

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01N-0196]

DMB

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Phenylpropanolamine; Proposal to Withdraw Approval of New Drug Applications and Abbreviated New Drug Applications; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is proposing to withdraw approval of 16 new drug applications (NDAs) and 8 abbreviated new drug applications (ANDAs). These are the approved applications for prescription and over-the-counter (OTC) drug products containing phenylpropanolamine. FDA is offering the holders of the applications an opportunity for a hearing on the proposal. All other drug products containing phenylpropanolamine that are considered new drugs (e.g., extended-release products and any prescription product) are also subject to this notice. FDA is taking this action because of the association of phenylpropanolamine with increased risk of hemorrhagic stroke.

DATES: Submit written requests for a hearing by [*insert date 30 days after date of publication in the Federal Register*]. Submit data and information in support of the hearing request by [*insert date 60 days after date of publication in the Federal Register*]. An applicant planning to withdraw or reformulate a product covered by the applications listed in this notice should inform the agency as early as possible, preferably on or before [*insert date 60 days after date of publication in the Federal Register*].

ADDRESSES: A request for a hearing, supporting data, and other comments are to be identified with Docket No. 01N-0196 and submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Communications pertaining to withdrawal or reformulation of products covered by applications listed in this notice should be directed to the Division of Pulmonary and Allergy Drug Products (HFD-570), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, rm. 10B-45, Rockville, MD 20857, or the Office of Generic Drugs (HFD-600), 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

For information on medical/scientific issues: Gerald M. Rachanow or Robert L. Sherman, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

For general information concerning this notice: Mitchell Weitzman, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

Phenylpropanolamine is an ingredient used in prescription and OTC drug products as a nasal decongestant to relieve stuffy nose or nasal congestion and in OTC weight control drug products to control appetite. Phenylpropanolamine was included in the agency's OTC drug review. Although phenylpropanolamine was regarded as effective for weight control and as a nasal decongestant, final classification of the ingredient was deferred pending the resolution of issues pertaining to its safety.

II. Products Subject to This Notice

This notice applies to all OTC and prescription immediate-release and extended-release drug products containing phenylpropanolamine that are marketed under approved applications. The agency is aware that a number of prescription products and some OTC extended-release products containing phenylpropanolamine, all of which are considered new drugs, have been marketed

without an approved application. This notice also applies to all of these products. This notice does not apply to immediate-release OTC drug products marketed under the OTC drug monograph system; FDA intends to address these products in a separate document to be published in a future issue of the **Federal Register**.

The following applications are affected by this notice:

Application Number	Drug	Applicant
NDA 11-694	Dimetane-DC Syrup.	A. H. Robins Co., P.O. Box 8299, Philadelphia, PA 19101.
NDA 12-152	Ornade Extended-Release Capsule. ..	SmithKline-Beecham, 1250 South Collegeville Rd., P.O. Box 5089, Collegeville, PA 19426.
NDA 12-436	Dimetapp Extended-Release Tablet. ...	Whitehall-Robins, 5 Giralda Farms, Madison, NJ 07940.
NDA 13-087	Dimetapp Elixir.	Do.
NDA 18-050	Corsym Extended-Release Suspension..	Medeva Americas, Inc., 755 Jefferson Rd., P.O. Box 1710, Rochester, NY 14603.
NDA 18-099	Contact Extended-Release Capsule. ...	SmithKline Beecham Consumer Health, L. P., 1500 Littleton Rd., Parsippany, NJ 07054.
NDA 18-298	Tavist-D Extended-Release Tablet.	Novartis Consumer Health, Inc., 560 Morris Ave., Summit, NJ 07901.
NDA 18-556	Demazin Extended-Release Tablet. ...	Schering-Plough HealthCare Products, Three Oak Way, P.O. Box 603, Berkeley Heights, NJ 07922.
NDA 18-809	Phenylpropranolamine Hydrochloride (HCL) Chlorpheniramine Maleate Extended-Release Capsule..	Schwarz Pharma, 6140 West Executive Dr., Mequon, WI 53092.
NDA 19-410	Hycomine Syrup.	Endo Pharmaceuticals, Inc., 500 Endo Blvd., Garden City, NY 11530.
NDA 19-411	Hycomine Pediatric Syrup.	Do.
NDA 19-613	Contact Extended-Release Tablet.	Novartis Consumer Health, Inc.
NDA 20-640	Tavist-D Extended-Release Tablet.	Do.
ANDA 71-099	Bromatapp Extended-Release Tablet.	Teva Pharmaceuticals, USA, 1090 Horsham Rd., P.O. Box 1090, North Wales, PA 19454.
ANDA 88-359	Drize Extended-Release Capsule.	B. F. Ascher & Co., Inc., 15501 West 109th St., Lenexa, KS 66219.
ANDA 88-681	Chlorpheniramine Maleate and Phenylpropranolamine HCL Extended-Release Capsule..	Chelsea Laboratories, 896 Orlando Ave., West Hempstead, NY 11552.
ANDA 88-687	Biphetap Elixir.	Morton Grove Pharmaceuticals, Inc., 6451 Main St., Morton Grove, IL 60053.
ANDA 88-688	Bromanate Elixir.	Alpharma, U.S. Pharmaceuticals Division, 333 Cassell Dr., suite 3500, Baltimore, MD 21224.
ANDA 88-723	Bromanate DC Syrup.	Do.
ANDA 88-904	Myphetane DC Syrup.	Morton Grove Pharmaceuticals, Inc.
ANDA 88-940	Chlorpheniramine Maleate and Phenylpropranolamine HCL Extended-Release Capsule..	Geneva Pharmaceuticals, Inc., 2555 West Midway Blvd., P.O. Box 446, Broomfield, CO 80038.

