TAB 14

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 20 1994

R. William Soller, Ph.D.
Senior Vice President and Director
of Science and Technology
Nonprescription Drug Manufacturers
Association
1150 Connecticut Avenue, N.W.
Washington, D.C. 20036

Re: Docket No. 81N-0022
Comments No. RPT7, CP11, CP14, and C107

Dear Dr. Soller:

This letter responds to numerous comments that have been submitted on the effectiveness of phenylpropanolamine hydrochloride (PPA) as an over-the-counter (OTC) weight control drug product. As you know, the agency's position on the safety of PPA was discussed in a letter to you dated March 9, 1993. Because of unresolved safety issues concerning PPA for OTC weight control use, the agency did not categorize or discuss PPA in the tentative final monograph for OTC nasal decongestant drug products, published in the Federal Register of January 15, 1985 (50 FR 2220), or in the notice of proposed rulemaking for OTC weight control drug products (certain active ingredients), published in the Federal Register of October 30, 1990 (55 FR 45788), or in the final rule for OTC weight control drug products (certain active ingredients), published in the Federal Register of August 8, 1991 (56 FR 37792). The agency will fully discuss safety and effectiveness issues and propose specific labeling for OTC weight control drug products containing PPA in a future issue of the Federal Register.

After reviewing the submitted data and other available information on the effectiveness of PPA for OTC weight control use, the Office of OTC Drug Evaluation has determined that PPA is effective, at a daily dosage of 75 milligrams (mg) in a controlled-release dosage form. Further, we have determined that OTC PPA weight control drug products should bear labeling that mentions use in conjunction with an appropriate weight loss diet. We have also determined that the existing data are inadequate to support immediate-release doses of 25 to 50 mg PPA.

BACKGROUND

As you know, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) recommended that PPA is effective for weight reduction at an oral dosage of 25 to 50 mg in a single dose, not to exceed 150 mg daily, for time periods up

to 12 weeks. (See 47 FR 8466 at 8475.) (In the preamble to the Panel's report, the agency limited the dosage level to that which was in use on December 4, 1975, i.e., an immediate-release dose of 25 to 37.5 mg and a controlled-release dose of 75 mg, not to exceed 75 mg daily.) The Panel based its recommendations on the basis of eight studies. In its evaluation, the Panel recognized that each of the studies had at least one defect. However, the Panel found that the combined evidence of the studies was sufficient to establish the effectiveness of PPA for weight control use.

In the preamble to the Panel's report, the agency noted that the unaltered conclusions of the Panel were being issued to stimulate discussion and comment on the full sweep of the Panel's deliberations. The agency emphasized that it had not evaluated the Panel's findings, but pointed out that the Panel had concluded that "while weight control drug products may assist in reducing an individual's appetite, a significant weight loss can be achieved only if accompanied by a reduction in total daily caloric intake below the energy output." (See 47 FR 8466 at 8468.) The agency also noted the Panel's recommendation to include under DIRECTIONS the following: "This Product's Effectiveness is Directly Related to the Degree to Which You Reduce Your Usual Daily Food Intake." The agency expressed concern that the past promotion of some products may have engendered a misunderstanding among potential consumers that weight loss results directly from the use of the drug product and that dieting is unnecessary. At that time, the agency encouraged manufacturers to incorporate the statement in the labeling of their PPA weight control products. Today, that statement is even more relevant. Our conclusion that PPA is effective is based upon clinical studies (described below) where subjects' caloric intake was restricted.

As a result of the agency's discussion in the preamble to the Panel's report, manufacturers submitted additional studies in support of PPA's effectiveness, both before and after the closing of the administrative record for the rulemaking for OTC weight control drug products on July 26, 1982. Most of these studies were conducted a number of years ago and do not follow currently accepted clinical testing procedures. Deficiencies are common, especially in study design. Some studies were crossover in design, with results typical of crossover studies for weight control drugs. There is a marked effect of sequence; i.e., whether a subject lost or gained weight on placebo depended on whether the subject received placebo before or after PPA. For this reason, crossover studies are not a good model for weight control drugs and these studies do not support the effectiveness of PPA.

