NEW DRUG APPLICATION NO. 16–880

Test Drug: Voranil (Clortermine hydrochloride) 50 mg Tablets, Code: CL/TM (1000).

Manufacturer: CIBA Pharmaceutical Co.

Studies reviewed: 54.

Because such a large number of studies have been submitted and different protocols and comparison drugs were used in this NDA we shall concentrate on the double-blind studies in which placebo was a control on normal obese subjects.

Voranil is indicated for the management of exogenous obesity as a short-term, i.e., several weeksadjunct in a regimen of weight reduction based on caloric restriction. The planned duration of therapy for all 54 studies was 8 weeks. A description of the studies with respect to type of patient, control drug and dietary restrictions is shown in table 1.

Each study was analyzed separately as shown in the attached tables. Our conclusions are based on the covariate table. For our analysis probabilities equal to or less than 5 percent shall be considered to differ significantly from chance.

Conclusions

Only two protocols covered normal patients with a placebo control. As seen in table 1 there was no dietary control for Protocol 101, and a 1000-calorie dietary control for Protocol 102, 102L.

1. Protocol 101
   (*a*) None of the 8 studies had significant initial weight differences.
   (*b*) Three of the eight studies showed a significant drug effect greater than that of placebo.
2. Protocol 102,102L
   (*a*) None of the 23 studies showed significant initial weight differences.
   (*b*) Four of the 23 studies showed a significant drug effect greater than that of placebo.
3. Reference to table 1 and the attached tables show that only one other study (Protocol 203–5, Study 161 880, Diabetic patients) showed a significant drug effect greater than that of placebo.

MEMORANDUM

U.S. GOVERNMENT.

To: Dr. Robert Knox.
From: Lawrence Hauptman.
Subject: NDA 16–880 Voranil—hemoglobin values.

1. As requested I have examined the hemoglobin values from two studies, Jackson and Sobotka. I have compared both studies to the "normal" values (mean 13.6; standard deviation, 1.2) given. "Normal Hemotological Values in the Central American Populai.

2. The mean and standard deviation for the Jackson data were 13.1 and 1.47, respectively. The mean and standard deviation for the Sobotka data were 12.4 and 0.73 respectively.

3. It is unlikely that either the Jackson data (PL. 04) or the Sobotka data (PL. 001) come from a normal distribution with mean, 13.6 and standard deviation 1.2.

4. The Jackson data could have come from a normal distribution with a mean and standard deviation equal to the observed values, 13.1 and 1.47.

5. It is unlikely (PL. 02) that the Sobotka data came from a Normal distribution with mean and standard deviation equal to the observed values 12.4 and 0.73.

6. Disregarding the form of the distribution, the hypothesis that the Jackson data came from a distribution with mean, 13.6, could not be rejected at the .05 level. However, for the Sobotka data the same hypothesis could be rejected at an extremely small significance level (P-.000002).

7. Of the 45 values from the Sobotka study, 38 ended in an even number while 7 ended in an odd number. Under the hypothesis that even and odd endings are equally likely the probability of the above event or of one mere extreme is extremely low, P-.000001.