020919_ORIGINAL APPROVAL_PACKAGE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

20-919

Trade Name: Geodon Injection

Generic Name(s): (ziprasione mesylate)

Sponsor: Pfizer, Inc.

Agent:

Approval Date: June 21, 2002

Indication: Provides for the treatment of acute agitation in schizophrenic patients for whom treatment is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation

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APPLICATION NUMBER:

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20-919

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-919

Pfizer, Inc.
Attention: Nickie V. Kilgore, D.V.M.
Senior Associate Director, Worldwide Regulatory Affairs
50 Pequot Avenue MS6025-B2168
New London, CT 06320

Dear Dr. Kilgore:

Please refer to your new drug application (NDA) dated December 17, 1997, received December 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Geodon (ziprasidone mesylate) for Injection.

We acknowledge receipt of your submissions dated December 21, 2001, February 13, 2002, March 21, 2002, March 31, 2002, June 7, 2002, and June 12, 2002. Your submission of December 21, 2001 constituted a complete response to our March 6, 2001 action letter.

This new drug application provides for the use of Geodon (ziprasidone mesylate) for Injection for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation.

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, text for the patient 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 the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-919." Approval of this submission by FDA is not required before the labeling is used.

Phase IV Commitment

The pharmacokinetic data submitted do not provide a justification for eliminating our recommendation for an assessment of the reproductive toxicity of IM ziprasidone [to include dosing during all stages of development]. The recommendation was made based on a concern that SBECD may affect the

reproductive toxicity potential of ziprasidone, particularly considering that ziprasidone and SBECD, each alone produces adverse effects on reproduction.

Therefore, we remind you of your postmarketing study commitment (email of June 19, 2002) to conduct an assessment of the reproductive toxicity of IM ziprasidone. This study should be conducted Phase 4 using ziprasidone in combination with SBECD. If formulation problems are potentially dose-limiting, you should consider alternative dosing regimens, e.g., b.i.d. dosing. Please refer to the ICH document, Detection of Toxicity to Reproduction for Medicinal Products [ICH-S5A, Sept 1994] for guidance.

Submit clinical protocols to your IND for this product. Submit non-clinical and chemistry, manufacturing, and controls protocols, and all final study 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."**

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). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until June 2005. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a

Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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,

{See appended electronic signature page}

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

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/21/02 07:50:34 AM

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-919

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-919

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

Dear Dr. Ritrovato:

Please refer to your new drug application (NDA) dated December 17, 1997, received December 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Geodon (ziprasidone mesylate) Intramuscular Injection.

We acknowledge receipt of the following submissions:

February 5, 1999	May 4, 1999	August 25, 1999
March 10, 2000	April 17, 2000 (2)	May 19, 2000
June 2, 2000	September 6, 2000	September 29, 2000
October 3, 2000	November 21, 2000	December 22, 2000
January 2, 2001	February 9, 2001	

Your submission of September 6, 2000, constituted a complete response to our action letter of December 17, 1998.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, you must address several outstanding concerns related to the capacity of IM ziprasidone to prolong the QTc interval.

Specifically, you have provided relatively little empirical data assessing the effects of IM ziprasidone on the QTc interval at Tmax. As far as we can determine, there are 12-14 patients who have had EKGs performed within 2 hours of a second 20 mg dose given 4 hours after the first dose (the maximum recommended daily dose). This experience is insufficient to adequately assess the effects of the maximum plasma level achieved at this dose on the QTc interval. Indeed, on average, the plasma level at 2 hours after dosing with IM ziprasidone may be as little as one-half the Cmax, so it is not even clear how many of these few patients actually have had EKGs performed at relevant plasma levels. Therefore, it will be critical for you to submit an adequate assessment of the effects of IM ziprasidone on the QTc interval at Tmax after a second 20 mg IM dose. This is especially important because we cannot assume that the risk of a given plasma level is the same when achieved after an IM dose compared to an oral dose, given the much shorter Tmax for the IM

compared to the oral (about 1 hour or less vs about 6 hours, respectively).

Further, you have provided no empirical plasma level data at Tmax following a second 20 mg dose of IM ziprasidone. While we acknowledge the simulations you have performed and submitted (via fax on 2/26/01), and while we have not yet had an opportunity to review this submission, it is unlikely that these simulations will be considered an adequate substitute for empirically derived plasma level data at this critical time point.

In this regard, it will be important for you to address the question of patients who may achieve Cmax plasma levels considerably greater than the mean. Even if we were to conclude that the Cmax's seen after the maximum IM dose were approximately equal to the maximum plasma levels achieved with oral ziprasidone, we would need to be reassured that the highest plasma levels achieved after maximum IM dosing are not only no greater than those achieved after maximum oral dosing, but that there are not an increased number of patients who might achieve these levels after IM compared to oral dosing.

We recognize that you may feel that the decreased time spent at plasma levels near Cmax with IM dosing compared to oral dosing may lessen the risk of a given plasma level. However, unless you can submit data that support this conclusion, we are hesitant to accept its validity.

We expect that these issues can be adequately addressed only with data from additional studies. We urge you to consult with us before you prepare your response to this letter, and especially on the design of such studies.

Pharmacology / Toxicology

We remind you that an assessment of reproductive toxicity of IM ziprasidone [to include dosing during all stages of development] needs to be conducted as a Phase 4 commitment (cf. Agency's action letter, December 17, 1998). Please refer to the ICH document, Detection of Toxicity to Reproduction for Medicinal Products [ICH-S5A, Sept 1994], for guidance.

Please submit final toxicokinetic data for the 1-month IM toxicity studies in rat and dog. The reports submitted for both of these studies stated that, "Due to a lack of long term stability data at the time of submission of this report, final reported serum concentrations may change slightly."

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 has been approved by any non-US regulatory bodies, we ask that you provide us any approved labeling for ziprasidone along with English translations when needed.

World Literature Update

Prior to the approval of ziprasidone, we require an updated report on the world 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 pre-clinical 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.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

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

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

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., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

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

_____ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

35 § 552(b)(5) Draft Labeling