III. Recent Data on the Safety of Phenylpropranolamine

A. Introduction and Rationale for Developing a Study

Spontaneous case reports and published case series, accumulated from 1969 to 1991, suggested a possible association between phenylpropranolamine use and an increased risk of hemorrhagic stroke. At that time, however, it was not possible to prove or disprove an association. In an effort to resolve this issue, representatives of the manufacturers of products containing phenylpropranolamine and agency staff met in 1991 to plan a study that could further examine

whether there was an association between phenylpropanolamine use and the risk of hemorrhagic stroke. An epidemiologic case-control study was determined to be the most feasible study design to evaluate the possible association between exposure to phenylpropanolamine and a rare outcome such as hemorrhagic stroke. The industry sponsors of the study selected investigators at Yale University School of Medicine to conduct the study. The following discussion is based on the study report (Ref. 1) submitted to FDA.

B. The Yale Hemorrhagic Stroke Project

1. Study Design

The Yale Hemorrhagic Stroke Project (Ref. 1) was designed as a case-control study. Because several case reports had described strokes in young women who took phenylpropanolamine as an appetite suppressant, often after the first dose, the study examined three questions: (1) Whether all users of phenylpropanolamine (the study cohort included men and women aged 18 to 49 years), compared with nonusers, had an increased risk of hemorrhagic stroke; (2) the possible association between phenylpropanolamine use and hemorrhagic stroke by type of exposure (appetite suppressant or cough-cold product); and (3) among women age 18 to 49 years, the possible association between first use of phenylpropanolamine and hemorrhagic stroke and the possible association between use of phenylpropanolamine-containing appetite suppressants and hemorrhagic stroke.

The study was performed between December 1994 and July 1999 and involved men and women 18 to 49 years old who were hospitalized with a primary subarachnoid hemorrhage (SAH) or a primary intracerebral hemorrhage (ICH). Eligible case subjects had no prior history of stroke and were able to be interviewed within 30 days of their event. The subjects were recruited from hospitals in four geographic regions of the United States.

Both SAH and ICH were determined by clinical symptoms and specific diagnostic information from computed tomography (CT). Magnetic resonance imaging was accepted for the diagnosis of

SAH or ICH only if other studies were not diagnostic. Subjects were ineligible for enrollment if they died within 30 days, were not able to communicate within 30 days of their stroke, had a previously diagnosed brain lesion predisposing to hemorrhage risk (e.g., arteriovenous malformation, vascular aneurysm, or tumor), or had a prior history of stroke. Subjects who first experienced stroke symptoms after being in the hospital for 72 hours (e.g., for an unrelated matter) were also excluded.

