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APPROVAL PACKAGE FOR: :

APPLICATION NUMBER

20-919

Medical Review(s)

MEMORANDUM

DATE: June 20, 2002

FROM: Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-919

SUBJECT: Action Memo for NDA 20-919, for the treatment of acute agitation in schizophrenic patients

NDA 20-919, for the treatment of acute agitation in schizophrenic patients, was submitted by Pfizer, Inc., on 12/17/97. The Agency most recently issued an Approvable letter on 3/6/01, and the sponsor submitted a complete response on 12/21/01.

This response has been reviewed by the review team, all of whom recommend that the application be approved. I agree, although there is one issue that I believe needs to be explicitly addressed for the record.

In our 3/6/01 Approvable letter, we asked the sponsor to document that the maximum (and mean) Cmax's achieved after the maximum IM dosing approximated those achieved after the maximum oral dose, and to document that there were not more patients that achieved the higher Cmax's after the IM dosing compared to the number of patients achieving the higher Cmax's after oral dosing.

In a study performed to address these questions, the Cmax's were found to be similar, but 2 patients developed extremely high Cmax's (— and — mcg/L, compared to a mean of between 150-250 mcg/L) after IM dosing. These patients' plasma levels were excluded from the kinetic analyses because they were considered outliers by Agency reviewers. However, given our original concern about possible increased numbers of patients achieving high plasma levels with the IM product, I believe it is worth explaining why these values were considered spurious.

The sponsor has documented that these Cmax values were inconsistent with values immediately before and after the Cmax values, and also inconsistent with concurrent metabolite levels. For these reasons, they considered (and we agree) these plasma levels to be in error, and not reflective of an increased potential of the IM to produce more outliers than the oral product.

Given this, I will issue the attached Approval letter, with appended labeling.

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Russell Katz
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MEDICAL OFFICER

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 19, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Geodon IM (ziprasidone IM) for the acute treatment of agitation in schizophrenia

TO: File NDA 20-919
[Note: This overview should be filed with the 12-21-01 response to our 3-6-01 approvable letter. The reader is referred to my 2-28-01 and 12-8-98 memos to the file for a more complete summary of the administrative history and data in support of this application.]

Ziprasidone IM is an intramuscular formulation of the antipsychotic drug ziprasidone that is being proposed for use in the treatment of "acute agitation in schizophrenic patients who are being considered for treatment with oral ziprasidone but are in need of intramuscular antipsychotic medication for initial control of the agitation."

We issued an approvable letter on 3-6-01 that included the following requests and comments:

- We expressed concern that the development program for ziprasidone IM contained insufficient ECG data at appropriate times after dosing for patients receiving the maximum recommended dose. In a 5-14-01 meeting with Pfizer, we discussed the design of study A1281063 that was intended to address this concern, and we reached agreement on an appropriate design. The 12-21-01 response included the results of this study.
- We reminded Pfizer of the need for a phase 4 reproductive toxicity study with ziprasidone IM. The 12-21-01 response included a pk based argument regarding why such a study would not add any useful information over what was already known, and requested an opportunity to discuss this.
- We asked Pfizer to submit the final TK data for the 1-month IM toxicity studies in the rat and dog. They responded with a set of recalculated values, and commented that these new data would not change the original interpretation.
- We asked for a regulatory status update, along with approved labeling where available. They provided this update, along with approved labeling in 5 countries.

- We asked for a world literature update, and they provided this.
- Finally, we proposed draft labeling, and asked that they respond to this. The 12-21-01 response did include a modified version of labeling based on our draft.

Results of Study A1281063:

-This study compared ziprasidone IM at doses of 20 mg, followed by 30 mg 4 hours later, with haloperidol IM, at doses of 7.5 mg, followed by 10 mg 4 hours later. The sponsor included a second dose of ziprasidone that is 50% higher than the recommended dose in order to more fully explore the ECG effect. They looked at change from baseline in QTc at Cmax after both injections. The study results were reviewed by both the safety group (reviews by both Drs. Hammad and Racoosin) and OCPB (review by Dr. Gobburu).

