CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-483

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-483 SUPPL # 000 HFD # 130

Trade Name Geodon Oral Suspension 10 mg/ml

Generic Name ziprasidone HCL

Applicant Name Pfizer

Approval Date, If Known March 29, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Protocol A1281131 was a food effect and bioavailibity study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Keith Kiedrow, PharmD
Title: Regulatory Project Manager
Date: March 29, 2006

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Thomas Laughren
3/29/2006 02:32:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-483

Pfizer Global Research & Development
Attention: Christopher L. McCawley, MS, VMD
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Dear Dr. McCawley:

We acknowledge receipt on September 30, 2005, of your resubmission of September 29, 2005, to your new drug application for Geodon (ziprasidone hydrochloride) Oral Suspension.

We consider this a complete response to our action letter of November 21, 2003. Since a reinspection is necessary, your resubmission is classified as a Class 2. Therefore, the user fee goal date is March 31, 2006.

If you have any questions, call LT Keith Kiedrow, Pharm.D., Regulatory Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

CAPT Steven D. Hardeman, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Steve Hardeman
10/19/2005 10:38:14 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-483

Pfizer Global Research & Development
Attention: Brian A. Green, M.S.
50 Pequot Avenue
New London, CT 06320

Dear Mr. Green:

Please refer to your new drug application (NDA) dated September 26, received September 27, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act Geodon (ziprasidone HCl) 10 mg/mL Oral Suspension.

We acknowledge receipt of your submissions dated October 17, 2002, February 4 and 24, May 5 and 22, June 3, 16, 18, 25, and 27, and July 10, 2003.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Deficient Bioequivalence Study

This submission included study reports on 4 bioequivalence studies (3 single dose, 1 multiple dose). The Agency considers only two of the studies, Study 128-056 (single dose) and Study A1281037 (multiple dose), relevant to the drug product under consideration based on the proportional similarity of composition of the to-be-marketed formulation. Of these two studies, we consider the single dose bioequivalence study, 128-056, to be the pivotal study since the FDA Guidance - Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations recommends that single dose BE studies are generally more sensitive to detect the true formulation difference.

Our Division of Scientific Investigations completed their review of your pivotal single dose BE study, 128-056, and has found the study is not acceptable for review. Specifically, the quality control (QC) results are insufficient to demonstrate the accuracy of the ziprasidone data obtained in Protocol 128-056. Among three QC samples, only one QC sample (low QC) was relevant to the plasma ziprasidone levels observed in this study. Furthermore, for [redacted] analytical runs, at least one low or mid QC failed because the result was greater than [redacted] error or failed due to other processing errors. Since several low and mid QCs failed, the QC results are insufficient to demonstrate the accuracy of the ziprasidone data obtained in Protocol 128-056.

Although the multiple dose study showed that the suspension is bioequivalent to the capsule, we believe that a multiple dose study design is less sensitive to detect formulation differences *in vivo*.

In addition, the 90% confidence interval for the ratio of test/reference (suspension compared to capsule) for Cmax marginally meets the 80-125 BE criterion (80.1 – 100.3%). Even though these results nominally meet bioequivalence standards, the data suggest potential *in vivo* differences of the suspension that should be adequately characterized, especially in the absence of a reliable single dose study. Therefore, it is important to evaluate the *in vivo* differences between ziprasidone suspension and capsule in a well-conducted single dose bioequivalence study.

In order to evaluate the true formulation difference between two formulations and to support the approval of the suspension formulation strictly from a bioequivalence (BE) standpoint, you will need to conduct another single dose BE study. The single dose BE study should be conducted under fasted conditions using the to-be-marketed suspension formulation manufactured at the proposed commercial manufacturing site (Pfizer Inc., Lititz, PA) and compare it to the reference product.

In addition, the food-effect on the to-be-marketed suspension formulation should be evaluated.