Several studies evaluated PPA in combination with caffeine. These studies provide no definitive support for the effectiveness of PPA alone, unless it can be shown that caffeine has no effect on weight loss. In addition, because of misuse of PPA-caffeine combination products, in the Federal Register of June 29, 1984 (49 FR 26814), the agency established October 29, 1984 as the final date such products could be legally marketed.

The results of one 6-week study (Ref 1), comparing 25 mg immediate-release PPA (3 times a day at meals) and placebo, are marginally significant. However, only the data for week 6 are provided in the report. Because this study cannot be fully analyzed and interpreted, the results cannot be considered conclusive.

All of the submitted studies will be discussed in a notice of proposed rulemaking (tentative final monograph) for OTC weight control drug products in the Federal Register at a future date. Only those studies that are adequately designed, well-controlled, and support the effectiveness of PPA are discussed in this letter.

The agency's preestablished criterion for a weight control ingredient to be considered effective has been that it must demonstrate statistically significant weight reduction in double-blind, placebo-controlled studies lasting 6 to 12 weeks, with assessments made at weekly or biweekly intervals. Based upon this criterion, a number of recently conducted, well-controlled studies support the effectiveness of 75 mg controlled-release PPA. All of the studies limited daily caloric intake.

STUDIES SUPPORTING EFFECTIVENESS

Weintraub study (Ref. 2). This was a randomized, double-blind, placebo-controlled, parallel study of 75 mg controlled-release PPA compared with placebo in mildly to moderately overweight women aged 18 to 44. In addition to PPA or placebo, the study involved the use of a 14-week, physician-managed program of behavior modification, personalized diets, and exercise initiated at the beginning of a 2-week run-in period during which neither PPA nor placebo was used. Subjects were instructed to expend 300 calories 3 times per week at a physical activity of their choice. Subjects also participated in one session in which they were instructed in the basic principles of behavior modification involving awareness of eating patterns and the stimuli for food consumption.

After a 2-week run-in period, 106 subjects were randomized to the two treatments and weighed bi-weekly for 12 weeks. Compliance with the diet and exercise program was monitored. Seventy-eight subjects completed the 12-week study, with a 6.1 kilogram (kg)

(13.42 lb) mean weight loss in the PPA group and an 4.3 kg (9.46 lb) mean weight loss in the placebo group (two-sided p-value <0.05). Twenty-eight subjects left the study prematurely, 13 in the PPA group and 15 in the placebo group. Using the last observation carried forward analysis (LOCF), mean weight loss was 5.1 kg (± 0.6) (11.22 lb ± 1.6) in the PPA group and 3.3 kg (±0.5) (7.26 lb ± 1.1) in the placebo group (two-sided p-value <0.01). In the observed case analysis (subjects still on therapy after a given number of weeks), there were significant drug-placebo differences in weight loss only at weeks 10 and 12. This well-controlled study supports the effectiveness of 75 mg controlled-release PPA in inducing weight loss when used in a physician-managed, integrated weight control program.

Schteingart study (Ref. 3). In this double-blind, placebo-controlled, parallel study, 102 men and women 18 to 60 years of age, who were 15 to 45 percent overweight according to the Metropolitan Life Insurance Company body weight charts, were randomized to a 75 mg sustained-release PPA capsule or an identical appearing placebo capsule at 10 a.m. daily for 6 weeks. Eighty-five subjects completed a 2-week washout phase and entered the trial; 64 completed 6 weeks of double-blind treatment. Subjects were evaluated at 2-week intervals. All subjects were put on a 1,200 calorie high-fiber diet consisting of 54 percent carbohydrate, 26 percent protein, and 20 percent fat. Dietary compliance was not monitored. Following participation in the double-blind phase, subjects could participate in a 40-week open phase in which they received 75 mg PPA daily. The investigator reported that at the end of the double-blind treatment phase the mean weight loss was 5.7 lb for the PPA group and 2.4 lb for the placebo group (p=0.003).