Mean changes from baseline in QTc were 4.6 and 6.0 msec for the first doses of ziprasidone and haloperidol, respectively, and 12.8 and 14.7 msec for the second doses of ziprasidone and haloperidol, respectively. Since the second ziprasidone dose was 50% higher than the recommended dose, OCPB modeled the predicted plasma concentrations and QTc values at a second 20 mg IM dose. It turns out that the predicted Cmax from ziprasidone IM is 208 µg/L, compared to 202 µg/L for oral ziprasidone (at 80 mg bid, the maximum recommended dose). Since the CV is similar for both oral and IM ziprasidone, it can be predicted that the distribution of outliers would be similar for both routes. The pharmacokinetic variability for haloperidol IM was roughly comparable to that seen for ziprasidone.

There were no instances for either drug of patients exceeding 480 msec for QTc. However, following the second injection, there was a slight excess for ziprasidone over haloperidol for patients exceeding a 30 msec increase from baseline (72% vs 58%) and also for a 60 msec increase from baseline (8% vs 0%), however, it is of course true that the ziprasidone dose was 50% higher than recommended. Based on these findings, both the safety group and OCPB concluded that the sponsor had adequately addressed our concerns, and I agree. They did, however, suggest several changes to the labeling proposed by Pfizer regarding this study.

Reproductive Toxicity Study:

-We have not accepted the sponsor's argument for not doing a repro study, since our request was based on a finding that each of ziprasidone and SBECD alone demonstrated adverse effects on reproduction. Pfizer has now agreed to conduct such a study post approval.

Toxicokinetic Data for Rat and Dog Studies:

-The pharm/tox group has found the final TK data from the 1-month IM studies acceptable.

Regulatory Status Update and Foreign Labeling:

-Dr. Glass reviewed the regulatory status update. Ziprasidone IM is approved in 5 countries at this point. A review of the labeling in these countries did not reveal any new safety concerns we have not been aware of.

World Literature Update:

-No new safety information was revealed in the literature update.

Revised Labeling:

-We reached agreement with the sponsor on final labeling as of 6-19-02.

Conclusions and Recommendations:

-I recommend that we issue an approval letter for this NDA with the mutually agreed upon final labeling.

cc:

Orig NDA 20-919 (Zeldox IM)

HFD-120

HFD-120/TLaughren/RKatz/JRacoosin/JBoehm/RGlass/SHardeman

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/s/

Thomas Laughren
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REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-919

Sponsor: Pfizer

Drug: Geodon IM (ziprasidone IM)

Material Submitted: Response to Approvable Letter of 3/6/01

I. Regulatory Background

Ziprasidone is an "atypical" antipsychotic with serotonin (5-HT_{2A}) and dopamine (D₂) antagonist properties. The oral dosage form was approved for marketing in the U.S. on February, 5, 2001 with a bolded warning describing ziprasidone's ability to prolong the QTc and the associated risks of sudden death. The NDA for ziprasidone IM received a "non-approval" letter on 12/17/98 (stating that concerns of the effects of ziprasidone on the QTc prolongation had not been adequately addressed), followed by an "approvable" letter on 3/6/01 (requesting more information regarding effects on the QTc interval at maximal concentration). An Advisory Committee Meeting was held prior to the issuance of the "approvable" letter of 3/6/01 (see below).

The current re-submission includes the study report for Protocol A1281063, an open label study assessing the pharmacokinetics and QTc effects of ziprasidone and haloperidol following intramuscular administration to patients diagnosed with schizophrenia or schizoaffective disorder. Please refer to reviews by Dr. Tarek Hammad (HFD-120, safety team) and Dr. Joga Bobburu (Office of Clinical Pharmacology and Biopharmaceutics) for a detailed review of Study A1281063. Because efficacy for ziprasidone IM in the treatment of acute agitation in patients diagnosed with schizophrenia had been adequately addressed in previous submissions (please see review of 11/13/98), this current review will comment only on the sponsor's proposed labeling, foreign labeling submitted, and the submitted updated literature review.

