CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-825

Pfizer, Inc.
Attention: Charles A. Ritrovato, Pharm.D.
Eastern Point Road
Groton, CT 06340

OCT 3 1997

Dear Dr. Ritrovato:

Please refer to your pending March 17, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ziprasidone) 20mg, 40mg, 60mg, and 80mg Capsules.

We need your assistance to complete our review of the clinical section of your submission.

We trust you are aware of our interest in determining the extent to which ziprasidone prolongs the QT interval. It is apparent from the ECG data in the NDA that ziprasidone is associated with a dose dependent increase in the QTc. While one of your consultants, , has suggested that the observed changes may not be clinically significant, we cannot affirm his conclusion without further evalutaion of this finding.

Toward this end, we ask that you conduct in vitro studies with ziprasidone to assess its effect on potassium channels and on duration of action potentials. We ask that you characterize the action potential duration in Purkinje fibers for ziprasidone, the major metabolites of ziprasidone and an active comparison group, e.g., sotalol. Multiple concentrations of each agent should be studied to generate dose response curves. The maximum concentration range should be several factors greater than the maximum plasma concentration achieved in humans.

We are also aware that you have engaged an expert in cardiology, to assess the cardiovascular data for this current submission. It is our impression that he has, on the basis of his view that the ECGs were not accurately read, created an independent data base of ECG parameters from the tracings obtained for patients in your development program. Furthermore, it is our understanding, based on his re-reading and re-analysis of the ECG data, that he has concluded that ziprasidone has no demonstrable effect on the QT interval. If true, this would represent a strikingly different view of ziprasidone than is apparent from the data we have in hand. It is particularly difficult to understand how the observed dose dependency would be affected by more accurate reading of the ECGs.

Although we have not yet seen and are not even officially aware of report, we raise the issue now to avoid future delay in the review of the application. If you intend to present a different view of the data than what has already been presented in the NDA, we need to alert you now that, for us to evaluate such a revised view, we will need to have the complete database upon which that view is based, including readable copies of all the ECG tracings that were re-read and

all the revised parameter estimates. This will allow us to check on the validity and accuracy of method for estimating QT. We would also like this material in an electronic file so that we can conduct our own analyses of these data.

If our review were to sustain our currently tentative conclusion that ziprasidone is associated with a dose dependent prolongation of the QTc, it is likely that we will want you to obtain a considerably larger exposure to ziprasidone than obtained thus far in order to better estimate the rate of sudden unexplained death (SUD) with this drug. This additional experience could come from a large open trial, but the design must include careful followup of patients to ascertain vital status and standardized rules for classifying deaths. We wish to alert you to this possible requirement at this early stage in order to give you time to develop a protocol and be prepared to launch this additional study, since future decisions and actions regarding ziprasidone may be based in part on data derived from this expanded database.

You should also know that it is very likely we will bring ziprasidone to the PDAC early in 1998. We will of course alert you once a date for this meeting has been established.

We would appreciate your prompt written response so we can continue our evaluation of your NDA and will be happy to discuss with you any of the above noted issues and requests.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours.

/S/

10/3/97

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-825

Pfizer, Inc.
Attention: Charles A. Ritrovato, Pharm.D.
Eastern Point Road
Groton, CT 06340

MAY 12 1997

Dear Dr. Ritrovato:

Please refer to your pending March 17, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ziprasidone) 20mg, 40mg, 60mg, and 80mg Capsules.

Although Pfizer's routine clinical monitoring and clinical quality assurance audits have identified no information questioning the integrity of the study data, in view of current questions about the reliability of data provided by , we are requesting that you reanalyze the efficacy data for trial omitting their data. The reanalysis should include the observed cases and last observation carried forward for all efficacy variables including the PANSS Total, PANSS Negative Subscale, BPRS Total, BPRS Core, and the CGI Severity.