In the future, you should, to the extent of your knowledge, include three QC samples within the expected plasma levels of drug of interest in the study (Consult the Bioanalytical Method Validation Guidance published in May 2001 for reference). This means that more than three QC samples may be needed if a broader range of standard curve was validated previously and subjects' samples are skewed. In this specific NDA, a total of three QC samples were included in the bioanalytical assay for two BE studies (128-056 & A1281037) in support of the approval of the new suspension formulation. However, only one QC sample fell within the range of the plasma levels observed in study 128-056 & two QC samples fell within the range of the plasma levels observed in study 1281037.

Chemistry, Manufacturing, and Controls (CMC) Information Deficiencies

1. In the DESCRIPTION section of the draft package insert, correct the spelling of the inactive component, propylparaben.

2. Please submit the Letter of Authorization(s) for the Type III DMF(s) for the associated packaging component, Exacta-Med Oral Dispenser (2 mL and 8 mL).

3. Please refer to pages 565 – 599 in Volume 1.3, Specifications, Test Procedures, and Results for the components of the drug product.

4. [redacted]

5.

6. Submit updated stability data (primary and supportive). A value of 0% is not acceptable for reporting an analytical result lower than the Limit of Detection. In the updated stability data, report the value as either less than the Limit of Detection (LOD) or less than the Limit of Quantitation (LOQ).

7. Please refer to your April 4, 2003 response to the CMC question via the FDA inspector. In order for the Agency to state that Lot QCRS7G184-19QCS (Source: Lot 32,389-69-1F) is of acceptable identity, strength, quality, purity, and potency, provide the assay results for this drug substance lot. The Agency notes that the retest date for ziprasidone hydrochloride monohydrate (NDA 20-825) remains unchanged.

8. The proposed specification (release and stability) of [redacted] maximum for [redacted] should be tightened to [redacted] maximum as recommended by ICH Q3B [Impurities in New Drug Products], or you may provide data demonstrating that this impurity has been qualified to the [redacted] limit.

9. Refer to pages 83 and 84 in Volume 1.2. Repeat the compatibility experiment using the final commercial formulation with both the 2 mL and 8 mL oral dispensers.

Microbiology Deficiencies

1. Please provide a description of the manufacturing facility and the cleaning, sanitation, disinfection, and manufacturing procedures designed to limit microbial contamination in the drug product.

2. A microbial limit of [redacted] CFU for total aerobic microorganisms is too high for an aqueous oral drug product.

3. Microbial limits testing on only one batch per year is unacceptable. Microbial limits testing should be conducted on a batch by batch basis until a product history is established.

4. Microbial limits testing should be included in the stability protocol.

5. Please provide the results of preservative effectiveness testing for the drug product.

Other Comments Not Pertaining to the Not Approval Action
***In Vitro* Dissolution Method and Specifications**

- We find your proposed dissolution method acceptable: USP apparatus II, paddle speed 100 rpm, 900 ml 0.05 M NaH2PO4 pH 7.5 buffer with 2% sodium dodecylsulfate(SDS) at 37°C, bottom sample introduction. However, based on the dissolution profiles from the biobatch, we are requesting that you agree to tighten the dissolution specification from Q= [redacted] at 30 minutes to Q= [redacted] at 30 minutes.

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 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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 this 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

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/s/

Russell Katz
7/18/03 08:11:49 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-483

INFORMATION REQUEST LETTER

Pfizer Global Research & Development
Attention: Christopher L. McCawley, MS, VMD
Associate Director, Worldwide Regulatory Strategy
50 Pequot Avenue
New London, CT 06320

Dear Dr. McCawley:

Please refer to your September 26, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Geodon (ziprasidone HCl) Oral Suspension.

We also refer to your submission dated December 15, 2004.

We have completed our review of your submission and have the following comments:

- Sponsor's Question :

  Does the division concur that Pfizer has adequately characterized the in-vivo performance of the oral suspension relative to the capsule and that no additional studies are required to support the approval of N21- 483. If not, what course of action is required to secure NDA approval?