The study was flawed in some respects. Subjects weighing more or less than the preset limits were enrolled in the study, suggesting that the protocol was not strictly followed. Placebo subjects weighed 11.7 lbs more, on average, than the PPA subjects, a potentially important imbalance. This difference in baseline weights is not considered a major problem because both groups were comparably overweight and baseline weight was used as a covariate in the analysis of variance. There was also a differential dropout rate, with 15 discontinuations in the placebo group compared to 6 in the PPA group. Bias resulting from the differential dropout rate is unlikely given the similarity of the observed cases analysis, the LOCF analysis, and the greater weight loss in the PPA dropouts. Although flawed in some ways, this study provides evidence of the effectiveness of 75 mg controlled-release PPA over a 6-week period when used in conjunction with a reduced-calorie diet in moderately overweight subjects.

Greenway study (Ref. 4). This double-blind, placebo-controlled, randomized, parallel study involved 102 male and female subjects 18 to 60 years of age, who were 15 to 45 percent overweight as determined from the Metropolitan Life Insurance Company body weight charts. Following a 2-week placebo washout period, 98 subjects entered a 12-week, double-blind phase comparing a 75 mg PPA controlled-release capsule and an identical appearing placebo capsule, taken at 10 a.m. daily. Subjects were also placed on a 1,200 calorie diet, but compliance was not monitored. Subjects were evaluated at 2-week intervals. Eighty-five subjects (45 PPA subjects and 40 placebo subjects) completed the 14-week study; there were 13 dropouts. After 12 weeks of treatment, the overall mean weight loss was 5.96 lb for the PPA group and 2.35 lb for the placebo group ($p=0.023$). Weight loss in the PPA group leveled off after 8 weeks, but the advantage for PPA over placebo was consistent throughout the trial. This well-controlled study provides evidence that 75 mg controlled-release PPA taken once a day is effective for weight loss for up to 12 weeks in conjunction with a 1,200 calorie diet.

Atkinson study (Ref. 5). This double-blind, placebo-controlled, randomized, single-center, parallel study involved 125 male and female subjects 18 to 60 years of age, whose body weight was 15 to 45 percent in excess of normal as determined from the Metropolitan Life Insurance Company body weight charts. Following a 2-week placebo run-in phase, subjects entered a 12-week, double-blind active phase where they took either a 75 mg PPA controlled-release tablet or an identically appearing placebo tablet at 10 a.m. daily. All subjects were instructed to follow a 1,200 calorie diet during both the 2-week run-in phase and the 12-week, double-blind active phase. Although the protocol specified that subjects were to be 15 to 45 percent in excess of normal weight, subjects in fact weighed from 10.2 to 63.6 percent in excess of their ideal body weight. Subjects were evaluated at 2-week intervals. After 12 weeks of treatment, the overall mean weight loss was 9.9 lb for subjects in the PPA group and 4.5 lb for subjects in the placebo group ($p=0.0001$). This study supports the effectiveness of 75 mg controlled-release PPA taken once daily for a period of 12 weeks, in conjunction with a 1,200 calorie diet.

CONCLUSION

Three studies (Refs. 3, 4, and 5) clearly demonstrate the effectiveness of once daily PPA in a 75-mg controlled-release dosage form, combined with a reduced calorie diet. These studies were designed to simulate, reasonably closely, use in a self-care (OTC) setting. In the Schteingart study (Ref. 3), the recommended diet used was the same as the diet recommended in the package insert of a currently marketed OTC product. In addition, subjects were not monitored for dietary compliance, and were seen

only every 2 weeks during the 6-week treatment phase of the study, minimizing the impact of those visits. While some degree of subject monitoring is necessary in any clinical trial, the level of physician intervention and follow-up in these studies was modest. These studies support the effectiveness of PPA for up to 12 weeks. Another study (Ref. 2) provides supportive evidence of the effectiveness of PPA for weight control at this dosage. Therefore, the agency concludes that PPA is effective, at a daily dosage of 75 mg in a controlled-release dosage form, when used in conjunction with an appropriate reduced-calorie diet.

