Adult oral dosage is one tablet [capsule] at mid-morning with a full glass of water. Exceeding the recommended dose has not been shown to result in any additional weight loss . . . . Read and follow important Diet Plan enclosed."(new language underlined)

b. Warnings: "FOR ADULT USE ONLY. Do not take more than one tablet [capsule] per day (24 hours). Exceeding the recommended dose may cause serious health problems. Do not give this product to children under 12 years of age. Persons between 12 and 18 are advised to consult their physician before using this product. If nervousness, dizziness, sleeplessness, palpitations, or headache occurs, stop using this medication and consult your physician. If you are being treated for high blood pressure, depression, or an eating disorder or have heart disease, diabetes, or thyroid disease, do not take this product except under the supervision of a physician. . . .As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product." (new language underlined)

[Note, as shown above: The ANPR sentence -- "Do not exceed recommended dose" -- is proposed to be strengthened to: "Exceeding the recommended dose may cause serious health problems."]

[Note: The ANPR sentence -- "If you are taking a cough/cold or allergy medication containing any form of phenylpropanolamine, do not take this product" -- is proposed to be placed under a new separate heading entitle "DRUG INTERACTION PRECAUTION." (See also below.)]

c. Addition of a separate "Drug Interaction Precaution Section", as follows:

"DRUG INTERACTION PRECAUTION: If you are taking a cough/cold or allergy medication containing any form of phenylpropanolamine, or any type of nasal decongestant, do not take this product. Do not take this product if you are taking any

. . . continued

prescription drug, except under the advice and supervision of a physician. Do not use this product if you are presently taking a prescription monoamine oxidase inhibitor (MAOI) for depression or for two weeks after stopping use of a MAOI without first consulting a physician. [New language for this new section is underlined.]

4. Addition of a Consumer Labeling Leaflet:

PPA Working Party recommends that FDA should require a package insert in all PPA-containing OTC appetite suppressant products in order to more fully elaborate the additional components of a sensible weight control plan that includes PPA as an adjunct.

Reference to this package insert is made in the "Directions" section of the label, as follows: Read and follow important Diet Plan enclosed."

The components of such a package insert should include:

a. Statement of Identity;
b. Directions of use;
c. Warnings;
d. Additional new consumer information, including the following:

> "This product is intended for use by a motivated consumer as part of a program of sensible, reduced caloric intake and physical exercise to help control your appetite and lose weight. It is important to follow carefully the directions of use and to not exceed the recommended daily dose. If you have difficulty losing or controlling weight, experience undesirable side effects while using ~~this product, or are excessively overweight~~ (more than 45% over your ideal weight), you should seek professional medical advice."

e. Suggested sensible low-calorie diets and exercise program to be undertaken in conjunction with PPA use.

5. Advertising and Promotion:

. . . continued

a. Amplify the current NDMA Code of Advertising Practices (Point 2: "Advertising of a nonprescription medicine should urge the consumer to read and follow label directions."), include on a rotational basis such statements (printed statements for print advertising) as:

- "To achieve safe and effective weight loss while using this product, it is important to read and carefully follow label and package insert directions."

- "For best results, follow carefully the label and package insert directions."

b. Incorporate on a rotational basis the following concepts in print and video advertising:

- "Do not exceed the recommended dose."

- "For adult use only."

- "For best results, do not take more than [one capsule] each day."

c. Advertising and promotion will be directed to nonteen adults.

Reference copies of the proposed monograph label language with the augmented industry label language are appended in the Attachment.

Attachment: Prototype Labeling: OTC Appetite Suppressants Containing Sustained Release PPA, which consolidates ANPR and industry label language.

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PROTOTYPE LABELING: OTC APPETITE SUPPRESSANTS CONTAINING SUSTAINED RELEASE PPA

STATEMENT OF IDENTITY: Appetite Suppressant

PRODUCT DESCRIPTION (FRONT PANEL): AN AID TO APPETITE CONTROL IN CONJUNCTION WITH A SENSIBLE WEIGHT LOSS PROGRAM.

ON FRONT PANEL: Statement referring to warnings on back panel. E.g.: "See Warnings and Tamper Resistant Features on back panel."

DIRECTIONS: Adult oral dosage is one tablet [or capsule] at mid-morning with a full glass of water. Exceeding the recommended dose has not been shown to result in greater weight loss. This product's effectiveness is directly related to the degree to which you reduce your usual daily food intake. Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding 3 months, because this should be enough time to establish new eating habits. Read and follow important Diet Plan enclosed.

WARNINGS: FOR ADULT USE ONLY. Do not take more than one tablet [or capsule] per day (24 hours). {DELETE: Do not exceed recommended dose.} Exceeding the recommended dose may cause serious health problems. Do not give this product to children under 12 years of age. Persons between 12 and 18 are advised to consult their physician before using this product. If nervousness, dizziness, sleeplessness, palpitations or headache occurs, stop taking this medication and consult your physician. If you are being treated for high blood pressure, depression, or an eating disorder or have heart disease, diabetes, or thyroid disease, do not take this product except under the supervision of a physician. {MOVED BELOW: If you are taking a cough/cold or allergy medication containing any form of phenylpropanolamine, do not take this product.} As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

DRUG INTERACTION PRECAUTION: If you are taking a cough/cold or allergy medication containing any form of phenylpropanolamine, or any type of nasal decongestant, do not take this product. Do not take this product if you are taking any prescription drug, except under the advice and supervision of a physician. Do not use this product if you are presently taking a prescription monoamine oxidase inhibitor (MAOI) for depression or for two weeks after stopping use of a MAOI without first consulting a physician.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

EACH MAXIMUM STRENGTH TABLET CONTAINS: Active Ingredient: Phenylpropanolamine HCl 75 mg. (appetite suppressant time release). Inactive Ingredients: Cellulose Acetate, FD&C Yellow #10, FD&C Blue #1, FD&C Yellow #6, Hydroxypropyl Methylcellulose, Povidone, Propylene Glycol, Stearic Acid, Titanium Dioxide.

Manufacturer's Name and Address; Trademark Assignee; UPC Code; Lot Number; Expiration Date.

TRP STATEMENT: Blister Packaged For Your Protection. Do not use if individual seals are broken.

FOR TABLETS IN BLISTERS, PRINTED ON THE BLISTER: "Do not take more than one tablet (capsule) daily. Read label before using this product."