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APPLICATION NUMBER:

21-483

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-483
Drug:	Ziprasidone Oral Suspension, 10 mg/mL
Brand Name:	Geodon [®]
Sponsor:	Pfizer
Indication:	Treatment of Schizophrenia
OND Clinical Division:	DPP (HFD-130)
OCP Division:	DCPB 1 (HFD-860)
Submission Type:	Response to Non Approval Letter
Submission Date:	9/29/05
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader (Acting):	Andre Jackson, Ph.D.

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1. Executive Summary

1.1. Recommendation

Ziprasidone Oral Suspension is not bioequivalent to the approved ziprasidone oral capsules based on standard regulatory methods and criteria. In a single dose study under fasting conditions, the C_{max} and AUC(_∞) were 17% and 13% lower, respectively, for ziprasidone oral suspension compared to the capsule formulation. There was insufficient evidence in previous or this submission, from a clinical pharmacology perspective, to determine the clinical relevance of the difference in exposure (C_{max} and AUC) observed when ziprasidone oral suspension and capsules are compared.

Refer to Section 2.0 of Review for Comments on the Proposed Label

1.2. Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.2.1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this submission?

Background: Ziprasidone (Geodon) oral capsules were approved for the treatment of schizophrenia in February 2001. The recommended starting dose is 20 mg bid with food, and based on individual response, the daily dose may be titrated up to 80 mg. Ziprasidone capsules are available in strengths of 20, 40, 60, and 80 mg capsules. Food administration with Ziprasidone capsules 20, 40, and 80 mg was associated with increases in AUC of 46%, 88% and 101%, respectively. And increases in C_{max} of 9%, 61% and 96% for the 20 mg, 40 mg and 80mg capsules, respectively.

The sponsor submitted NDA 21-483 for Ziprasidone Oral Suspension on September 26, 2002. The Agency issued a Non-Approval (NA) letter on 7/18/03. The sponsor sought the approval of the oral suspension based on bioequivalence studies. Clinical safety and efficacy studies were not conducted. In the NA letter, the pivotal single dose bioequivalence study was not acceptable for review. It was determined that the quality control results were insufficient to demonstrate the accuracy of the ziprasidone data obtained in the study (Refer to NA letter and Clinical Pharmacology/Biopharmaceutics (CPB) review of the original NDA (9/26/02) for details). Due to the lack of a reliable single dose BE study comparing the Ziprasidone suspension to the currently marketed capsule, the sponsor was advised to conduct another single dose study under fasting conditions and also evaluate the effect of food on the to be marketed formulation.

The sponsor submitted a response to the NA letter for NDA 21-483 on September 29, 2003. The sponsor argued against the need for a single dose BE study. In this submission, the sponsor argued that a multiple dose BE study conducted under fed conditions submitted in the original NDA should be considered the pivotal study and should be the primary basis for approval of the Ziprasidone oral suspension. Hence, the sponsor argues that they should not be required to do an additional single dose study under fasting conditions (Refer to CPB review of 11/6/03 submission for details).

After review of the sponsor's rationale for not conducting an additional single dose study and to use the multiple dose study as the basis for approval, it was concluded that the reasons were inadequate and a 2nd NA letter was issued. The Agency noted that in order to evaluate the true

formulation difference between the two formulations and to support the approval of the suspension formulation strictly from a bioequivalence standpoint, the sponsor will need to conduct another single dose BE study. The single dose BE study should be conducted under fasting conditions using the to-be-marketed suspension formulation manufactured at the proposed commercial manufacturing site and compared to the reference product. In addition, the food effect on the to be marketed suspension formulation should be evaluated.

On 12/15/04, the sponsor submitted a preliminary report of a single dose BE study and a rationale why C_{max} was not important in determining in vivo performance of ziprasidone after administration of an oral suspension. The Agency responded that “based on the brief preliminary report submitted, it appears that the sponsor has adequately characterized the in vivo performance of the oral suspension relative to the capsule and that no additional studies are required at this time. However, this does not imply that the sponsor secures an approval status for NDA 21-483. Approval decision and labeling are part of review that will occur when the complete response to the non-approval letter is submitted. The Agency stated in its response that before the simulation results can be used to justify the failed BE (i.e. clinical relevance of lower C_{max}), the modeling results need to be thoroughly reviewed. The sponsor stated in the resubmission that the PK/PD modeling was supportive and not critical to the regulatory decision regarding approval and therefore was not included in this resubmission. In addition to the modeling and simulation report, it was recommended that the sponsor should provide global arguments regarding the clinical relevance of the lower C_{max} observed with the oral suspension. The sponsor submitted an analytical validation report in the submission. The reviewer commented that the analytical report seems adequate in its validation parameters.” (Refer to CPB review of 4/12/05 submission for details). This submission includes the Final Study Report for protocol A1281131 for which summary data was previously reviewed. The submission also includes a response to the Agency’s recommendation to the sponsor to provide global arguments to support the rationale that the differences observed in C_{max} (10-17% across studies) and AUC are clinically not relevant.

1.2.2. Is the Ziprasidone Oral Suspension Bioequivalent to the approved Ziprasidone Oral Capsule?

Ziprasidone Oral Suspension (OS) was found not to be bioequivalent to the approved oral capsule. The 90% CIs for C_{max} and AUC(∞) were not contained entirely within 80% to 125% regulatory limits. The C_{max} and AUC(∞) of Ziprasidone were 17% and 13% lower respectively, for OS compared to the capsule.