For each case subject, random digit dialing (matched to the first three digits of the case subject) was used to identify two control subjects who were matched on: (1) Gender, (2) race (African-American versus non-African-American), (3) age (within 3 years for case subjects less than 30 years old and within 5 years for subjects 30 years or over), and (4) telephone exchange. Cases and control subjects were interviewed to ascertain medical history, medication use, and habits affecting health, such as use of tobacco and alcohol. Interviews of control subjects were completed within 30 days of the subject's stroke event to minimize seasonal differences in the likelihood of exposure to cough-cold drug products. Eligibility criteria for control subjects were the same as for case subjects except for the stroke event. During the consent procedure, all subjects (cases and controls) were told that the study was designed to examine causes of hemorrhagic stroke in young persons without specific mention of phenylpropanolamine or other potential risk factors. Case and control subjects were interviewed by a trained interviewer using a structured questionnaire developed for this study. Subjects were classified as exposed to phenylpropanolamine if they reported use within 3 days of the stroke event for case subjects or a corresponding date for control subjects. Reported exposures were verified by the study investigators, who documented the actual product(s) used and their ingredients.

The exposure window refers to the interval before the focal time when the subject's exposure to phenylpropanolamine was assessed. For all analyses except first-dose use, the exposure window was defined as the index day before focal time and the preceding 3 calendar days. For first-dose use, a subject was considered exposed if phenylpropanolamine use occurred on the index day before

the focal time or on the preceding calendar day, with no other phenylpropanolamine use during the preceding 2 weeks. To maintain a consistent reference group for all analyses, nonexposure was defined as no use of phenylpropanolamine within the 2 weeks preceding the focal time. Exposure windows were defined similarly in the matched case controls, based on the focal time for the corresponding case.

2. Statistical Analysis

Case and control subjects were compared on a variety of clinical and demographic features, including those used in matching. Statistical comparisons were made using chi-square tests and the Fisher's exact test (where appropriate) for categorical variables, and the Student *t*-test for continuous variables. For the analyses of the primary endpoints, conditional logistic models for matched sets (with a variable number of controls per case) were used to estimate odds ratios, lower limits of the one-sided 95 percent confidence intervals, and p-values for the risk factors under investigation. One-tailed statistical results were reported because the focus of the study was whether phenylpropanolamine use increases the risk of stroke. Each logistic model was estimated with two mutually exclusive binary exposure terms: (1) The subject's primary exposure status as defined by the specific aim (e.g., phenylpropanolamine use in the 3-day window; yes/no), and (2) phenylpropanolamine users who were not exposed within the 3-day window (but with some exposure within 2 weeks of the focal time).

In multivariate conditional logistic models (using asymptotic methods), adjustments were made for race (African-American compared with non-African-American), history of hypertension (yes/no), and current cigarette smoking (current compared with never or ex-smoker) as these are major risk factors for stroke. Other underlying diseases and/or conditions were also examined to determine if any of these, when added to this basic adjusted model, altered the matched odds ratio by at least 10 percent.

3. Study Results

There were 702 case subjects, including 425 subjects (60 percent) with an SAH and 277 (40 percent) with an ICH, and 1,376 control subjects. Hemorrhage was associated with an aneurysm in 307 subjects (44 percent), an arteriovenous malformation in 50 subjects (7 percent), and a tumor in one subject (0.1 percent). Two control subjects were located for each of 674 case subjects (96 percent) and one control subject for each of 28 case subjects (4 percent). All control subjects were matched to their case subjects on gender and telephone exchange. Age matching was successful for 1,367 controls (99 percent) and race matching was achieved for 1,321 controls (96 percent). Twenty-seven case subjects and 33 control subjects reported phenylpropanolamine use within the 3-day exposure window.

Compared with control subjects, case subjects were significantly more likely to be African-American (21 percent compared with 17 percent). Case subjects were also more likely to report lower educational achievement (20 percent did not graduate from high school compared with 9 percent of control subjects), current cigarette smoking (51 percent compared with 30 percent), a history of hypertension (39 percent compared with 20 percent), family history of hemorrhagic stroke (9 percent compared with 5 percent), heavy alcohol use (14 percent compared with 7 percent), and recent cocaine use (2 percent compared with less than 1 percent). For all other clinical variables examined, case and control subjects were not dissimilar. Case subjects were significantly ($p < 0.05$) less likely to report use of nonsteroidal anti-inflammatory drugs and significantly more likely to report use of caffeine and nicotine in the 3 days before their event. Of the factors examined, only education was found to change the adjusted odds ratio for the association between phenylpropanolamine and hemorrhagic stroke by more than 10 percent, and this demographic factor was included in all subsequent models.