We are also requesting that the safety data obtained from be re-evaluated to determine if it is consistent with safety data from other investigators. Unlike the efficacy re-analysis, this should not be limited to Study , but should include all studies in which As an example of the type of exploration that may be useful, you may want to examine the current "1% Table" of adverse events to determine if omitting data from alters the reported incidences in any significant way.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Steve Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

/S/

5/9/97

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-825

MAR 21 1997

Pfizer, Inc.
Attention: Charles A. Ritrovato, Pharm.D.
Eastern Point Road
Groton, CT 06340

Dear Dr. Ritrovato:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	(ziprasidone) 20, 40, 60, 80 mg Capsules
Therapeutic Classification:	Standard
Date of Application:	March 18, 1997
Date of Receipt:	March 17, 1997
Our Reference Number:	20-825

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 16, 1997, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact CDR Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/ 3/21/97

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Central Research Division
Pfizer Inc
Eastern Point Road
Groton, CT 06340
Tel 860 441 4100

Central Research

March 18, 1997

Department of Clinical Research

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research HFD #120
Office of Drug Evaluation I
ATT: DOCUMENT CONTROL ROOM #10B-34
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Leber:

RE: **New Drug Application #20-825 - (ziprasidone) Capsules**
IND-# / User Fee ID #3172

Pursuant to Paragraph 505(b) of the Federal Food, Drug and Cosmetic Act, and Paragraph 314.1 of the Code of Federal Regulations, Title 21, we are submitting a New Drug Application (#20-825) for (ziprasidone) Capsules.

is an antipsychotic agent indicated for management of the manifestations of psychosis, in both the acute and long-term settings. is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents and its mechanism of action is believed to be mediated through a combination of dopamine type 2 (D_2) and serotonin type 2A ($5HT_{2A}$) receptor antagonism. The commercial name of for ziprasidone was deemed acceptable by the CDER Labeling and Nomenclature Committee on August 22, 1996 (Consult #649).

The chemistry, preclinical, and clinical data obtained during the investigation of under IND have been organized in this Application in accord with the requirements as currently set forth under Paragraph 314.50 of the Code of Federal Regulations, Title 21. This Application is also provided in electronic format as discussed with the Division on July 30, 1996 and February 6, 1997. Text and imaged information supplied electronically is identical to that provided in hardcopy. Please note, however, that case report forms (CRFs) and case report form tabulations are being supplied electronically only, in accordance with a waiver granted by CDER (reference letter of Dr. Janet Woodcock dated September 3, 1996, attached).

Applications for marketing approval of ziprasidone are soon to be filed in Canada and most European countries. Currently, ziprasidone is not marketed in any country.

This NDA contains safety data from a total of 4165 Phase I/II/III subjects treated in the ziprasidone clinical program, including Pfizer Central Research (4064) and Pfizer Japan (101). Of the 4064 Central Research subjects 2878 received ziprasidone, 501 received placebo and 685 received a comparative agent.

Data in this NDA establish the safety and efficacy of in the treatment of psychosis. Four randomized, double-blind, placebo-controlled, multicenter trials provide substantial evidence of efficacy

in acute and maintenance therapy. Of the 2878 subjects exposed to , 443 received the drug for six months or longer and 205 subjects were treated for at least 12 months.

The manufacturing site identified in this Application is located in Brooklyn, NY. As such, the Sponsor hereby certifies that a field copy of portions of this Application has been provided to the FDA district office in Brooklyn, NY, and that it is an exact copy of the Chemistry, Manufacturing and Controls section, FDA Form 3439 and the Application Summary contained in the archival and review copies of this NDA.

This Application consists of 156 volumes, numbered consecutively beginning with Volume 1.1 and ending with Volume 1.156. With the exception of CRFs and CRF tabulations supplied electronically as noted above, we have provided a complete archival copy (blue binders) of all 156 volumes and review copy of 241 volumes (technical sections). Twelve additional copies of the Application Summary (NDA Section 2, Volumes 1.1 and 1.2) have been included for individual reviewers as necessary. Attachment I of this letter provides the location for the various sections of this NDA and additional explanatory notes about the Application.

In accordance with the requirement of the Generic Drug Enforcement Act of 1992, and in connection with this Application, to the best of its knowledge, Pfizer, Inc. did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

Routine clinical monitoring of these trials and a Pfizer clinical quality assurance audit of study have identified no information that would bring into question the integrity of the study data generated by

therefore, we have no reason to believe that our observations or conclusions regarding integrity of data are unreliable.

Please be advised that the applicable user fee for this submission has been remitted in accordance with the Prescription Drug User Fee Act of 1992. We believe NDA-20-825 to be complete for review by the Division and look forward to working closely with the Division.

Should you have any questions regarding the organization or content of this Application, please contact Dr. Charles A. Ritrovato at (860) 441-6899 (phone) or (860) 441-1085 (fax).

Sincerely yours,

7/7/97

Steven W. Ryder, M.D.
Vice President
U.S. Clinical Operations

Charles A. Ritrovato, Pharm.D.
Senior Associate Director
Regulatory Strategy & Registration

Enclosures
Serial No. 000