The sponsor conducted a single dose study (Protocol A1281131) that evaluated the effect of food on the oral suspension and evaluated whether the oral suspension was bioequivalent to the approved capsule formulation. This study was an open-label, 3-period crossover study designed to compare 3 treatments. The 3 treatments are: 1) 20 mg OS (2 mL of 10 mg/mL) under fasting conditions 2) 20 mg OS (2 mL of 10 mg/mL) under fed conditions and 3) 20 mg capsule (1 x 20 mg) under fasting conditions. There was a 3 day washout period between treatments. Fourteen subjects (2 subjects within each treatment sequence) were assigned randomly to receive the 3 treatments in 1 of 6 treatment sequences. Statistical analyses from study A1281131 are provided in Tables 1 and 2.

Table 1: Statistical Analyses of PK Parameters of Ziprasidone after Administration the Oral Suspension Compared to the Oral Capsule

Pharmacokinetic Parameter	Adjusted Geometric Means		Point Estimate	90% CI
	Ziprasidone OS Fasted (Test) (N=13)	Ziprasidone Capsule Fasted (Ref.) (N=13)		
C _{max} (ng/mL)	24.5	29.7	82.68	67.35, 101.50
AUC(∞) (ng*h/mL)	212.0	242.7	87.36	76.92, 99.23
AUC(0-T) (ng*h/mL)	203.1	228.1	89.05	77.56, 102.24

1.2.3. Does Food have an effect on Ziprasidone Pharmacokinetics?

A high fat meal increased the C_{max} and AUC (∞) of ziprasidone following administration of the OS by 63% and 97%, respectively. The increase in ziprasidone concentration after a high fat meal is similar to that observed when ziprasidone capsules are administered with a high fat meal. Statistical analyses to evaluate the effect of a high fat meal is provided in the following table.

Table 2: Statistical Analyses of C_{max}, AUC(∞), and AUC(0-T) for Ziprasidone OS Food Effect

Pharmacokinetic Parameter	Adjusted Geometric Means		Point Estimate	90% CI
	Ziprasidone OS Fed (Test) (N=13)	Ziprasidone OS Fasted (Ref.) (N=13)		
C _{max} (ng/mL)	40.0	24.5	163.03	133.18, 199.57
AUC(∞) (ng*h/mL)	417.3	212.0	196.83	173.64, 223.13
AUC(0-T) (ng*h/mL)	408.5	203.1	201.09	175.52, 230.37

1.2.4. What is the sponsor's rationale that the results are not clinically relevant even though the 90% CI for C_{max} and AUC are not contained in the regulatory criteria of 80 to 125%?

The sponsor argues that the fact that in study A1281131 the 90% CI around the point estimate for AUC and C_{max} are not contained within the regulatory criteria for bioequivalence is not clinically relevant under conditions of actual use of Ziprasidone. C_{max} is 10 -17% lower after administration of the OS compared to the capsule formulation. The sponsor states that study A11281131 was designed to evaluate the effect of food and was not powered to demonstrate bioequivalence between the OS and capsule formulations. The sponsor still maintains that other studies, in particular the multiple dose study submitted in the original application, should be considered the primary basis for approval. However, the Agency has reviewed these studies and determined that they are inadequate to support approval of Ziprasidone OS strictly on the basis of bioequivalence. The previous studies were determined to be inadequate for evaluation of differences in formulation between Ziprasidone capsules and oral suspension. The multiple dose study (A1281037) was determined by the Agency to be supportive and not pivotal. The following table provides a summary of statistical results for bioequivalence studies submitted in previous submissions and this resubmission. Studies 128-056, A1281037 used formulations that were determined to be similar (Study A1281037 had difference in flavoring agent; Study 128-056

had less than 10% difference in excipients) to the commercial formulation. Study A1281131 used the to be marketed formulation. The other studies used pilot formulations.

Table 3: Summary of Statistical Results for Bioequivalence Studies

Study ^e	N	Point Estimate (90% CI) for OS vs. Capsule	
		AUC	Cmax
A1281131 ^a	12	87% (77 – 99%)	83% (67 – 102%)
128-034 ^b	11	94% (90 – 98%)	87% (71 – 106%)
128-056 ^b	12	94% (90 – 99%)	85% (77 – 94%)
128-055 ^{b,c}	12	87% (82 – 93%)	90% (80 – 100%)
A1281037 ^{b,d}	16	96% (86 – 108%)	90% (80 – 100%)

^aFasted conditions; ^bFed conditions; ^cZiprasidone free base; ^dMultiple dose, repeated measure design; ^eSingle dose unless otherwise stated

The sponsor contends that the principal concern about a lower Cmax is the possibility of diminished efficacy. The sponsor states that a review of pharmacodynamic properties of antipsychotic drugs and data obtained from Ziprasidone PET dopamine-D2 occupancy clinical studies suggest that a reduction in Cmax will not impair efficacy. The sponsor states that the range of ziprasidone Cmax achieved with the oral suspension results in a degree of receptor occupancy that is well within the region associated with antipsychotic efficacy. Dopamine-D2 and Serotonin-5HT2 receptor occupancies were evaluated for ziprasidone in several single dose studies in the original application. Sixty five percent occupancy was reported to occur at a ziprasidone concentration of about 35 to 40 ng/mL. This serum concentration is consistent with the trough concentration achieved by the lowest approved dosage regimen of ziprasidone capsules (20 mg BID) which has a mean trough concentration of 37 ng/mL. The sponsor argues that based on the serum concentration – dopamine-D2 receptor occupancy relationships, changes in dopamine-D2-receptor occupancy at therapeutic doses of ziprasidone would be expected to be smaller than the associated changes in Cmax. Hence, small differences in Cmax on the order of those seen with the oral suspension would not be expected to have a clinically meaningful impact in terms of efficacy response. The sponsor again proposes that the Cmax values of interest should be those observed with the clinical regimen (i.e. multiple dose administration under fed conditions).