Analyses of the study results were consistent with an association between hemorrhagic stroke and use of phenylpropanolamine (in a nasal decongestant or weight control drug product) in the 3 days prior to the event. Such use of phenylpropanolamine, compared with no use in the prior

2 weeks, was associated with a relative risk for hemorrhagic stroke of 1.67 (unadjusted odds ratio) ($p=0.040$). The corresponding adjusted odds ratio was 1.49 (lower limit of the one-sided 95 percent confidence interval (LCL)=0.93, $p=0.084$).

The relative risks of hemorrhagic stroke observed with use of the two types of phenylpropanolamine-containing products (in the 3-day exposure window, compared with no use in the prior 2 weeks) were as follows. For cough-cold products, the unadjusted odds ratio was 1.38 ($p=0.163$) and the adjusted odds ratio was 1.23 (LCL=0.75, $p=0.245$). For weight control products, the unadjusted odds ratio was 11.98 ($p=0.007$) and the adjusted odds ratio was 15.92 (LCL=2.04, $p=0.013$).

To analyze the relation between recency of phenylpropanolamine exposure and risk for hemorrhagic stroke, odds ratios were also calculated according to the timing of the most recent phenylpropanolamine use. The prespecified definition for current use was use of any phenylpropanolamine-containing product on the day of the event (before focal time) or the preceding calendar day. Prior use was defined as use 2 or 3 calendar days before the focal time. The odds ratio was slightly higher for current use (adjusted odds ratio (AOR)=1.61, LCL=0.93, $p=0.078$) than for prior use (AOR=1.16, LCL=0.47, $p=0.393$). Within current use, odds ratios were then calculated according to first use or nonfirst use. First use was defined as current use with no other use within the prior 2 weeks. Nonfirst use included other uses within the 2-week interval. The odds ratio was higher for first use (AOR=3.14, LCL=1.16, $p=0.029$) than for nonfirst use (AOR=1.20, LCL=0.61, $p=0.329$). All first uses of phenylpropanolamine ($n=13$) reported in these data were in cough-cold drug products.

In women using phenylpropanolamine in weight control drug products (3-day exposure window, versus no use in the prior 2 weeks), the unadjusted odds ratio for hemorrhagic stroke was 12.19 ($p=0.006$) and the adjusted odds ratio was 16.58 (LCL=2.22, $p=0.011$). Among the Hemorrhagic Stroke Project subjects, all hemorrhagic stroke events that occurred within the 3-day exposure window were in women. In the analyses of the possible association between

hemorrhagic stroke and first day use of phenylpropanolamine, 11 of the 13 first day use events were in women (7 cases compared with 4 controls). The unadjusted odds ratio was 3.50 ($p=0.039$) and the adjusted odds ratio was 3.13 (LCL=1.05, $p=0.042$).

Based on the findings that risk for hemorrhagic stroke seemed to be concentrated among current users, the association between current phenylpropanolamine dose and risk for hemorrhagic stroke was examined. Among 21 exposed control subjects, the median current dose of phenylpropanolamine (i.e., total amount taken on the index day or preceding day) was 75 milligrams (mg). Analysis according to dose shows that the odds ratio was higher for current doses above the median (greater than 75 mg) (AOR=2.31, LCL=1.10, $p=0.031$) than for lower doses (AOR=1.01, LCL=0.43, $p=0.490$). Among first-dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropanolamine. To examine the potential effect of ambiguity in the correct focal time, the odds ratios were recalculated after excluding all 154 case subjects who were classified as having a definite ($n=76$) or uncertain ($n=78$) sentinel symptom preceding the stroke event. The magnitude of the adjusted odds ratios did not change substantially.

4. Study Conclusions

According to the investigators, several features of the study supported the validity of the study findings regarding an association between phenylpropanolamine use and risk for hemorrhagic stroke in subjects between 18 and 49 years of age. First, in addition to the finding of elevated odds ratios that reached statistical significance, the magnitude of the odds ratios for phenylpropanolamine use as an appetite suppressant (15.92) and as a first-dose use (3.14) remained large even after adjustment for important clinical features. Second, the data showed an association between both types of phenylpropanolamine drug products (nasal decongestants and weight control products) and hemorrhagic stroke. Because so few men were exposed to phenylpropanolamine in this study ($n=19$), it was not possible to determine whether their risk for hemorrhagic stroke (in association with use of phenylpropanolamine) is different from that of women.

5. FDA's Evaluation of the Study

Observational studies, particularly case-control studies, are potentially subject to a number of biases, and this case-control study is no exception. The hallmark of a good case-control study is that biases are anticipated and measures are instituted in the design and analysis stages to minimize biases to the greatest extent possible.