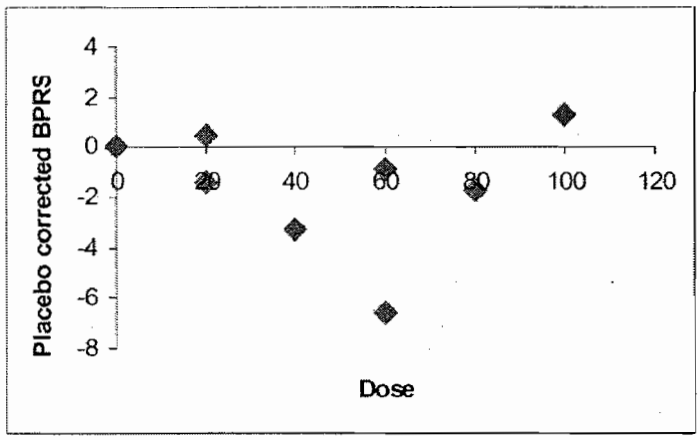
- Agency Response :

  Based on the brief preliminary report submitted, it appears that you have adequately characterized the in-vivo performance of the oral suspension relative to the capsule and that no additional studies are required at this time. You should amend your application with a resubmission to contain a complete response to the action letters of July 18, 2003 and November 21, 2003. Your resubmission should include a complete report of the BE and food effect study, electronic data set as SAS transport files, complete assay validation report, proposed labeling and should also provide global arguments to support that the differences observed in Cmax (10-17% lower across studies) and AUC are clinically irrelevant.

We note that you have conducted modeling and simulation to support that the differences in Cmax are unlikely to be clinically relevant. Although we are not certain if modeling and simulation results provided in this submission are critical to the regulatory decision regarding

clinical relevance of Cmax, we would like to share our initial thoughts on the preliminary information submitted regarding this modeling and simulation.

The labeled doses do not show a clear dose response relationship (see the figure below from studies 106, 114 and 115 used in the modeling and simulation report).



1. Based on the model, the concentration needed to achieve half maximal effect (DC50) was 6700 mcg/L, which was about 20-fold higher than the observed plasma concentrations, which is unrealistic. Before the simulation results can be used to justify the failed BE study (i.e. clinical relevance of lower Cmax), the modeling results need to be thoroughly reviewed. Any further discussion regarding this would be part of the NDA review.

2. We request that you submit all appropriate NONMEM data sets and control streams in electronic format as XPT and TXT files.

3. In addition to the modeling and simulation report, you should provide global arguments regarding the clinical relevance of the lower Cmax observed with the oral suspension.

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

Sincerely,

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

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/s/

Russell Katz
4/26/05 08:41:32 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-483

INFORMATION REQUEST LETTER

Pfizer Global Research & Development
Attention: Brian A. Green, M.S.
Associate Director I, Regulatory Strategy
Policy and Registration
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Dear Mr. Green:

Please refer to your new drug application (NDA) dated September 26, 2002, and received September 27, 2002 that was submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for GEODON® (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL.

We acknowledge the amendment dated February 4, 2003.

We are reviewing the chemistry, manufacturing, and controls section of your submission and have the following questions. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the current specifications for the following:
    a. NDA 20-825, GEODON® (ziprasidone hydrochloride) Capsules, 20mg, 40mg, 60mg, and 80mg.

    b. NDA 20-919, GEODON® (ziprasidone mesylate) IM, 20mg/mL.
        1. ziprasidone mesylate drug substance

If you have any questions, call Donald N. Klein, Ph.D., Review Chemist, at (301)594-5537.

Sincerely,

Thomas F. Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Thomas Oliver
4/21/03 07:52:45 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-483

INFORMATION REQUEST LETTER

Pfizer Global Research & Development
Attention: Brian A. Green, M.S.
Associate Director I, Regulatory Strategy
Policy and Registration
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Dear Mr. Green:

Please refer to your new drug application (NDA) dated September 26, 2002, and received September 27, 2002 that was submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for GEODON® (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL.

We acknowledge the amendment dated February 4, 2003.

We are reviewing the chemistry, manufacturing, and controls section of your submission and have the following questions. We request a prompt written response in order to continue our evaluation of your NDA.