The sponsor also states that IM depot formulations of other antipsychotics (e.g. risperidone, haloperidol) have reduced Cmax but have been shown to effective antipsychotic.

Despite its value as an index to therapeutic potential, D2 occupancy cannot fully and reliably predict clinical response. The actual mechanism of action of ziprasidone in schizophrenia and bipolar disorder is not known. The receptor occupancy theory presented in this submission is similar to that presented in the original and subsequent submissions. The reviewers determined that the receptor occupancy theory were supportive and not sufficient rationale for approval. This reviewer agrees with the original conclusions.

Kofi A. Kumi, Ph.D. _____

RD/FT Initialed by Andre Jackson, Ph.D. _____

CC: NDA 21-483, HFD-130, HFD-860 (Mehta, Baweja, Jackson, KumiK), CDR (Biopharm)

9 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

3. Appendix

3.1. Ziprasidone Hydrochloride Oral Suspension Commercial and Clinical Formulations

3.2. Individual Study Report: Protocol A1281131

3.3. Summary of Dr. Veneeta Tandon's Review

3.4. Summary of Dr. Wen-Hwei Chou's Review

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2.1. Comparison of Ziprasidone Hydrochloride Oral Suspension Commercial and Clinical Formulations

Table 1: Comparison of Ziprasidone Hydrochloride Oral Suspension Commercial and Clinical Formulations

Formulation Identity	10 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL	40 mg/mL
Component					
Ziprasidone Hydrochloride Monohydrate, Pharm					
Methylparaben, NF					
Propylparaben, NF					
[REDACTED]					
Citric Acid, anhydrous, USP					
Sodium Citrate, USP					
Sodium Chloride, USP					
[REDACTED]					
Xylitol, NF					
[REDACTED]					
Xanthan Gum, NF					
[REDACTED]					
Polysorbate 80, NF					
Colloidal Silicon Dioxide, NF					
[REDACTED]					
[REDACTED] Cherry					
Purified Water, USP					
TOTAL (mg/mL)					

- (a) Equivalent to 10 mg/mL of ziprasidone based on a theoretical potency of [REDACTED] of ziprasidone hydrochloride.
- (b) Used to adjust final batch weight.
- (c) Used to adjust pH if necessary.

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2.2. Individual Report for Single Dose Food Effect and Bioequivalence Study

Title (A1281131): Phase 1, Open-Label Single Dose, Three Treatment, Three Period Crossover Study to Determine the Pharmacokinetic of Ziprasidone Oral Suspension under Fed and Fasting Conditions and of Ziprasidone Capsule under Fasting Conditions in Healthy Subjects

Background: Ziprasidone is an atypical antipsychotic, currently approved for oral administration under fed conditions as Geodon capsules in the treatment of schizophrenia. In order to facilitate dose titration, and for individuals who have difficulty swallowing capsules, an oral suspension (OS) formulation has been developed. For all formulations tested thus far, ziprasidone displays positive food effect. Food administration with single doses of 20, 40, and 80 mg (as capsules) was associated with increases in AUC of 46%, 88%, and 101%, respectively. And, C_{max} increased by 9%, 61% and 96%, respectively. In addition to the positive food effect, oral ziprasidone pharmacokinetics which are non-linear under fasting conditions, become linear with food across the 20 to 80 mg BID clinical dose range. After oral administration of the capsule with food, peak concentrations are reached in about 6 to 8 hours and elimination occurs with a mean half-life of 6.6 hours. Steady state is achieved within 1 to 3 days. The present study was intended primarily to assess the effect of food on the OS, and secondarily to obtain information on the pharmacokinetics of the commercial capsule formulation and OS in the fasted state.

Objectives: 1) Compare the pharmacokinetics of a single oral suspension (OS) dose of 20 mg ziprasidone under fed versus fasting conditions 2) Compare the pharmacokinetics of a single OS dose of 20 mg ziprasidone under fasting conditions versus a single oral dose of ziprasidone 20 mg commercial capsule formulation under fasting conditions.

Study Design: This was an open-label, 3-period crossover study designed to compare 3 treatments. The 3 treatments are: 1) 20 mg OS (2 mL of 10 mg/mL) under fasting conditions 2) 20 mg OS (2 mL of 10 mg/mL) and 3) 20 mg capsule (1 x 20 mg) under fasting conditions. At least, there was a 3 day washout period between treatments. Fourteen subjects (2 subjects within each treatment sequence) were assigned randomly to receive the 3 treatments in 1 of 6 treatment sequences as follows:

Treatment Sequences for 3-Period Crossover Design

Treatment Sequence	Period 1	Period 2	Period 3
1	20 mg OS Fasted	20 mg OS Fed	20 mg CAP Fasted
2	20 mg CAP Fasted	20 mg OS Fasted	20 mg OS Fed
3	20 mg OS Fed	20 mg CAP Fasted	20 mg OS Fasted
4	20 mg CAP Fasted	20 mg OS Fed	20 mg OS Fasted
5	20 mg OS Fed	20 mg OS Fasted	20 mg CAP Fasted
6	20 mg OS Fasted	20 mg CAP Fasted	20 mg OS Fed

OS: Ziprasidone oral suspension, CAP: Ziprasidone oral capsule

Blood samples for pharmacokinetic analyses were collected at predose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours postdose. Vital signs measurements and adverse event (AE) assessments were performed on Day 1 (predose and 6 hours postdose) and Day 2 (36 hours postdose, prior to discharge from the CRU in each dosing period). Ziprasidone OS Lot# 03-002447 (Lot# 90872L-G2) and Ziprasidone capsule Lot # 03-003754 (commercial Lot#: 0394K02A-G1) were used in the study.