However, as I discussed in my March 9, 1993 letter (Comment No. LET86, Docket No. 81N-0022), because of unresolved safety concerns regarding a possible increased risk of stroke associated with OTC PPA drug products, the agency intends to categorize PPA in Category III (insufficient data) for safety in a proposed rule for OTC weight control drug products. As I mentioned in that letter, one possible explanation for the occurrence of the reactions to PPA in users of PPA weight control drug products, rather than PPA cough-cold drug products, is a greater tendency of users of PPA weight control drug products to exceed the recommended dose. Whether or not this is true, we believe it is extremely important that consumers be informed in labeling that taking more than the recommended dose will not increase weight loss and can be dangerous. Further, we believe that product labeling should strongly state that PPA weight control drug products should not be used by persons under 18 years of age, unless recommended by a doctor.

The proposed voluntary changes in package labeling, advertising, and promotion of PPA weight control drug products that you have submitted (Comment No. C107, Docket No. 81N-0022) address our concerns and are a reasonable first step toward improving labeling of PPA weight control drug products and should be implemented industry-wide on a voluntary basis as soon as possible. FDA will propose specific labeling for OTC PPA weight control drug products in a future issue of the Federal Register.

I also want to point out that although the agency has concluded that 75 mg controlled-release PPA is effective for weight control, such controlled-release dosage forms are regarded as new drugs for which an approved new drug application (NDA) is required under 21 CFR 200.31. Section 200.31 states that timed-release formulations that contain a quantity of an active drug ingredient that is not generally recognized as safe for administration as a single dose are regarded as new drugs within the meaning of Section 201(p) of the Federal Food, Drug, and Cosmetic Act. Unless additional studies or supportive data provide evidence that an immediate-release dosage form is safe and effective, PPA will not be included in a final monograph.

An approved NDA will be necessary upon the effective date of a final rule for OTC weight control drug products to demonstrate that PPA in a controlled-release dosage form is properly manufactured and controlled to release the drug at a safe rate. Any such product without an approved NDA will be subject to regulatory action after the final rule becomes effective. I want to strongly suggest that manufacturers start preparing (and submitting) their NDAs now.

The Office of OTC Drug Evaluation intends to recommend to the Commissioner that the agency respond to the effectiveness data on PPA in the above manner. We ask that you share this letter with interested manufacturers of OTC PPA drug products. Any comment you or interested manufacturers wish to make on the above information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, Maryland 20857.

We hope this information will be helpful.

Sincerely yours,

William E. Gilbertson, Pharm.D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

REFERENCES

(1) Bradley, M. H., "Double Blind Safety and Efficacy Evaluation of Phenylpropanolamine HCL in Obese Patients with Controlled Hypertensive Disease," unpublished study in Comment No. RPT7, Docket No. 81N-0022, Dockets Management Branch.

(2) Weintraub, M. et al. "Phenylpropanolamine OROS (Acutrim) vs. Placebo in Combination With Caloric Restriction and Physician-Managed Behavior Modification," Clinical Pharmacology and Therapeutics, 39:501-509,1986, in Comment No. RPT7, Docket No. 81N-0022, Dockets Management Branch.

(3) Schteingart, D., "A Double-Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine (75 mg) Compared With Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket No. 81N-0022, Dockets Management Branch.

(4) Greenway, F., " A Double-Blind Clinical Evaluation of Phenylpropanolamine (75 mg) Compared With Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP11, Docket No. 81N-0022, Dockets Management Branch.

(5) Atkinson, R., "A Double-Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine (75 mg) Compared With Placebo in the Treatment of Exogenous Obesity," unpublished study in Comment No. CP14, Docket No. 81N-0022, Dockets Management Branch.