1. Refer to page 605 in Volume 1.3. Provide a copy of the most current batch record, either executed or master.

2. Provide a copy of the Certificate of Analysis of each drug substance lot used in the manufacture of each drug product lot presented in the NDA submission. Specifically, the drug product lots submitted as supportive stability data and the drug product lots submitted as the primary stability data.

If you have any questions, call Donald N. Klein, Ph.D., Review Chemist, at (301)594-5537.

Sincerely,

Thomas F. Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Thomas Oliver
4/21/03 07:58:59 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Donald N. Klein, Ph.D., HFD-120, Tel. No. (301)594-5537
(Reviewing Chemist) (Fax) (301)594-2859

Through: Thomas F. Oliver, Ph.D., HFD-120, Tel. No. (301)594-5551
(Chemistry Team Leader)

SUBJECT: Methods Validation for NDA No. 21-483
Product: GEODON (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL
Applicant: Pfizer Inc
Address: 50 Pequot Avenue
New London, CT 06320

TO: Northeast Regional Laboratory, HFR –NE560 4/11/03
(FDA Method ValidationLaboratory)

Date NDA Received by CDER: 9/27/02 Chemical/Therapeutic Type 3S

Special Handling Required: none listed

DEA Class N/A PAC: 46832 (NDA's)

This is to confirm the suitability of the proposed manufacturing controls as described in the subject application. The samples identified in the attached Form 2871a (Methods Validation Request and Reporting Record) will be provided to you by the applicant. Please perform the tests indicated in item 3 of 2871a as described in the accompanying MV package, and summarize your laboratory results in item 4. Also, please include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

Because of statutory time limits for processing applications, we request your report to be submitted promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. Please promptly advise the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist.
The statutory reviewing period ends July 27, 2003.

Upon completion of the requested validation/verification, please assemble the necessary documentation (i.e., the original signed 2871a with original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying memoranda). At the bottom of the report signed by the laboratory director, place the filing code: **"MR/Method Validation Report."** Send by overnight courier to the above reviewing chemist.

ENCLOSURE: Form 2871a and NDA/ANDA Methods Validation Package.

Form 2871 (8/96)

G.T. No. 93-3
Originator:

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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/s/

Thomas Oliver
4/21/03 07:49:37 AM

Date: April 11, 2003

To: Food and Drug Administration Method Validation Laboratory
Northeast Regional Laboratory, HFR-NE500
158-15 Liberty Ave.
Jamaica, NY 11433
Attention: Method Validation Chemist

From: Donald N. Klein, Ph.D., Review Chemist, HFD-120

Through: Thomas F. Oliver, Ph.D., Chemistry Team Leader, HFD-120

Subject: Laboratory Assignments for NDA Methods Validation (MV)

NDA No: 21-483 **Product**: GEODON (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL

Applicant: Pfizer Inc.

Attached is one method validation (MV) package with MV request forms (2871 & 2871a) and a Receipt of Samples Form.

As a part of the NDA review, validation of the analytical methods submitted by the applicant is required. To help accomplish this, Compliance Program (CP 7346.832) requires the review chemist in the Office of New Drug Chemistry to initiate this validation. In this regard, the appropriate laboratories referenced above are requested to perform the NDA method validation testing.

Northeast Regional Laboratory, HFR-NE560, is asked to send a letter to the applicant requesting the samples as required by the compliance program [CP 7346.832]. The letter should be directed to:

Pfizer Global Research & Development
Attention: Brian A. Green, M.S.
Associate Director I, Regulatory Strategy
Policy and Registration
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Phone: (860)732-0959

Samples should be directly sent to the laboratory named above. When samples have been received by the FDA Laboratory, the Receipt of Samples Form should be returned to the reviewer.

All investigational and analytical work conducted under this assignment should be charged to PAC 46832.

