

"It seems that because of the lack of sleep the subjects felt dull and dizzy during the mornings following the fenfluramine test nights..."

"... It is then questionable whether day time drowsiness is a manifestation of a truly sedative effect of fenfluramine, or rather a symptom of fatigue following primary excitation. No facilitation of normal sleep has ever been reported, although a few cases of insomnia were" (page 188). Any claims as to sedation or tranquilizing effect will have to take into account Dr. Gagnon's paper. If you disagree with Dr. Gagnon's findings we request that you supply clinical evidence to refute them. The case report forms submitted for Dr. Hollingsworth and Dr. Rosenberg are practically illegible. This should be corrected.

The case report forms for Dr. Anderson give no actual dates, only the elapsed time. The dates that are recorded elsewhere on the case report forms are ambiguous. Actual dates should be supplied for the starting and stopping of medication on all case report forms.

Page 262 is out of context. Please clarify as to its proper location.

With regard to Study #3027 (Newman and Weger) in which the greatest number of patients, the highest dosage of fenfluramine, and the longest periods of treatments were adopted, we find it difficult to analyze the raw data, since the dosage levels used on any given patient were changed so often and at irregular intervals. We request that you tabulate for each patient the duration in weeks that each dosage level and the number of lbs. lost during each such period, as well as the initial and final weight difference.

Because of the voluminous nature of this NDA and associated INDs 1703 and 4402, we request that you submit a tabulation, both alphabetical and chronological, of all clinical investigators and their protocols so that we may more easily locate the protocols for each investigator.

On page 245 you state: "The number of patients in the study was small and therefore no definitive statement may be made regarding the results" (Dr. Rosenberg's Study #2016). A randomized double-blind crossover technique was described for this study; there were 29 patients on fenfluramine and 33 patients on placebo for a total of 62 patients, and this number is more than that for any other investigator doing controlled studies, with the sole exception of Roginsky. If Dr. Rosenberg used too few patients, then the rest of the investigators did likewise.

On page 256 in connection with Dr. Bacon's study you state "... fenfluramine equal to placebo in effectiveness. However, subjects lost more weight in the first period of the study regardless of drug (fenfluramine or placebo) used. Therefore, design of study not good to detect weight loss effect. Also, study period too short." The design was a double-blind crossover and the study period was the same as that used by Dr. Fisch and Dr. Rosenberg, viz., 4 weeks. What study period do you consider adequate?

The submission of June 17, 1969 is an uncontrolled study by Dr. Lange which does not materially alter the situation concerning evidence for efficacy of fenfluramine.

We are withholding comments concerning the labeling until the NDA is satisfactory in other respects.

ROBERT O. KNOX, M.D.,
Medical Officer.

MEDICAL OFFICER'S REVIEW OF NDA 16-618

OCTOBER 23, 1969.

Product: Fenfluramine

Trade name: Ponderex

Sponsor: A. H. Robins Co., Richmond, Va.

PREVIOUS REVIEWS

1. Richard Zoppa, M.D., reviewed this application on 8-29-67. *His summary has been reviewed and approval is not recommended for the following reasons:*

(1) *Controlled studies the capsule formulation did not include a restricted low caloric diet which is necessary in any weight reduction program.*

(2) *Controlled studies using the tablet formulation were not well-controlled i.e. they were "open" in design, not "double-blind". (3019, 3020, 3022, and 3023)*

(3) *The application is submitted for the tablet formulation only; data from the capsule formulation cannot be applicable in the absence of data equating the biologic availability of the two formulations.*