Analytical Method: Serum samples were assayed for ziprasidone using solid-phase extraction and a validated LC/MS/MS assay. The assay had a range of 0.5 to 250 ng/mL for ziprasidone concentration. The Lower Limit of Quantitation (LLOQ) was 0.5 ng/mL. The precision of the assay was between 1 to 11.1% and the accuracy was greater than 96%. The analytical method is acceptable.

Data Analysis: Pharmacokinetic parameters were determined using non-compartmental methods. Log transformed (natural log) AUC (∞), AUC (0-T), and C_{max} were analyzed using a mixed effects model containing fixed effects for sequence, period and treatment and random effects for subjects (within sequence). Estimates of adjusted mean differences (Test- Reference) and corresponding 90% confidence intervals were estimated from this model. The estimated difference and 90% confidence intervals for the true difference were exponentiated to derive estimates of the ratio (Test/Reference) of adjusted geometric means and the 90% confidence interval for the true ratio.

Results: Each of the 12 subjects that completed the study was administered a single dose of 20 mg ziprasidone on 3 different occasions separated by 4 or 5-day washout period. The mean serum ziprasidone concentrations versus time profiles following administration of 20 mg ziprasidone OS fasted, 20 mg ziprasidone OS fed and 20 mg ziprasidone capsule fasted are provided in the ATTACHMENT. The following table contains summary statistics for the pharmacokinetic parameters. The study results indicated that a high fat meal increased the C_{max} and AUC (∞) of ziprasidone following administration of the OS by 63% and 97%, respectively. The relative bioavailability assessment suggested that the C_{max} and AUC (∞) values were 17% and 13% lower, respectively, for the OS compared to the capsule.

Summary Statistics of Pharmacokinetic Parameters Values of Ziprasidone

Pharmacokinetic Parameter ^a	Ziprasidone OS Fasted (N=13)	Ziprasidone OS Fed (N=13)	Ziprasidone Capsule (Fed) (N=12)
C _{max} (ng/mL)	27.0 ± 10.4	43.3 ± 15.8	32.4 ± 12.7
T _{max} (h)	3.0 (2.0, 6.0)	6.0 (4.0, 10.0)	4.0 (3.0, 6.0)
AUC (∞) (ng*h/mL)	225 ± 73	438 (111)	249 ± 76.6
AUC (∞) (ng*h/mL)	217 ± 71.3	430 (112)	238 ± 82.9
T ½ (h)	6.38 ± 2.10	4.35 (0.86)	7.51 ± 5.43

Arithmetic mean ± SD for C_{max}, AUC and T 1/2; median (range) for T_{max}.

A summary of statistical analysis of pharmacokinetic parameters for ziprasidone OS fed versus ziprasidone OS fasted is contained in the following table.

Statistical Analyses of C_{max}, AUC(∞), and AUC(0-T) for Ziprasidone OS Food Effect

Pharmacokinetic Parameter	Adjusted Geometric Means		Point Estimate	90% CI
	Ziprasidone OS Fed (Test) (N=13)	Ziprasidone OS Fasted (Ref.) (N=13)		
C _{max} (ng/mL)	40.0	24.5	163.03	133.18, 199.57
AUC(∞) (ng*h/mL)	417.3	212.0	196.83	173.64, 223.13
AUC(0-T) (ng*h/mL)	408.5	203.1	201.09	175.52, 230.37

Administration of ziprasidone OS with a high fat meal increased the C_{max}, AUC(∞) and AUC(0-T) by 63%, 97% and 101%, respectively, compared to administration of ziprasidone OS under fasted conditions. There was a significant positive effect of food on the pharmacokinetics of ziprasidone OS. Peak serum concentration of ziprasidone were reached at approximately 3 and 6 hours after administration of ziprasidone OS under fasted and fed conditions, respectively. Administration of ziprasidone OS with a high fat meal delayed the absorption of ziprasidone.

Statistical analyses of C_{max}, AUC(∞) and AUC(0-T) values of ziprasidone for evaluation of the bioavailability of the OS formulation relative to the commercial capsule are provided in the following table

Pharmacokinetic Parameter	Adjusted Geometric Means		Point Estimate	90% CI
	Ziprasidone OS Fasted (Test) (N=13)	Ziprasidone Capsule Fasted (Ref.) (N=13)		
C _{max} (ng/mL)	24.5	29.7	82.68	67.35, 101.50
AUC(∞) (ng*h/mL)	212.0	242.7	87.36	76.92, 99.23
AUC(0-T) (ng*h/mL)	203.1	228.1	89.05	77.56, 102.24

Mean C_{max}, AUC(∞) and AUC(0-T) values for ziprasidone OS were 17%, 13% and 11% lower, respectively, compared to ziprasidone capsule under fasted conditions. The T_{max} and T_{1/2} values of ziprasidone following administration of the OS were comparable to those observed with the capsule.

Safety Summary: The most reported treatment related adverse events were asthenia, headache and somnolence and there was a similar incidence of these adverse events in all three treatments. The sponsor reported an overall low incidence of AE in healthy volunteers with a dose of 20 mg ziprasidone. There was no apparent difference among the 3 treatment periods in AE profile, severity or incidence.