Advisory Committee Meeting

A Psychopharmacological Drug Advisory Committee meeting was held on February 15, 2001. The majority of the members agreed that the sponsor had submitted sufficient evidence supporting the efficacy of ziprasidone IM, but expressed concern that the safety of ziprasidone IM as a treatment of agitation in schizophrenia and schizo-affective disorders had not been adequately addressed. According to The Final Minutes, the committee discussed concerns regarding doses above ziprasidone IM 20 mg and the effects on the cardiovascular system (primarily the QTc prolongation), especially in a situation when a patient taking oral ziprasidone required one and possibly two IM doses to treat agitation.

II. World Literature Update

The sponsor conducted a world literature search for all published articles pertaining to the safety of ziprasidone intramuscular published during the period of August 1, 1997 through September 20, 2001. The literature search was conducted by Donna M. Zyry, DVM, MS, who is currently the Manager of Information Research and Services, and has been employed by Pfizer, Inc since 1994. The abstracts and publications selected by this search were further reviewed by Charles Ritrovato, Pharm.D., Senior Director of Worldwide Regulatory Affairs at Pfizer Inc., who did not identify notable safety concerns in the literature that he reviewed.

In the current submission, the sponsor submitted abstracts only of the publications identified in their world literature search. My review of the sponsor's submitted abstracts did not reveal any unexpected safety findings.

III. Foreign Regulatory Status

Ziprasidone IM is currently marketed in the following countries:

1. Argentina: approved on March 1, 2001 (tradenname Zeldox)
2. Armenia: approved on May 21, 2001 (tradenname Zeldox)
3. Brazil: approved December 5, 2001 (tradenname Geodon)
4. Sweden: approved August 17, 2000 (tradenname Zeldox), and
5. Uruguay: approved October 23, 2001 (tradenname Zeldox).

The sponsor submitted labels from these five non-US countries. A review of these labels did not reveal any unexpected safety information.

IV. Sponsor's Proposed Labeling

The following are comments regarding the sponsor's proposed labeling changes:

1. p. 7: proposed addition of the statement

1

Comment: The primary efficacy variables for the cited study were: 1) the area under the curve (AUC) for the Behavioural Assessment Scale (BAS) from 0 to 4 hours after the first IM dose, 2) change from baseline to 4 hours of CGI-S score, and 3) change from baseline to study endpoint of the CGI-S. Therefore, the data to support this statement has not been reviewed, and it is recommended that this statement be removed from the proposed labeling.

2. p. 9: under the section QT Prolongation.

Comment: The list of drugs which should not be used concomitantly with ziprasidone has since been revised, and this should be reflected in the current proposed labeling.

3. p. 10, at the end of the third paragraph and on p. 11 in the first paragraph:

Comment: The sponsor proposes adding information regarding

It is recommended that both of these comments be deleted from the proposed labeling.

4. p. 24 -25: Table of treatment-emergent adverse event in short-term fixed dose intramuscular trials:

Comment: In this recent proposed labeling, the sponsor has chosen to do a comparison of ziprasidone IM at doses of 2, 10 and 20 mg. In the previous submission, the sponsor presented a table comparing the pooled data base of ziprasidone IM from the fixed dose studies (Studies 121, 125 & 126) with haloperidol IM (Study 121); although the previously proposed table was an uncommon format for labeling, it did provide relevant prescriber information when they may be comparing the intramuscular drugs available for use.

5. Please refer to reviews by Dr. Tarek Hammad (HFD-120, safety team), Dr. Judith Racoosin (HFD-120, safety team), and Dr. Joga Bobburu (Office of Clinical Pharmacology and Biopharmaceutics) for further comments regarding labeling changes for ziprasidone IM.

V. Financial Disclosure Information

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Senior Director of Medical Finance at Pfizer, Inc. signed the Form 3454 testifying that, to his knowledge, there was no financial arrangement made with investigators that could affect the outcome of the submitted study as defined in 21 CFR 54.2 (a), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

VI. Conclusions/Recommendations

Please refer to the reviews by Dr. Tarek Hammad (HFD-120, safety team) and Dr. Joga Bobburu (Office of Clinical Pharmacology and Biopharmaceutics) for safety conclusions and recommendations based on their detailed reviews of Protocol A1281063. The sponsor's submitted labeling from non-US countries and the submitted world literature update did not provide any new safety information that had not been previously addressed in the proposed U.S. labeling. Please see above for comments regarding the sponsor's proposed labeling.

