CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB - 5 2001

NDA 20-825

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

Dear Dr. Ritrovato:

Please refer to your new drug application (NDA) dated March 18, 1997, received March 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziprasidone 20, 40, 60, 80 mg Capsules.

We acknowledge receipt of the following submissions:

September 15, 2000	October 3, 2000	October 20, 2000
October 24, 2000	November 21, 2000	November 28, 2000
December 1, 2000	December 12, 2000	December 22, 2000
January 2, 2001	January 25, 2001	

Your submission of October 20, 2000 constituted a complete response to our action letter of September 8, 2000.

This new drug application provides for the use of ziprasidone 20, 40, 60, 80 mg Capsules for the treatment of schizophrenia.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-825." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated October 20, 2000.

These commitments are listed below.

1. A Dose Response Study for QTc Effect
2. A Study of Sudden Unexpected Death with Ziprasidone and other Atypical Antipsychotics
3. Studies to Demonstrate Possible Advantages for Ziprasidone

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

In our action letter of September 8, 2000, we requested that you rapidly notify the Agency of specific adverse events (photosensitivity reaction, jaundice, hepatitis, increased transaminases, ketoacidosis, hyperosmolar coma, and marked glucose intolerance). Your proposal to submit monthly line listings of these events is acceptable.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632)(21 CFR 314.55 (or 601.27)). The Agency has not made a determination if a health benefit would be gained by studying ziprasidone in pediatric patients for its approved indications. FDA is deferring the requirement for submission of the pediatric assessments of safety and effectiveness because pediatric studies should be delayed until additional safety data have been collected and reviewed. FDA will inform you on or before June 1, 2001 whether pediatric studies are required under the rule. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specific time at which you must submit the required assessments.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

As stated in the action letter of September 8, 2000, the proprietary name " is not in compliance with 21 CFR 201.10(c)(5). This regulation prohibits the designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient. However, your proposed alternative proprietary name "Geodon" is acceptable. Please note, if you choose not to use "Geodon" as the proprietary name for this product, the name you choose and its use in the label must conform to the specifications under 21 CFR 201.10 and 201.15. Please submit any proprietary name to the Agency for our review prior to its implementation.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-825

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

SEP – 8 2000

Dear Dr. Ritrovato:

Please refer to your new drug application (NDA) dated March 18, 1997, received March 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ziprasidone 20, 40, 60, and 80 mg Capsules.

We acknowledge receipt of your submissions dated March 10, April 17, May 19, June 2, and July 14, 2000. Your submission of March 10, 2000, constituted a complete response to our June 17, 1998 action letter.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues:

1. Labeling

   Accompanying this letter (Attachment 1) is the Agency's proposal for the labeling of ziprasidone. We believe it presents a fair summary of the information available on the benefits and risks of ziprasidone.

   We have proposed a number of changes to the draft labeling submitted in your original submission. We will be happy to discuss these proposed changes in detail, and to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. Foreign Regulatory Update/Labeling

   We require a review of the status of all ziprasidone actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If ziprasidone is approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for ziprasidone along with English translations when needed.

3. World Literature Update

Prior to the approval of ziprasidone, we require an updated report on the world's archival literature pertaining to the safety of ziprasidone. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of ziprasidone. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

4. Expeditious Reporting of Certain Serious Adverse Events

In order for certain serious adverse events to be identified in postmarketing reporting as possibly associated with the use of ziprasidone, it is necessary that these be reported as 15 day reports, even though they might already be mentioned in labeling under "Other Events." The list of such events includes:

a. photosensitivity reaction
b. jaundice
c. hepatitis
d. increased transaminases
e. ketoacidosis
f. hyperosmolar coma
g. marked glucose intolerance

5. Post-marketing Studies

a. Dose Response for QTc Effect

One of the issues discussed at the PDAC meeting for ziprasidone was that the dose response curve for ziprasidone's QTc effects has not been adequately explored. Therefore, we ask that you commit to conducting a more definitive dose response trial to explore more thoroughly the upper end of this curve to better understand what the risks might be in those patients who happen to have such exposures.

b. Additional Drug Interaction Studies

Another issue of concern at the PDAC meeting was that there is little systematic experience with ziprasidone in combination with other drugs that prolong the QTC interval. Thus, we ask that you commit todesigning and conducting additional studies

to attempt to address this concern.