Pharmacokinetic Summary: The data from this study indicated that a standard FDA high fat breakfast resulted in an increase in C_{max} and AUC of 63% and 93%, respectively. The magnitude of the effect of food is similar to that observed with the capsule formulation. Therefore, the current label for ziprasidone capsules specifies administration with food is appropriate for the OS as well.

Statistical analyses indicate that Ziprasidone OS is not bioequivalent to Ziprasidone capsule. The 90% CI was not entirely contained within the 80 to 125% interval.

Conclusion: Administration of Ziprasidone OS with high fat meal increased the C_{max} and AUC(∞) of Ziprasidone by 63% and 97%, respectively.

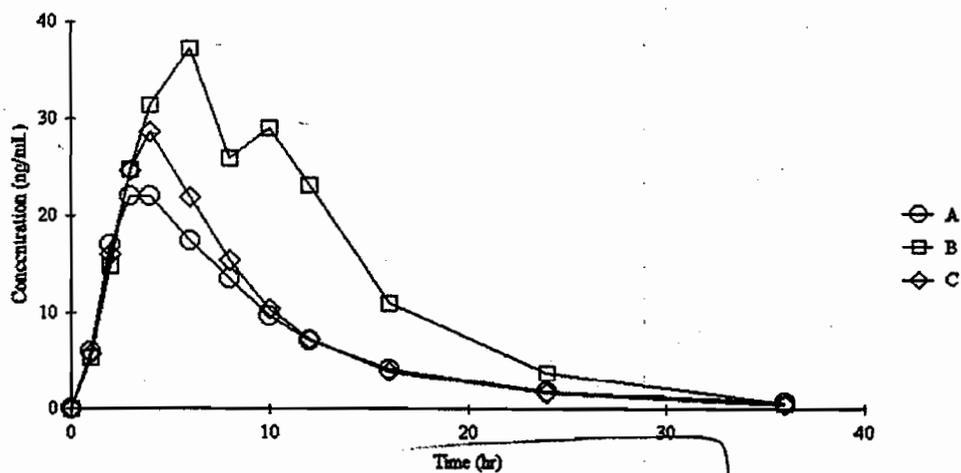
When administered under fasted conditions, the C_{max} and AUC(∞) of Ziprasidone were 17% and 13% lower respectively, for OS compared to the capsule. The 90% CIs for C_{max} and AUC(∞) were not contained entirely within 80% to 125%.

Reviewer Comments: *The study indicated that 20 mg Ziprasidone oral suspension is not bioequivalent to the approved 20 mg oral capsule. Both AUC and Cmax were not contained within the regulatory criteria of the 90% CI being within 80% to 125%. High fat meal had significant effect with AUC and Cmax after administration of Ziprasipradone increasing by 97% and 63%, respectively. It approved, it is recommended that the oral suspension be taken with food.*

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**Figure 1. Mean Serum Ziprasidone Concentration-Time Profiles
Protocol A1281131**



Treatment A: 20 mg ziprasidone OS fasted (N=13)

Treatment B: 20 mg ziprasidone OS fed (N=13)

Treatment C: 20 mg ziprasidone capsule fasted (N=12; Subject 10001016 who discontinued after receiving the capsule under fasted conditions in period 1 was not included in the mean plots)

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Table 13.5.2.1
 Ziprasidone Protocol A1281131
 Individual and Summary of Cmax Values of Ziprasidone

Subject	Cmax (ng/mL)		
	Treatment A	Treatment B	Treatment C
1002			
1003			
1004			
1005			
1006			
1008			
1009			
1013			
1014			
1015			
1017			
1018			
1019			
N*	13	13	12
Mean	27.0	43.3	32.4
SD	10.4	15.8	12.7
Min			
Median	25.0	44.3	35.3
Max			
CV%	38	37	39
Geometric Mean	25.1	40.4	29.4

* Two subjects discontinued from the study. Subject 1016 received Treatment C only and was not included in Summary Statistics and Statistical Analyses. Subject 1018 received Treatment A and B only and was included in Summary Statistics and Statistical Analyses for Food Effect.

Treatment A = 20 mg Ziprasidone OS Fasted
 Treatment B = 20 mg Ziprasidone OS Fed
 Treatment C = 20 mg Ziprasidone Capsule Fasted
 Source Data: Table B5.2
 Date of Generation: 17NOV2004

Table 13.5.2.2
 Ziprasidone Protocol A1281131
 Individual and Summary of Tmax Values of Ziprasidone

Subject	Tmax (hr)		
	A	B	C
1002			
1003			
1004			
1005			
1006			
1008			
1009			
1013			
1014			
1015			
1017			
1018			
1019			
N *	13	13	12
Mean	3.69	6.46	4.17
SD	1.18	2.18	1.19
Min			
Median	3.00	6.00	4.00
Max			
CV%	32	34	29

* Two subjects discontinued from the study. Subject 1016 received Treatment C only and was not included in Summary Statistics and Statistical Analyses. Subject 1018 received Treatment A and B only and was included in Summary Statistics and Statistical Analyses for Food Effect.

