SUMMARY AND EVALUATION

Although more drug-treated than placebo subjects lost weight in each of 5 studies, the significance of the drug—placebo differences cannot be evaluated due to

1. Drop-out rates of 3–40% which eliminated entirely some of the proposed subgroups.
2. Protocol deviations e.g. too few subjects varying acceptance criteria regarding amount of overweight, irregular treatment administration variation in return appointment intervals, etc.
3. A high incidence of non-treatment-related weight changes due to intercurrent illness (Asian flu epidemic) and dietary excesses during the year-end holiday season.
4. Lack of information regarding comparability of population groups for each study (e.g., private patients vs. clinic).

Such inter-study variations preclude reliable conclusions being drawn from pooled data. Further, such "pooling" would fail to reflect results of 4 additional studies which were conducted under Master Protocol No. 25 and which were previously judged not to establish superiority of fenfluramine to placebo.

However in order to evaluate roughly the trend favoring drug over placebo in this heterogeneous group of obese subjects, we note the combined results from these 5 studies as follows:

Studies were initiated in 81 drug and 83 placebo subjects.

Sixty-three drug treated subjects had 6-week weight determinations. 39/63 (62%) lost more than 5 lbs.; 13/63 (20%) lost more than 10 lbs.

Sixty-one placebo-treated subjects had 6-week weight determinations. 14/61 (23%) lost more than 5 lbs. 2/61 (3%) lost more than 10 lbs.

Range of weight losses

Fenfluramine: 12 patients lost 11–14½ lbs. One patient lost 31 lbs.

Placebo: 2 patients lost 12 and 18 lbs.

Although comparative efficacy evaluation favors drug over placebo (20%/3%) the therapeutic merit is questionable for a drug, for which only 1 in 5 subjects is likely to benefit from the recommended course of treatment.

"For 'proof of efficacy', it is necessary to establish the proportion of patients who can be expected to receive optimal benefit. . . . If a new drug is intended to provide a cure for a heretofore fatal disease, variability and a rather high rate of failure will be condoned. However, if it is for relief of a symptom such as pain—for which we have a number of analgesica—then its efficacy must be great. Relief must occur in nearly all patients with pain of similar origin and like severity." (K. C. Kohlstaedt, M.D., Proof of Efficacy—Industry's Point of View, in Pharmacologic Techniques in Drug Evaluation, Vol. 2, page 18)—Nedine and Siegler, Ed. 1967.

CONCLUSIONS

The results of the 6 studies reviewed are inadequate individually and collectively to establish anorevigenic efficacy for fenfluramine under the conditions of recommended clinical usage.

Since fenfluramine is to be indicated as adjunctive therapy in the management of obesity, the current study design which specifically excluded dietary restrictions, may be inherently inadequate to establish efficacy under conditions of recommended clinical usage.

"Full disclosure" labelling information for drugs in this category should include the proportion of subjects likely to benefit, as well as the range and rate of weight loss which may be anticipated as a result of the recommended course of treatment, in order to enable a physician to evaluate the potential therapeutic benefit for a particular patient.

Finally, this review of circumscribed case data from 6 efficacy studies in no way constitutes an adequate over-all evaluation of the safety and efficacy of fenfluramine for marketing, as required by the Regulations.