Donald N. Klein 4/11/03
Donald N. Klein, Ph.D., Review Chemist, HFD- 120

cc: NDA 21-483
HFD-120/T.Oliver
HFD-120/P.David
HFD-120/D.Klein
HFD-354/Compendial Operations
HFC-140/Division of Field Science
HFD-920/Division of Testing and Applied Analytical Development
HFR-NE560/ Northeast Regional Laboratory

RECEIPT OF SAMPLES

Upon receipt of samples by the Method Validation Laboratory, this form should be returned to the reviewer.

From: Food and Drug Administration Method Validation Laboratory
Northeast Regional Laboratory, HFR-NE500
158-15 Liberty Ave.
Jamaica, NY 11433

To: Donald N. Klein, Ph.D.,
Review Chemist, HFD-120
Fax: (301)594-2859

NDA: 21-483

Product: GEODON (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL

Applicant: Pfizer Inc.

Date of Receipt of Samples: _____

Signature of Receiver: _____

Klein, Donald N

From: Klein, Donald N
Sent: Friday, April 04, 2003 2:03 PM
To: Cooney, Peter H
Cc: Hardeman, Steven D; Oliver, Thomas F
Subject: FW: FW EDR - NDA 021483 from PFIZER GLOBAL drug name GEODON (ZIPRASIDONE HCL) ORAL


FW: EDR - NDA 021483 from PFIZ...


N21483(BC)dated2040 3primarysta...


N21483MicroConsult4 0403.PDF

Peter,

Attached is the pdf for a Micro. consult for NDA 21-483. I'm forwarding the EDR as well as the 3 month primary stability data (2/4/03 amendment (BC)) received on 2/12/03. The applicant had to change the formulation due to a reaction of the flavorant component with the drug substance yielding new impurities [redacted] in the drug product. This is the reason we have only [redacted] months of stability data after the NDA was received on 9/27/02. The original application stability data with the old formulation [redacted] new impurities is considered supportive stability data.

Don Klein
Review Chemist, HFD-120

-----Original Message-----
From: Hardeman, Steven D
Sent: Friday, October 04, 2002 1:29 PM
To: Klein, Donald N
Subject: FW EDR - NDA 021483 from PFIZER GLOBAL drug name GEODON (ZIPRASIDONE HCL) ORAL

FW EDR - NDA 021483 from PFIZER GLOBAL drug name GEODON (ZIPRASIDONE HCL) ORAL SUSP

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-805, Microbiology Division			FROM: Don Kleyn, HFD-120	
DATE: 4/4/03	~~END NO.~~	NDA NO.: 21-483	TYPE OF DOCUMENT: Original NDA (BC) Amdt	DATE OF DOCUMENT: 9/27/02; 2/5/03
NAME OF DRUG: Geodon (ziprasidone HCl) Oral Spansule 35	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG: treatment of schizophrenia	DESIRED COMPLETION DATE: 6/1/03
NAME OF FIRM: Pfizer Inc.				(PDUFA date is 7/29/03)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER (SPECIFY BELOW): dry product Microbiology; specifications and stability testing.

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please evaluate the proposed dry product specifications limits for MICRO issues as well as the stability testing (refer to the 2/5/03 Amendment (primary stability data).

SIGNATURE OF REQUESTER: Donald M. Kleyn 4/4/03	METHOD OF DELIVERY (Check one): ☒ MAIL (e-mail) ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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

/s/

Thomas Oliver
5/22/03 02:30:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-483

INFORMATION REQUEST LETTER

Pfizer Global Research & Development
Attention: Brian A. Green, M.S.
Associate Director I, Regulatory Strategy
Policy and Registration
Worldwide Regulatory Affairs
50 Pequot Avenue
New London, CT 06320

Dear Mr. Green:

Please refer to your new drug application (NDA) dated September 26, 2002, and received September 27, 2002 that was submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for GEODON® (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL.

We acknowledge the amendments dated October 17, 2002, February 4, 2003, and May 5, 2003.