Treatment A = 20 mg Ziprasidone OS Fasted
 Treatment B = 20 mg Ziprasidone OS Fed
 Treatment C = 20 mg Ziprasidone Capsule Fasted
 Source Data: Table B5.2
 Date of Generation: 17NOV2004

**Ziprasidone Protocol A1281131
Individual and Summary of AUC(INF) Values of Ziprasidone**

Subject	AUC(INF) pred (hr*ng/mL)		
	Treatment A	Treatment B	Treatment C
1002			
1003			
1004			
1005			
1006			
1008			
1009			
1013			
1014			
1015			
1017			
1018			
1019			
N*	13	13	12
Mean	225	438	249
SD	73.0	111	76.6
Min			
Median	231	431	242
Max			
CV%	32	25	31
Geometric Mean	215	423	238

* Two subjects discontinued from the study. Subject 1016 received Treatment C only and was not included in Summary Statistics and Statistical Analyses. Subject 1018 received Treatment A and B only and was included in Summary Statistics and Statistical Analyses for Food Effect.

Treatment A = 20 mg Ziprasidone OS Fasted
 Treatment B = 20 mg Ziprasidone OS Fed
 Treatment C = 20 mg Ziprasidone Capsule Fasted
 Source Data: Table B5.2
 Date of Generation: 17NOV2004

Table 13.5.2.4
 Ziprasidone Protocol A1281131
 Individual and Summary of AUC(0-T) Values of Ziprasidone

Subject	AUClast (hr*ng/mL)		
	A	B	C
1002			
1003			
1004			
1005			
1006			
1008			
1009			
1013			
1014			
1015			
1017			
1018			
1019			
N *	13	13	12
Mean	217	430	238
SD	71.3	112	82.9
Min			
Median	224	423	233
Max			
CV%	33	26	35
Geometric Mean	207	414	224

* Two subjects discontinued from the study. Subject 1016 received Treatment C only and was not included in Summary Statistics and Statistical Analyses. Subject 1018 received Treatment A and B only and was included in Summary Statistics and Statistical Analyses for Food Effect.

Treatment A = 20 mg Ziprasidone OS Fasted
 Treatment B = 20 mg Ziprasidone OS Fed
 Treatment C = 20 mg Ziprasidone Capsule Fasted
 Source Data: Table B5.2
 Date of Generation: 17NOV2004

Table 13.5.2.5
Ziprasidone Protocol A1281131
Individual and Summary of Half Values of Ziprasidone

Subject	HL $t_{1/2}$ (hr)		
	Treatment A	Treatment B	Treatment C
1002			
1003			
1004			
1005			
1006			
1008			
1009			
1013			
1014			
1015			
1017			
1018			
1019			
N*	13	13	12
Mean	6.38	4.35	7.51
SD	2.10	0.861	5.43
Min			
Median	5.87	4.37	5.63
Max			
CV%	33	20	72
Geometric Mean	6.10	4.27	6.42

* Two subjects discontinued from the study. Subject 1016 received Treatment C only and was not included in Summary Statistics and Statistical Analyses. Subject 1018 received Treatment A and B only and was included in Summary Statistics and Statistical Analyses for Food Effect.

Treatment A = 20 mg Ziprasidone OS Fasted
 Treatment B = 20 mg Ziprasidone OS Fed
 Treatment C = 20 mg Ziprasidone Capsule Fasted
 Source Data: Table B5.2
 Date of Generation: 17NOV2004

Ziprasidone Protocol A1281131

Summary of Serum Ziprasidone Concentrations Versus Time Data

Treatment	Time (hr)	N*	NALQ	Mean (ng/mL)	SD (ng/mL)	CV%	Median (ng/mL)	Min (ng/mL)	Max (ng/mL)
A	0.00	13	0	0.00	0.00	—	0.00		
	1.00	13	13	5.97	4.94	83	4.38		
	2.00	13	13	17.0	15.0	88	8.95		
	3.00	13	13	21.9	12.3	56	17.4		
	4.00	13	13	22.0	9.65	44	22.9		
	6.00	13	13	17.3	6.30	36	16.8		
	8.00	13	13	13.4	5.85	44	12.6		
	10.00	13	13	9.58	3.69	38	8.29		
	12.00	13	13	7.01	2.41	34	6.42		
	16.00	13	13	4.04	1.59	39	3.70		
	24.00	13	13	1.67	0.955	57	1.41		
	36.00	13	8	0.571	0.562	98	0.637		
	B	0.00	13	0	0.00	0.00	—	0.00	
1.00		13	13	5.35	8.56	160	2.54		
2.00		13	13	14.8	12.7	86	7.80		
3.00		13	13	24.6	18.5	75	15.8		
4.00		13	13	31.4	17.1	55	32.3		
6.00		13	13	37.2	14.8	40	34.0		
8.00		13	13	25.8	10.2	40	23.6		
10.00		13	13	28.9	10.6	37	25.6		
12.00		13	13	23.1	10.9	47	21.8		
16.00		13	13	11.0	5.79	53	8.97		
24.00		13	13	3.68	2.27	62	1.91		
36.00		13	6	0.442	0.513	116	0.00		
C		0.00	12	0	0.00	0.00	—	0.00	
	1.00	12	12	5.71	4.87	85	3.84		
	2.00	12	12	16.0	9.41	59	16.2		
	3.00	12	12	24.6	12.5	51	26.9		
	4.00	12	12	28.5	14.1	49	28.0		
	6.00	12	12	21.8	9.48	43	20.8		
	8.00	12	12	15.3	7.05	46	15.3		
	10.00	12	12	10.4	4.18	40	10.2		
	12.00	12	12	7.25	2.83	39	7.02		
	16.00	12	12	3.80	1.20	32	3.89		
	24.00	12	12	1.59	0.580	37	1.49		
	36.00	12	6	0.370	0.407	110	0.278		

* Two subjects discontinued from the study. Subject 1016 received Treatment C only and was not included in Summary Statistics and Statistical Analyses. Subject 1018 received Treatment A and B only and was included in Summary Statistics and Statistical Analyses for Food Effect.

