DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Ida Hellander, M.D.
Sidney M. Wolfe, M.D.
Public Citizen
Health Research Group
2000 P St., NW
Washington, D.C. 20036

JUN -3 1992

Re: Docket No. 91P-0203/CP1

Dear Drs. Hellander and Wolfe:

This responds to your citizen petition dated May 23, 1991, requesting that the Food and Drug Administration (FDA) immediately revise the approved labeling of the antidepressant Prozac (fluoxetine), manufactured by Eli Lilly and Company (Lilly), to include a boxed warning regarding its association with intense, violent suicidal preoccupation, agitation, and impulsivity in a small minority of patients.

We have reviewed your citizen petition and have evaluated all currently available, relevant evidence. Because this evidence is not sufficient to reasonably conclude that the use of Prozac is possibly associated with suicidal ideation and behavior (suicidality), we are denying your request. However, we will continue to carefully examine any information that might suggest a potential relationship.

BACKGROUND

On December 29, 1987, FDA approved Lilly's antidepressant Prozac. In response to some reports of suicidal ideation among Prozac patients, Lilly revised its labeling on May 24, 1990, to include "suicidal ideation" in the list of adverse effects under the heading "Postintroduction Reports." Shortly prior to this revision, Dr. Martin Teicher published a paper in the American Journal of Psychiatry in February 1990 describing six patients who, during treatment with Prozac, experienced either the onset or the intensification of suicidal ideation. A few additional published case reports and numerous drug experience reports to FDA's Spontaneous Reporting System followed this publication.

In response to the concerns raised by these reports, Lilly conducted an extensive reanalysis of its clinical trial experience with Prozac to search for evidence concerning the induction or intensification of suicidality by Prozac. Lilly's controlled studies produced no evidence of a causal relationship between suicidality and Prozac either in a depressed population or in a nondepressed group being treated for obesity.

After hearing from private citizens, representatives from FDA, the National Institute of Mental Health (NIMH), Lilly, and six invited individuals with relevant expertise or interest, including Dr. Ida Hellander of HRG, the committee considered the following questions:

1. Is there credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors?

2. If so, does the evidence indicate that a particular drug or drug class pose a greater risk than others?

3. If the whole class or a particular drug causes emergence and/or intensification of suicidality, what actions, if any, should the agency take?

4. Even in the absence of sufficient evidence to establish causation, do the large volume of reports and/or the type of reports received justify some agency action, e.g., a modification of labeling for some or all antidepressants?

After several hours of discussion, the committee voted unanimously (10-0) "no" on the first two questions. It found that the evidence was not sufficient to conclude that antidepressants in general, or Prozac in particular, cause the emergence and/or intensification of suicidality and/or other violent behaviors. The committee then combined questions three and four into one question of whether there should be a labeling change. Based upon the available evidence, the committee voted 6-3 against any change in labeling. The majority concluded that the evidence was not strong enough to justify the suggestion of even the possibility of a causal linkage in labeling. Of those who wanted a labeling change, all agreed that it should be for the entire class of antidepressants, rather than for Prozac in particular. However, there was a consensus that more research is needed to further explore the relationship between suicidality and the use of, not only Prozac, but other antidepressants as well.

CONCLUSIONS OF FDA

Upon analyzing the case reports, clinical trials, conclusions of the PDAC, and other relevant evidence, we have concluded that a change in labeling is not warranted at this time. There is no reasonable evidence of an association between the use of Prozac and suicidality.

The case reports of patients who experienced suicidal ideation while undergoing Prozac treatment are inconclusive. Most concern patients being treated for depression. Because depressed patients think about and commit suicide far more frequently than

.lthough currently available data do not present reasonable evidence of an association between the use of Prozac and the emergence or intensification of suicidality, we are concerned that more information is needed on this issue. We will continue our careful evaluation of data in our spontaneous reporting system and encourage additional research on this matter. If further research or our SRS discloses reasonable evidence of an association, we will take all necessary steps to protect the public health.

Sincerely yours,

Carl. C. Peck, M.D.
Director
Center for Drug Evaluation
and Research