Strict diagnostic criteria, as described in section III.B.1 of this document, were developed to ensure accurate identification of hemorrhagic stroke cases in the target population. A number of steps were taken to minimize misclassification bias. One of the investigators confirmed the stroke by reviewing the medical records of suspected cases, without knowledge of the exposure status. Inclusion and exclusion criteria were clearly defined for both cases and controls. Exposure was clearly defined, an exposure window was identified, and exposure was ascertained by trained interviewers. Interviewers were randomly assigned to cases or controls, and questions were asked about multiple medications, thus blinding subjects to the exact exposure under study. Because phenylpropanolamine use might be seasonal, controls were identified and interviewed within 30 days of the date of their matched case subject's stroke, to ensure that cases and controls had an equal opportunity of exposure. Controls were also matched to cases for day of the week and time of day of the stroke. This matching strategy ensured the probability that exposure to any medication or other covariates (e.g., alcohol drinking or cigarette smoking) was similar between cases and controls.

The investigators attempted to identify two controls per case by using random digit dialing (with a match for the first three digits of the telephone number). This was considered a good strategy for two reasons. First, controls were chosen completely at random. Second, controls were population-based, so that the results are generalizable to the source population from which the cases and controls were drawn. Matching on race and educational level was slightly unequal between cases and controls. The investigators further controlled for these inequalities by adjustment during analysis. The agency concludes that matching was largely successful.

The investigators reduced the possibility of misclassification of phenylpropanolamine use by using a highly structured questionnaire. Each reported medication was verified by asking subjects to present the actual container or by picking out reported brand-name medications from a book containing photographs. Verification of medication use in the 3-day window prior to the focal time was 96 percent and 94 percent for cases and controls, respectively. The investigators conducted two additional steps to further ensure that the possibility of exposure misclassification error was reduced to an absolute minimum: (1) Only “definite” and “possible” exposure responses were considered in the analyses, and (2) the use of other OTC drugs between cases and controls was compared to ensure that the cases did not have greater recall of the use of any drugs as a reason for their stroke. Based on this analysis, the agency finds no evidence of recall or misclassification bias.

A key element in designing a case-control study of a rare event is calculating the sample size and/or power to ensure the study is large enough to detect a difference if one really exists. FDA had concerns that the study might be underpowered to detect an association because the original sample size calculation was based on an odds ratio of five for an association between hemorrhagic stroke and first-day use of phenylpropanolamine. This ratio was not determined by any public health or clinical considerations, but on considerations related to time and cost constraints. The investigators difficulties in recruiting controls contributed to the study taking longer than expected. Despite these limitations, this was the largest prospective case-control study ever conducted on hemorrhagic stroke. In spite of initial reservations about the adequacy of sample size and power, the agency finds that this study identified an association between phenylpropanolamine use and hemorrhagic stroke, as explained below.

The agency notes that the three most important risk factors (race, history of hypertension, and cigarette smoking) were included in the multivariate analysis (basic adjusted model). The confounding effect of the other covariates was examined if adding any of them to the basic model

altered the odds ratio estimate by 10 percent. High school education was the only covariate determined to change the odds ratio by at least 10 percent.

Because the study had a matched design, the agency considers the conditional logistic regression model appropriate to calculate both unadjusted and adjusted odds ratios. In addition, the number of exposures was small, particularly for analysis of appetite suppressant and first use. Thus, the authors calculated the confidence interval of the unadjusted odds ratio based on an exact method.

Hypertension is the single most important risk factor for a stroke. Misclassification of hypertension status could result in residual confounding. FDA examined the possible effects of this residual confounding on the results of the study. The agency found that the odds ratio for appetite suppressant use was 15.92, a substantial increase in risk. Its very magnitude makes it difficult to explain by confounding alone. Because product labeling advises hypertensive persons to avoid phenylpropanolamine use, the association of phenylpropanolamine use with hypertension should be negative. Such a negative association would result in biasing the result towards no association if the confounding factor is not controlled for. In addition to the steps taken by the investigators, the agency examined this further by additional analyses restricted to subjects without a past history of hypertension, and the results were not significantly different, thereby providing additional evidence that confounding by hypertension was not present in the study.

FDA requested that the Yale investigators explore the possible impact of cigarette smoking and alcohol consumption in more detail. The investigators found that the odds ratios for phenylpropanolamine and stroke were essentially unchanged by inclusion of any quantitative measures of smoking and alcohol consumption.