Treatment A = 20 mg Ziprasidone OS Fasted
 Treatment B = 20 mg Ziprasidone OS Fed
 Treatment C = 20 mg Ziprasidone Capsule Fasted

3.3. Summary of Previous OCPB Reviews

Appears This Way
On Original

Appears This Way
On Original

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Ziprasidone
PRODUCT (Brand Name):	Geodon
DOSAGE FORM:	Oral Suspension
NDA:	21-483
NDA TYPE:	Response to Non Approval Letter
SUBMISSION DATE:	9/29/03, 10/23/03
SPONSOR:	Pfizer
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

BACKGROUND

This submission is in response to the non approval letter sent to the sponsor on July 18, 2003. During the review the single dose BE Study 128-056 was found unacceptable as the quality control results were insufficient to demonstrate the accuracy of ziprasidone data obtained from the study. On July 28, the sponsor responded to the DSI comments on the QC samples. Since then the sponsor's direction has been towards getting Agency's acceptance on considering the multiple dose study A1281037 as the pivotal BE study.

Due to the lack of a reliable single dose BE study comparing the ziprasidone suspension to currently marketed capsule, the sponsor was asked to conduct another single dose study under fasted condition and also evaluate the effect of food on the to-be-marketed formulation. The sponsor has argued against the agency's decision and has provided their rationale for doing so.

The sponsor argues that the multiple dose study should be considered the pivotal study and hence they should not need to do additional single dose study under fasted conditions.

The sponsor's argument for using the multiple dose study as the pivotal BE study is given briefly in the following bullets along with the Agency's comments to these points.

1

Sponsor's Responses/Justifications:

1. In the Not-Approvable Letter, it states that *"Of these two studies [128-056 and A1281037, we consider the single dose bioequivalence study, 128-056, to be the pivotal study since the FDA Guidance ...recommends that single dose BE studies are generally more sensitive to detect the true formulation difference. "*

The sponsor makes the following arguments in support of their view that a multiple dose BE study should be considered as the pivotal BE study:

- Precedence: Previous bioequivalence testing of orally administered Geodon (as a capsule formulation, NDA (20-825) linking various capsule formulations with commercial formulation employed multiple-dose steady-state administration, and was found acceptable as a basis for approval. This includes all of the pivotal studies (128-035, 128-047, 128-041) in the capsule submission. The pharmacokinetics of ziprasidone HCl, as the active ingredient of any oral formulation, has been difficult to characterize in a single-dose study. The reason for adopting the multiple-dose approach is outlined in the study report for the earliest of these studies (128-035) which states, "A commercial capsule formulation of ziprasidone is currently under development. A previous study which investigated the single-dose bioequivalence of a proposed commercial capsule resulted in greater than accepted intra-individual variability"

Agency's view to this Argument:

Review of the OCPB section of N 20825 was completed March 3, 1998 during which the General BA/BE guidance was not issued. With the advancement of science and current standards, a multiple dose BE study under fed conditions cannot be accepted. As stated by the sponsor the multiple dose study with the capsules was accepted due to high intra-individual variability from the single dose studies. The sponsor agrees that there was no difference in the intra-individual variability between the single (24% for Cmax, 5% for AUC) and multiple dose (27% for both Cmax and AUC) BE studies in the case of oral suspension. Hence, this precedence cannot be taken into account since new standards in terms of single dose BE are current standards for assessing BE.

- The regulations allow for multiple-dose study design under certain circumstances which are applicable for Geodon OS. According to the CFR in effect at that time, multiple-dose studies are allowable under certain circumstances. These include instances where "[t]here is a difference in the rate of absorption but not in the extent of absorption" (21 CFR 320.7(a)(3)(i)). An inspection of the pharmacokinetics in the single dose studies in the submission indicate a consistent formulation difference in the direction of a shorter Tmax and 10-15% lower Cmax for the suspension versus the capsule with no significant difference in AUC. This is consistent with the CFR provisions mentioned.

Agency's view to this Argument:

The CFR citation is an error, the correct citation should be 21 CFR 320.27(a)(3)(i). However, this applies to general bioavailability studies as well and not explicitly for BE studies. It also infers to an intentional change of rate. This was not the case with Geodon oral suspension. The General BA/BE guidance is based on the Agency's current thinking of BE testing and is also along the BE testing requirements from the Office of Generic Drugs. The single dose BE study design is the current standard for BE testing unless there are justifiable safety or tolerability issues that require studies in patients and/or titration.

- There is similar precedent for the Anticonvulsant Trileptal Oral Suspension.

Agency's view to this Argument:

Trileptal submission had a reliable single dose study, hence the Agency could evaluate what the differences in Cmax from the failed BE study could translate to or its effect on efficacy. However, in the case of Geodon suspension, the conduct of the single dose study is unreliable.

Additional Responses by the Sponsor to the statements in the NA letter:

2. In the Not-Approvable Letter, it states that...*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.*

The sponsor states that the matter of Cmax marginally meeting BE criteria does not alter the fact that bioequivalence was demonstrated. It is also important to keep sight of the fact that AUC easily met the bioequivalence criterion in all studies and this appears to be the clinically relevant parameter for this type of drug. This is further discussed below.

Bioequivalence issues aside, it is apparent through an examination of all the studies in the submission that Cmax for the suspension is consistently about 10-15% lower than for the capsule. This point was raised at the pre-NDA meeting, and Pfizer was asked to include a rationale in the submission for its clinical significance or lack thereof.

