JAN 31 1991

Statistical Review and Evaluation
(Addendum 2)

NDA #: 19-839/Drug Class 1C

Applicant: Pfizer Central Research

Name of Drug: Sertraline HCl

Indication: Depression

Documents Reviewed: Amendment of 9-14-90, Enclosures #3 and #4

Clinical Reviewer: Hillary Lee, Ph.D. (HFD-120)

A. Enclosure #4 (HAMD Subscale Analysis)

Some of the items included in the HAMD Total may be confounded with adverse effects rather than being one hundred percent representative of efficacy. Because of this confounding, the clinical reviewer, the group leader (clinical) and I requested of the sponsor analyses excluding items 4 (early insomnia), 5 (middle insomnia), 6 (late insomnia), 9 (agitation), 10 (psychic anxiety), 11 (somatic anxiety), 12 (somatic symptoms - GI) and 13 (somatic symptoms-general). The total of the reduced set of items has been referred to as Subscale 5 in the sponsor's amendment. The sponsor's analyses are presented in Appendix A of this report, as are the original results for comparison.

Reviewer's Comments

The 100mg group is seen to show the most consistent evidence of efficacy, with both OC and LOCF analyses at least marginally significant (two-sided P<.10) for all analyses done at Week 3 or later. These analyses at weeks 4, 5, 6, as well as "last visit" were statistically significant by both OC and LOCF analyses (two-sided P<.05).

Conclusion

Results for the 100mg group are highly significant for all weekly analyses after Week 3 (p<.016) and at least marginally significant at Week 3. These results are more persuasive than the original analyses of the entire HAMD-scale (see Appendix A).

B. Enclosure #3 (Analysis of Suicide Attempts Data)

The overall incidence rates of suicide attempts in sertraline therapeutic depression studies, as provided originally by the sponsor, are presented in Appendix B. The incidence rate (per patient-year) of suicide attempts for sertraline is .0177 compared

to .0239 for placebo according to this original analysis. Two of the sertraline attempts resulted in completed suicide; apparently none of the placebo attempts resulted in completed suicide.

It was seen from the case report forms that 3 out of the 5 suicide attempts shown under placebo occurred before the comparative double-blind phase of the studies started. Excluding those 3 suicide attempts (and hence also the washout exposure time), the new incidence rate (per patient-year) of suicide attempts for placebo is .0137 (sertraline rate remains .0177, the same as before). The sponsor utilized the number of suicide attempts per person-year of exposure in its analysis. In response to our request for a life table analysis the sponsor stated that sufficient data were not available (some studies are overseas) for the entire data base to permit such an analysis and, in addition, provided details of the statistical method followed in the original statistical analysis. In the absence of the complete information needed for a life-table analysis, this methodology seems reasonable.

The sponsor also provided (at our request) an analysis comparing suicide attempt rates for the comparative double-blind phase only (omitting the wash-out period data). The analysis supplied by the sponsor (Fax Transmittal on Nov. 7, 1990) contained an error in calculation of the appropriate p-values. The correct p-values are .54 for the new data set (omitting the wash-out period) and .80 for the original data set. (Dr. David Salsburg of Pfizer confirmed that the sponsor's calculations were incorrect due to the use of the wrong tail of the distribution.)

The sponsor also analyzed shifts to greater suicide tendency among patients with none at baseline by comparing the proportions of patients in the sertraline and placebo groups having a HAMD Item 3 score of 0 or 1 at baseline who shifted to a score of 3 or 4, where 0=absent, 1=feels life is not worth living, 2=wishes he were dead or any thoughts of possible death to self, 3=suicide ideas or gestures, 4=attempts at suicide. From Table 3 of Enclosure #3, these numbers (%) are 3/136 (2.2%) for sertraline and 1/51 (2.0%) for placebo. This analysis clearly does not suggest a concern.

Conclusion

Based on the examination of rates of clinical suicide attempts, rates of events defined by baseline to endpoint shifts in HAMD Item 3 (suicide) scores, and mean baseline to endpoint changes in HAMD Item 3 scores presented in Enclosure #3, this reviewer does not see any statistical evidence to indicate a concern for sertraline with respect to suicidal tendencies in the therapeutic depression trials.

REFERENCES: Barlow, R.E., Bartholomew, D.J., Bremner, J.M., and Brunk, H.D. (1972) Statistical Inference Under Order Restrictions, John Wiley & Sons, New York, Chapter 6, Isotonic Tests for Goodness of Fit.

Lehmann, E. L. (1959) Testing Statistical Hypotheses, John Wiley & Sons, New York, Section 4.5, Comparing Two Poison or Binomial Populations.

Japobrata Choudhury 1-26-91

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius 1-29-91

Dr. Dubey 1-30-91

cc:
Orig. NDA 19-839
HFD-120
HFD-120/CSO
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Lee
HFD-713/Dr. Choudhury
HFD-713/Dr. Dubey (File: DRU 1.3.2)
HFD-713/Group 2 File
HFD-344/Dr. Lisook
Chron.

meg/SERB/wp/NDA-19-839/1-7-91

This addendum consists of 3 pages of text and 2 appendices.

Appendix 8

Comparative Incidence Rates of Suicide Attempts in Sertraline Therapeutic Depression Studies

	Sertraline	Placebo	Active Control
Number of patients	2053	788	595
Number of patients - years exposure	507.9	209.0[1]	90.8
Number of suicide attempts	9	5	1
Incidence rates (per pt-yr) of suicide attempts	0.0177	0.0239	0.0110
Incidence rates (per 100 pt-yr) of suicide attempts	1.77	2.39	1.10
95% confidence limits[2] on incidence rates per 100 pt-yr	0.8-3.4	0.7-5.5	0.0-6.2

1 This figure includes 145.8 patient-years of double-blind placebo and 63.2 patient-years of single-blind placebo exposure.

2 The confidence limits per pt-yr were computed on the original proportions (e.g. 9/508) using the exact binomial distribution. The incidence rates and corresponding confidence limits were then each multiplied by 100 to give incidence rates and confidence intervals per 100 pt-yr.