The investigators examined the association between current phenylpropanolamine dose and risk for hemorrhagic stroke. Among 21 exposed control subjects, the median current dose of phenylpropanolamine (i.e., the total amount taken on the index day or preceding day) was 75 mg. The adjusted odds ratio was higher for current doses above 75 mg than for lower doses. Among

first dose users, four of eight cases and two of five controls were exposed to greater than 75 mg of phenylpropanolamine. As 75 mg is a single dose of many OTC extended-release phenylpropanolamine cough-cold drug products with recommended adult dosing every 12 hours (150 mg a day), the agency further evaluated the association between risk of hemorrhagic stroke and a range of current phenylpropanolamine doses. Exploratory analyses suggest that there may be an increased risk of hemorrhagic stroke with labeled doses at or above 75 mg a day. Although not statistically significant, a trend toward a dose-ordering of odds ratios was seen.

C. Additional Reports

FDA reviewed its adverse events reporting system (AERS) for spontaneous reports of hemorrhagic stroke from 1991 to 2000 and identified 22 cases, 16 in the 18 to 49 age group with 13 cases in women (Ref. 2). In all cases, the suspect drug was an extended-release product containing 75 mg of phenylpropanolamine per unit dose. Of 11 cases for which the indication of use was provided, 10 reported use for respiratory symptoms.

D. Advisory Committee Recommendations

On October 19, 2000, at a public meeting, FDA's Nonprescription Drugs Advisory Committee (NDAC) discussed the Yale Hemorrhagic Stroke Project and additional case reports of hemorrhagic stroke since 1991. The investigators of the Yale study presented the study results and their conclusions. Industry representatives raised concerns about the design of the study that they believed made interpretation of the results difficult (Ref. 3). When NDAC was asked if, taking all currently available information into account, the data support the conclusion that there is an association between phenylpropanolamine and an increased risk of hemorrhagic stroke, 13 of 14 committee members voted (with 1 voting "uncertain") that there is such an association (Ref. 4). When asked whether phenylpropanolamine can be generally recognized as safe for use as a nasal decongestant, 12 of the 14 committee members voted (with 2 abstaining) that phenylpropanolamine could not be considered to be generally recognized as safe for OTC nasal decongestant use. When

asked whether phenylpropanolamine can be generally recognized as safe for use as an appetite suppressant, 13 of the 14 committee members voted (with 1 abstaining) that phenylpropanolamine could not be considered to be generally recognized as safe for OTC weight control use. Minutes of the NDAC meeting are available in the Dockets Management Branch (address above) under the docket number listed in brackets in the heading of this document.

IV. The Agency's Tentative Conclusions on the Safety of Phenylpropanolamine

The agency concludes that the Yale study (Ref. 1) was well designed and demonstrated that the association between phenylpropanolamine use (as an appetite suppressant and first time use as a nasal decongestant) and an increased risk of hemorrhagic stroke was significant and was most striking in women. The case-control design was best suited for this study because the outcome under investigation was rare. All reasonable steps were taken to minimize bias and confounding. Quality control measures were built into the design. Analyses were appropriate for the type of study and were performed according to the protocol. The strengths of the study lie in the clarity of its objectives, the meticulous adherence to sound epidemiology practices in its design and execution, and the consistency of the findings, regardless of the analytic methods. Its only limitation was in the power and sample size, discussed earlier. Despite this limitation, the study was nevertheless able to find a consistent association between phenylpropanolamine use and hemorrhagic stroke, particularly in women.

Although the Yale study focused on men and women 18 to 49 years of age, the agency has no reason to believe that the increased risk of hemorrhagic stroke is limited to this population. While the Yale study was being conducted, FDA continued to receive spontaneous reports of hemorrhagic stroke with cough-cold products that contain high doses of phenylpropanolamine. Some reports indicate that only one dose was administered.

FDA believes that the data from the Yale study demonstrating an association between phenylpropanolamine and hemorrhagic stroke, taken together with spontaneous reports and reports in the published medical literature, provide evidence that nasal decongestant and weight control

drug products containing phenylpropanolamine are no longer shown to be safe. Because hemorrhagic strokes often lead to catastrophic, irreversible outcomes and the factors that may predispose some individuals to develop this adverse event are not fully known, individuals at risk cannot be adequately warned. The agency tentatively concludes that the benefits of the intended uses of this ingredient do not outweigh the potential risk. All of the applications listed in section II of this document are for nasal decongestant use of phenylpropanolamine. None are for appetite control.

