Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 24, 1991

FROM: PAUL LEBER, M.D.
DIRECTOR,
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

SUBJECT: Recommendation to Approve NDA 19-839 (Zoloft; sertraline)

TO: Robert Temple, M.D.
Director, ODE I

File NDA 19-839

This memorandum conveys my formal recommendation that Pfizer's NDA 19-839 for ZOLOFT (sertraline) be approved.

The administrative file documents that NDA review team under the direction of Dr. Thomas Laughren has completed its review of Pfizer's NDA for sertraline, including, in particular, the firm's response to the agency's 10/30/91 approvable action letter. The division's review has failed to find that any of the grounds enumerated in Section 505(d) of the Federal Food, Drug, and Cosmetic Act for the disapproval of an NDA apply, and consequently, we recommend that the NDA be approved as provided by Section 505(c)(1)(A) of the Act.

It is noteworthy that several foreign national drug regulatory authorities (see Dr. Laughren's 12/10/91 memorandum), presumably provided with the same body of information that is contained in the NDA submitted to us, have not yet been willing to allow sertraline's marketing in their respective countries. It is our understanding that these regulatory authorities are not concerned about the risks of sertraline for use, but by what may be considered the 'lack of robustness' of the clinical evidence supporting its efficacy in the treatment of depression.

This turn of events may seem somewhat surprising in view of the fact that the agency is traditionally more conservative than its European counterparts. Obviously, changes are underway throughout the western Europe, perhaps in response to the EEC's harmonization initiatives. In any case, with the

important exception of the UK's CSM/MCA, standards for antidepressant drug product approval seem to be becoming more demanding in regard to 1) the duration of controlled trials serving as sources of evidence of efficacy, 2) the need to document efficacy in hospitalized depressed patients (because these are presumed, arguably, to be more severely depressed), 3) the need to show efficacy in maintaining remission, 4) the need to show efficacy in preventing relapse of euthymic patients with a history of recurrent episodes of affective illness, and 5) a need to establish equivalency and/or superiority of a new antidepressant to already marketed drug products.

Many of these foreign regulatory initiatives have potential merit, but, given the perceived urgency we express as an institution for expediting the public's access to new, potentially promising, drugs, I do not believe we can successfully introduce similar, more demanding, requirements domestically, at least until there is a significant 'sea change' in our society's collective attitude toward Federal regulation of new drug approvals. Incidentally, if you disagree with my assessment, I would like to know because the division would certainly be willing to propose additional requirements, provided, of course, that we could be assured of support for the initiative from both the Office and the Center.

In any case, based upon our current interpretation of the Act's requirements, Pfizer's NDA for sertraline must be approved. Sertraline is safe for use, effective in use, and adequately labeled, a view confirmed, albeit not unanimously, by the vote of our public Advisory Committee (i.e., PDAC).

Furthermore, although sertraline may not be the most robustly powerful antidepressant drug product ever introduced (a point made forcefully by some of our advisors), it has some potential advantages. As a 'pure' serotonergic uptake inhibitor it shares with Prozac (fluoxetine), the only currently marketed drug of this type, freedom from the troubling side effects associated with the use of the classic tricyclic antidepressants (e.g., imipramine, desipramine, amitriptyline, etc.) and the dietary restrictions necessarily associated with the use of monamine oxidase inhibitors.

Sertraline and fluoxitine have not undergone head to head comparative clinical testing, but sertraline, and its major metabolite, nor-sertraline, have somewhat shorter elimination half-lives respectively than fluoxitine and nor-fluoxitine, a potential advantage.

In sum, the approval of Sertraline is readily justified under existing rules

and regulations. Approval may, however, for the reasons enumerated above, come under attack by constituencies that do not believe the agency is as demanding as it ought to be in regard to its standards for establishing the efficacy of antidepressant drug products.

Paul Leber, M.D.

cc: NDA 19-839
HFD-100 Temple
HFD-120: Katz,
Laughren,
Lee,
Knudsen,
David