Roberta L. Glass, M.D.
Medical Officer, Division of Neuropharmacological Drug Products

NDA 20-825
Div File
HFD-120: Laughren/Hardeman/Glass

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/s/

Roberta Glass
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Thomas Laughren
6/4/02 08:14:40 AM
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This NDA can be approved once we reach final agreement with the sponsor on the text of labeling; see memo to file for more detailed comments.--TPL

Review and Evaluation of Clinical Data

NDA: 20-919

Sponsor: Pfizer

Drug: Geodon IM (Ziprasidone)

Material Reviewed: Report for study # A1281063

Subject: Association between Ziprasidone IM and QT prolongation

Reviewer: Tarek A. Hammad, M.D., Ph.D., M.Sc., M.S.

Date Review Completed: 6/3/2002

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1 Background

Ziprasidone was first submitted as an oral formulation. That application was the subject of a Not Approvable (NA) letter dated 12/17/98 because of the finding with the oral ziprasidone formulation of a prolongation of the QTc interval. The NA letter required further characterization of this finding.

The sponsor responded to the NA letter in a submission dated 9/6/00 where the QT interval was evaluated in a clinical pharmacology study characterizing the nature and degree of the QTc prolongation. Briefly, the sponsor performed a clinical pharmacology study of ziprasidone and a number of newer, "atypical" (risperidone, quetiapine, and olanzapine) and older (thioridazine, haloperidol) anti-psychotic drugs which assessed their effect on the QT interval at each drug's T_{max}, with and without maximum metabolic inhibition. This study demonstrated that the QTc interval with ziprasidone was prolonged to a greater degree than with any of these comparator drugs (about 10-15 msec greater than that seen with haloperidol) except thioridazine, which had a substantially longer QTc interval than ziprasidone.

Subsequent to this re-submission, and following consideration at a meeting of the Psychopharmacological Drugs Advisory Committee (PDAC), the NDA for the oral formulation was approved on February 5, 2001.

Regarding the regulatory history of ziprasidone IM, it was first submitted in December 1997 for the indication of 'acute control and short-term management of the agitated psychotic patient'. Because the oral formulation was not approved (see above), the IM formulation also received a NA letter. Subsequently, Ziprasidone IM was resubmitted to the FDA and considered at PDAC on February 15, 2001.

On March 6, 2001, Ziprasidone IM received an Approvable Letter from the FDA. The Division of Neuropharmacological Drug Products had questions regarding the effect of IM ziprasidone on the QTc interval at the maximum dose to be recommended. Specifically, the sponsor has provided little empirical data on the plasma levels achieved at T_{max} for the maximum dose proposed (40 mg/day) and the duration of the QTc interval at this T_{max}.

2 Study Objective

This is a single blind, controlled, parallel, multi-center study designed to characterize the effect of the maximal recommended intramuscular dose of ziprasidone and haloperidol on the QTc interval at the observed C_{max}.

3 Study Design

3.1 *Selection of Patients*

This study recruited males and females, ages 18 or older, with a history of psychotic disorder for whom chronic antipsychotic therapy was indicated. Subjects were to have had a normal ECG, and to have been free from an acute exacerbation of psychosis for at least 3 months. Additionally, subjects were to have had screening and baseline clinical laboratory tests that were within normal limits.

3.2 Patient Preparation and Treatments

Period 1 (days -10 to -4): Subject's existing antipsychotic medications were tapered to the lowest possible dose.

Period 2 (days -3 to 0): Drug washout period. Serial ECGs collected on day 0 at times matching those planned for day 1. On the last day of Period 2 (day 0), subjects were randomized in a 1:1 ratio to either IM ziprasidone or IM haloperidol.

Period 3 (day 1): Single-blind study drug was administered as two IM injections four hours apart; the IM doses, in succession, were 20 mg (at approximately 8 AM) followed by 30 mg for ziprasidone and 7.5 mg followed by 10 mg for haloperidol.

Period 4 (days 2 to 4, plus at one week): Study drug washout period. Safety assessments were made and standard antipsychotic treatment reinstated.