Accordingly, the Director of the Center for Drug Evaluation and Research (CDER) concludes with respect to the NDA and ANDA products containing phenylpropanolamine listed in section II of this document that phenylpropanolamine is no longer shown to be safe for use under the conditions that formed the basis upon which the applications were initially approved. The Director is proposing to withdraw approval of those NDAs and ANDAs in accordance with section 505(e)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)(2)). This notice of opportunity for a hearing applies to all persons who manufacture or distribute a drug product that contains phenylpropanolamine and that are considered new drugs (e.g., extended-release products and any prescription product).

In lieu of requesting a hearing, manufacturers of products containing phenylpropanolamine as a nasal decongestant are urged to reformulate their products to remove phenylpropanolamine. Reformulated products may result in products that require an approved NDA or ANDA prior to marketing. Inquiries regarding proposed reformulations should be sent to the Division of Pulmonary and Allergy Drug Products (address above) or the Office of Generic Drugs (address above), as appropriate.

V. Notice of Opportunity for a Hearing

The Director has evaluated the information discussed above and, on the grounds stated, is proposing to withdraw approval of the previously listed NDAs and ANDAs. Therefore, notice is given to the holders of the NDAs and ANDAs listed in section II of this document that the Director

proposes to issue an order, under section 505(e)(2) of the act, withdrawing approval of the NDAs and ANDAs and all amendments and supplements thereto. The Director finds that new evidence of clinical experience, not contained in the applications or not available to the Director until after the applications were approved, evaluated together with the evidence available to the Director when the applications were approved, shows that phenylpropanolamine is not shown to be safe for use under the conditions that formed the basis upon which the applications were approved.

In accordance with section 505 of the act and part 314 (21 CFR part 314), applicants and all other persons subject to this notice are hereby given an opportunity for a hearing to show why approval of the NDAs or ANDAs should not be withdrawn.

An applicant who decides to seek a hearing shall file: (1) On or before [*insert date 30 days after date of publication in the **Federal Register***], a written notice of appearance and request for hearing, and (2) on or before [*insert date 60 days after date of publication in the **Federal Register***], the data, information, and analyses relied on to demonstrate that there is a genuine issue of material fact to justify a hearing, as specified in § 314.200. Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, a notice of appearance and request for a hearing, information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in § 314.200 and in 21 CFR part 12.

The failure of an applicant to file a timely written notice of appearance and request for hearing, as required by § 314.200, constitutes an election by that person not to use the opportunity for a hearing concerning the action proposed and a waiver of any contentions concerning the legal status of that person's drug products. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request

for a hearing that there is no genuine and substantial issue of fact that precludes the withdrawal of approval of the applications, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions under this notice of opportunity for a hearing are to be filed in four copies. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, the submissions may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

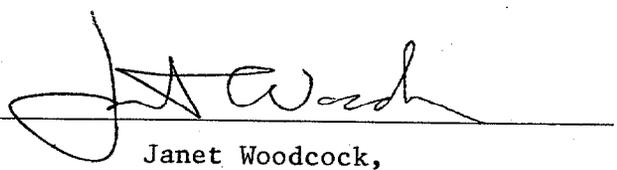
This notice is issued under the Federal Food, Drug, and Cosmetic Act (section 505 (21 U.S.C. 355)) and under authority delegated to the Director, CDER (21 CFR 5.82).

VI. References

The following references are on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Horwitz et al., "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of The Hemorrhagic Stroke Project," May 2000 in Comment No. C230, Docket No. 76N-052N and Comment No. C114, Docket No. 81N-0022.
2. Phenylpropanolamine Case Reports From 1991-2000 on File in Docket Nos. 76N-052N and 81N-0022.
3. Consumer Healthcare Products Association (CHPA), "Comments on the Hemorrhagic Stroke Project Report," May 24, 2000, in Comment No. C231, Docket No. 76N-052N and Comment No. C113, Docket No. 81N-0022.
4. Food and Drug Administration, Summary Minutes of Nonprescription Drugs Advisory Committee Meeting, October 19, 2000.

Dated: 6/1/01
June 1, 2001.



Janet Woodcock,
Director,
Center for Drug Evaluation and Research.

Display Date	_____
Publication Date	_____
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