c. A Study of SUD with Ziprasidone and other Atypical Antipsychotics

The most direct approach to exploring whether or not ziprasidone has a greater potential for fatal arrhythmias compared to other drugs in this class would be a head-to-head comparison to look at the endpoint of sudden unexplained death (SUD). Although the ideal study would be an RCT comparing ziprasidone, risperidone, olanzapine, and quetiapine, a simpler alternative could compare ziprasidone with a control group of any of the other three drugs. The study would need to be very large, probably on the order of 10,000 patients per group.

d. Studies to Demonstrate Possible Advantages for Ziprasidone

Given the concern that ziprasidone may have a greater potential for fatal arrhythmias compared to other drugs in this class, it would be useful to explore whether or not ziprasidone has any advantages over other drugs in this class, either for efficacy or safety. It would be informative, for example, to study the efficacy of ziprasidone in patients shown to be refractory or intolerant to other drugs in the class. Regarding safety and tolerability, it has been implied, but not shown in head-to-head comparisons, that ziprasidone may be associated with less weight gain than other atypical antipsychotics and that compliance with treatment may be greater. It would be informative to study questions such as these.

We would be happy to work with you in the design of any of the above studies.

6. Proprietary Name

As your were notified in the telephone conversation of August 8, 2000, with Steve Hardeman, R.Ph., of this Division, the proprietary name is not in compliance with 21 CFR 201.10(c)(5). This regulation prohibits the designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient. Two products, Zyvox and Vioxx, appear to be most problematic as potential medication errors.

As requested, we have consulted your alternative proprietary name "Geodon" to the Office of Post-Marketing Drug Risk Assessment and will forward their recommendation as soon as it is available.

7. Dissolution

We request that you adopt the following dissolution methodology:

Tier I Test

Apparatus:	USP (paddle)
Speed:	75 rpm
Medium:	900 mL (2% sodium dodecylsulfate-SDS, 0.05 M NaH_2PO_4 buffer, pH 7.5)
Temperature:	37 °C
Specification (Q):	Not less than % dissolved in minutes.

Tier II Test

Apparatus:	USP (paddle)
Speed:	75 rpm
Medium:	700 mL (1% pancreatin in 0.05 M NaH_2PO_4 buffer, pH 7.5)
Temperature:	37 °C
Specification (Q):	Not less than % dissolved in minutes.

8. Pharmacology / Toxicology

In the Division's action letter of June 17, 1998, the information regarding the genotoxicity data contained in the NDA was not complete. Each genotoxicity study provided in the NDA contained one or more deficiencies. Specifically,

- the Ames test did not include one of the tester strains, TA102, E. coli WP2uvrA, or E. coli WP2uvrA(pKM101), and there was no evidence of cytotoxicity or insolubility at the high concentration for any tester strain tested. You stated that concentrations "up to a concentration just below that which was insoluble in agar" were used. However, if insolubility was the concentration-limiting factor, some degree of precipitation should have been demonstrated at the high-concentration for each tester strain, with and without metabolic activation.

- the mouse lymphoma gene mutation assay and the in vitro chromosomal aberrations assays were inadequate due to the presence of precipitate at all concentrations tested. You attributed this to the low aqueous solubility of ziprasidone under the conditions of each assay; however, there was no documentation that solubility could not have been increased by use of a different vehicle.

- in the in vitro chromosomal aberration assays, higher drug concentrations should have been used in the presence of metabolic activation (the Mitotic Index was >50% of control at the high concentrations tested).

- the in vivo chromosomal aberration assays were inadequate because only one-half of the recommended number of metaphases per animal was analyzed and only one dose level was used (three dose levels are recommended if toxicity can be demonstrated, cf. OECD Guidelines).

Since the Ames test and the in vitro gene mutation and chromosomal aberration assays were positive, they do not need to be repeated. The in vivo chromosomal assay, however, was negative. Therefore, the in vivo assay must be repeated. Of the studies conducted, those comprising a standard battery of genotoxicity tests (cf. ICH Guideline, Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals) must be repeated. This is not a condition for NDA approval, but need to be conducted as a Phase 4 commitment.

Once we have resolved all labeling/proprietary name issues, we request that you submit 20 paper copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format -NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Steven D. Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5525.

Sincerely,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures

32 pages redacted from this section of the approval package consisted of draft labeling