3.3 Evaluation of ECGs and Calculations of QTc

Twelve-lead ECGs were obtained at screening and at similar intervals on days 0 and 1. In addition, on day 1 ECGs were obtained at 24 hour, and on day 2 ECG were obtained at 36 and 48 hours after first injection. The ECG and blood sampling times were concentrated within the first two hours after each injection to capture Cmax and times on either side of Cmax for each injection of study drug (see table below).

Schedule of measurements relative to IM dosing.

Time*	Dose	ECG	BP/Pulse	PK
0	X [#]	X (prior to first injection)	X (prior to first injection)	X [#] (prior to first injection)
0.25		X		X [#]
0.5		X	X [#]	X [#]
0.75		X		X [#]
1		X	X [#]	X [#]
1.25		X		X [#]
1.5		X		X [#]
1.75		X		X [#]
2		X	X [#]	X [#]
2.5		X		X [#]
3		X		X [#]
4	X [#]	X (prior to second injection)	X (prior to second injection)	X [#] (prior to second injection)
4.25		X		X [#]
4.5		X	X [#]	X [#]
4.75		X		X [#]
5		X	X [#]	X [#]
5.25		X		X [#]
5.5		X		X [#]

Time*	Dose	ECG	BP/Pulse	PK
5.75		X		X [#]
6		X	X [#]	X [#]
6.5		X		X [#]
7		X		X [#]
8		X	X [#]	X [#]
9		X		X [#]
12		X	X [#]	X [#]
16		X		X [#]
24		X [#]	X [#]	X [#]
36		X [#]		X [#]
48		X [#]	X [#]	X [#]
72			X [#]	X [#]

* Time relative to the first IM dose of study drug on day 1.

Only performed on day 1 or thereafter.

@ Only performed on day 0.

ECGs for each subject were blinded and assessed for PR, QRS, RR & QT durations taken from lead II QRS complexes using the [Measurement System which employs a magnification of the ECG and a digitizing cross-hair caliper to define the duration of each interval in milliseconds. The QT duration was measured manually by an eRT analyst in lead II from the beginning of the QRS complex to the end of the T-wave. For each ECG, the QT interval was measured for the first three consecutive normal and technically acceptable beats, and the results averaged to provide the QT interval for the tracing.

QTc intervals were computed by the equation $QTc = QT / (RR^b)$ where "b" was the slope of the regression of the $\ln QT$ on the $\ln RR$ using all baseline data. A regression of $\ln QT$ on $\ln RR$ was done for each hour of the day and then averaged across the day to obtain a single estimate of the baseline correction.

In the primary analysis, a mean QTc was calculated as the average of three QTc measurements obtained at and on either side of the observed C_{max} for each injection for each subject. Baseline values were those on day 0 (i.e., pre dose) that were collected at the same times of the day as day 1. Changes from baseline were calculated for each subject by subtracting the baseline QTc from the QTc obtained at C_{max} on day 1.

QTc data were also summarized by time point. For this secondary analysis, the differences between day 1 and day 0 QTc measurements were determined time point by time point and the results averaged across subjects to yield an average time profile for each treatment.

3.3.1 Changes in Planned Analyses

The method used to estimate the baseline QT correction factor was revised from that stated in the original protocol under "statistical analysis plan". The method in the statistical analysis plan allowed random subject slopes and intercepts for each individual. The estimate for the baseline correction factor would then be estimated as the population slope.

Alternatively, the method used in the current submission was to fit a simple linear regression at each time point and use the average slope across times as the correction factor for QT. The sponsor's justification is that the former method revealed a high degree of intra-subject variability in slopes while the latter method yielded a greater consistency across time in the slopes of the regressions.

3.4 Safety Assessments

Subjects remained in the clinical research facility for at least two days and nights after the last injection of study drug for washout, safety assessment, pharmacokinetic sampling, and reinstatement of antipsychotic treatment. In addition, follow-up safety assessment was conducted approximately one week after discharge. It is not clear if this one-week assessment was done by phone or in person. All clinically important abnormal laboratory test values occurring during the study were followed up until they returned to baseline or to levels acceptable to the investigator and the sponsor clinician, or until an explanatory diagnosis was made.