2 Page(s) Withheld

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Agency's view on this argument:

Agency current standards clearly states that the single dose BE study should be conducted under fasted conditions. Multiple dose BE study is not acceptable and hence arguments pertaining to fed or fasted conditions for multiple dose studies do not hold true. The issue of non linearity does not matter because the BE study or the food effect study would be conducted at only one particular dose and will be compared to the same dose of the oral capsule.

OVERALL RECOMMENDATION

The sponsor's response to the Non-approval letter does not provide any compelling arguments against the Agency decision and requirements. From Office of Clinical Pharmacology and Biopharmaceutics point of view, the initial recommendations made in the action letter still hold true. The following statements from the non-approval letter still hold true and continue to be the OCPB recommendations on N21-483:

"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 site (Pfizer Inc., Litz, PA) and compare it to the reference product.

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

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. _____

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number	21,483
Relevant IND/NDA	<ul style="list-style-type: none"> • IND34,629 • NDA 20,825 (Ziprasidone HCl capsule, 20, 40, 60, 80mg; approved February 2001) • NDA 20,919 (Ziprasidone mesylate, powder for reconstitution for IM injection)
Date of Submission	<ul style="list-style-type: none"> • 09/26/2002 • 02/04/2003 [N(BC)] original amendment: Minor CMC amendment- updated stability data] • 06/16/2003 (email, stability data update)
Brand Name	Geodon
Generic Name	Ziprasidone HCl monohydrate
Drug Class	Antipsychotics
Indication(s)	Schizophrenia
Dosage Form/strengths	oral Suspension (10mg ziprasidone per ml)
Dosing Regimen	Initial treatment: 20mg bid with food Maintenance treatment: 20-80mg bid with food
Route of Administration	po
Sponsor	Pfizer.
Priority Classification	S
Type of submission	New Drug Application (new formulation)
Clinical Division:	HFD-120/Neuropharmacological Drug Products
OCPB Division:	HFD-860/DPEI
Reviewer:	Wen-Hwei Chou, Pharm.D., Ph.D.
Team leader:	Ramana Uppoor, Ph.D.

1 Executive Summary

The sponsor is seeking approval of a new oral suspension formulation of ziprasidone for the treatment of Schizophrenia. This submission is entirely based on bioequivalence (BE) studies comparing the oral suspension against the currently marketed ziprasidone capsule. No clinical trial has been conducted with oral suspension in target population.

Overall, we find the Clinical Pharmacology & Biopharmaceutics section not acceptable to support the approval of Geodon (ziprasidone 10mg/ml) oral suspension. The true formulation difference between suspension and marketed capsule formulations can not be determined since BA/BE guidance recommends single dose BE to detect true formulation difference but no single dose BE studies submitted were found to be acceptable for review.

Specifically, sponsor submitted 4 BE studies (3 single dose, 1 multiple dose) all conducted under fed condition using 4 different suspension formulations to compare against reference ziprasidone capsule. Based on the proportional similarity in composition to the to-be-marketed suspension, Agency noted that only 2 out these 4 BE studies are to be considered relevant to support current NDA. One is single dose BE study (128-056) using pilot formulation which Agency considered to be pivotal BE study since BA/BE Guidance (published in March, 2003) recommends that

We find the proposed *in vitro* dissolution methods acceptable. However, we recommend tightening of the dissolution specifications.

Please forward following comments to the sponsor.

1.2 Comments to the Sponsor

1. BE studies to support the approval of suspension strictly from BE standpoint.

- FDA Guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations" recommends that single dose BE studies conducted under fasted state are generally more sensitive to detect the true formulation difference. Agency disagrees with sponsor's justification for multiple dose BE study to be considered pivotal in support of current NDA. The multiple dose BE study (A1281037) should only be considered to be supportive.
- The three fed single dose BE studies submitted were not acceptable to detect the true formulation difference between two formulations. One single dose BE study (128-056), which Agency considered to be pivotal in support of current NDA, was not acceptable for review because the quality control (QC) results were insufficient to demonstrate the accuracy of the ziprasidone data obtained in Protocol 128-056. The other two single dose BE studies were considered to be irrelevant based on the differences between the composition of pilot formulations and to-be-marketed formulation.
- In order to evaluate the true formulation difference between two formulations and to support the approval of suspension formulation strictly from BE standpoint, the sponsor should conduct another single dose BE study. The single dose BE study should be conducted under fasted state using to-be-marketed suspension formulation manufactured at the proposed commercial manufacturing site (Pfizer Inc., Lititz, PA) and compare to the reference product ziprasidone capsule.
- In addition, food-effect on the to-be-marketed suspension formulation should be evaluated.

2. Bioassay:

In the future, the sponsor should, to the extent of their 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 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.

3. In vitro dissolution method & specification

We find the proposed dissolution method acceptable: USP apparatus II, paddle speed 100rpm, 900ml 0.05 M NaH₂PO₄ pH 7.5 buffer with 2% sodium dodecylsulfate(SDS) at 37°C, bottom sample introduction. But based on the dissolution profiles from biobatch, we

NDA 21,483
Geodon (Ziprasidone suspension)

W Chou

recommend tightening of the dissolution specification from Q= at 30 minutes to Q= at 30 minutes.

1.3 SIGNATURES

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT initialed by Ramana Uppoor, Ph.D. _____

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Date: 06/25/2003

Briefing Attendees: Chen ML, Lazor J, Hunt J, Mehta M, Uppoor R, Chou W.

c.c.: NDA 21-483, HFD-120 (Hardeman S, Andreason P, Glass R, Klein D), HFD-860 (Mehta, Sahajwalla, Uppoor, Chou)

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