We are reviewing the chemistry, manufacturing, and controls section of your submission and have the following questions. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide actual samples of the GEODON® (ziprasidone hydrochloride) Oral Suspension packaged in the to be marketed container closure system [redacted]. Send 2 samples of each to the following address:

   Donald N. Klein, Ph.D.
   Review Chemist
   1451 Rockville Pike
   HFD-120
   Rockville, MD 20852

2. [redacted]

If you have any questions, call Donald N. Klein, Ph.D., Review Chemist, at (301)594-5537.

Sincerely,

Thomas F. Oliver, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
HFD-120
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

/s/

Thomas Oliver
5/20/03 07:21:36 AM

Groton Laboratories
Pfizer Inc
Eastern Point Road
Groton, CT 06340

Pfizer

Global Research & Development

Received 5/7/03

05 May 2003

Ella S. Walker
Food and Drug Administration
Northeast Regional Laboratory
158-15 Liberty Avenue
Jamaica, New York 11433

RE: NDA 21-483 Geodon (ziprasidone hydrochloride) Oral Suspension, 10 mg/mL

Dear Ms. Walker:

Enclosed is the necessary documentation and samples that were requested by FDA for performing method validation studies for Geodon Oral Suspension, 10 mg/mL.

In Section 4.5, *Samples and Methods Validation Package*, of the Geodon Oral Suspension NDA which your laboratory has received, complete, up-to-date information is provided for performing the proposed commercial testing of Geodon Oral Suspension, including all necessary test procedures and their respective validations.

In response to the items requested:

- Samples of the dosage form and non-compendial reference standards, sufficient to perform analysis in triplicate, are provided. A complete listing of the samples provided is included on the following page.
- The test procedures provided in Section 4.5.4, *Specification and Analytical Methods*, contain representative calculations, spectra and chromatograms, where applicable.
- The Pfizer test results for the dosage form lot provided in this registration package are included in Section 4.5.3, *Test Results*.
- Handling information (Material Safety Data Sheets) for the applicable compounds are appended to this document.

The samples included in this registration package are listed below with lot numbers and quantities provided and include enough sample to perform the required testing [redacted]

Identity	Lot Number	Quantity Provided
Reference Standard		
Drug Product Reference Standards	[redacted]	
Drug Product	Ziprasidone Hydrochloride Oral Suspension, 10 mg/mL	

Please feel free to contact me if you have any additional questions regarding the validation of the test procedures for Geodon Oral Suspension.

Sincerely,

Debra Webb
Regulatory CMC
(860) 715-2958

cc: Dr. Donald Klein, (FDA Reviewing Chemist)
R. Nosal (Pfizer)
C. Wood (Pfizer)
R. Orciari (Pfizer)
J. Dossena (Pfizer)
File 128 OS, SC
D. Beaulieu (Pfizer)
D. Arenson (Pfizer)
D. Wu-Linhares (Pfizer)
R. Reimer (Pfizer)
B. Green (Pfizer)

Appended Material Safety Data Sheets (MSDS)

Included in this attachment are the following:

- MSDS for Ziprasidone Hydrochloride Oral Suspension
- MSDS for Ziprasidone Hydrochloride
- MSDS for CP-78,459-1

22 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

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/s/

Donald Klein
5/7/03 12:36:17 PM
CHEMIST

D.Klein received this communication from Pfizer via regular mail on 5/7/03. This information pertains to the NDA 21-483 method validation.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-483

Pfizer Global Research & Development
Attention: Brian A. Green, M.S.
50 Pequot Avenue
New London, CT 06320

Dear Mr. Green:

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:	Geodon (ziprasidone HCl) 10 mg/mL Oral Suspension.
Review Priority Classification:	Standard (S)
Date of Application:	September 26, 2002
Date of Receipt:	September 27, 2002
Our Reference Number:	NDA 21-483

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 26, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 27, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products / HFD-120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products / HFD-120
Attention: Document Room, 4008
1451 Rockville Pike
Rockville, Maryland 20852

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}

Robbin Nighswander, R.Ph.
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Steve Hardeman
10/31/02 11:52:20 AM
Signed for Robbin Nighswander, R.Ph., CPMS