Classification by body system was according to the Coding Symbol Thesaurus of Adverse Reaction Terms (COSTART). The following safety assessments were made at defined intervals throughout the study:

- Adverse events (recorded from Period 1 through the follow-up visit at one week).
- Clinical laboratory tests (screening, days -3, 0, and prior to discharge from the study)
- Physical examination (complete: screening and prior to discharge from the study; brief: days -3, -2, -1, 0 and 1).
- Supine blood pressure and pulse rate (screening, mornings of all days in Periods 2, 3, and 4 including the day of discharge; on day 1, immediately prior to and 0.5, 1, and 2 hours after each IM injection and 8 and 12 hours after the first injection).
- Body weight (screening, morning of day 0).
- Body temperature (screening, day -3, morning of day 0 and day of discharge).
- Pain intensity of injection site (immediately prior to, 0.5, 1, and 2 hours after each injection, and 8 and 24 hours after first IM injection).

3.5 Sample size

Historical data from 100 healthy male placebo-treated subjects who had multiple ECGs collected over an eight-hour period were combined to estimate the within and between subject variability of QTc change (Bazett's formula) from baseline. Twenty-five subjects per group allowed the 95% confidence interval on the QTc change from baseline to be within ± 8 msec of the mean.

4 Study Findings

4.1 Patients

4.1.1 Disposition

Of 87 subjects screened for entry to the study, 58 (31 & 27 in ziprasidone and haloperidol, respectively) were randomized and received at least one dose of the study drug. Forty-nine (24 & 25) subjects completed the study and nine (6 & 3) discontinued. It is not clear why the number of patients that underwent lab testing is low. The sponsor states "Due to the schedule for laboratory tests, only 8 subjects (5 in the ziprasidone group and 3 in the haloperidol group) had blood samples drawn for laboratory tests during the study treatment or within one calendar day after the last dose of study drug".

Subject Evaluation Groups

	Ziprasidone	Haloperidol	Total
Randomized and received drug	31	27	58
Completed study	25	24	49
Evaluated for			
ECG	31	27	58
Pharmacokinetics	31	27	58
Assessed for safety			
Adverse Events	31	27	58
Lab Tests	5	3	8

4.1.2 Demographics

The distribution of subjects by gender, age, weight and race was generally comparable in the two treatment groups.

4.2 Results of ECG Assessment

No between group hypothesis tests were planned for this protocol. Two patients were excluded from the sponsor's ECG analysis because C_{max} could not be reliably estimated from the two post-dose plasma concentrations available (ZIP 50480035; HAL 50480036).

The tables below present a summary of the baseline and mean changes from baseline in HR, QT, and QTc after dosing in the two treatment groups. The two treatment groups had comparable mean baseline and mean change from baseline in QTc after the first and second injections at the respective C_{max} values. The mean change in heart rate in the ziprasidone group is about twice the change in the haloperidol group.

On the other hand, although categorical summaries of QTc show that the two groups have similar pattern after the first injection, ziprasidone had a higher proportion of patients with a change in QTc > 30 msec (18/25, 72%) than haloperidol (14/24, 58%) after the second injection. In addition, the ziprasidone group had one subject (1/25, 4%) with a QTc interval > than 450 and an increase from baseline > 60 msec (457 msec on day 1 compared with 395 on day 0, both at 5.5 hours after the first injection). A second subject in the ziprasidone group had a QTc interval >450 and an increase >60 msec (454 msec at

1.25 hour after the first injection compared to 378 msec on day 0). However, this subject discontinued prematurely from the study because she refused the second dose of IM ziprasidone. Adding this patient increases the total percentage of patient that had a change in QTc of more than 60 msec from 4% (1/25) to 8% (2/25).

Baseline and mean changes from baseline in HR, QT, and QTc after dosing in the two treatment groups at their respective Cmax values among completers.

	Ziprasidone (mean and 95% CI)		Haloperidol (mean and 95% CI)	
	Baseline (BL)	Change from BL at Cmax	BL	Change from BL at Cmax
Injection 1				
QTc (msec)	380 (373, 388)	4.6 (0.4, 8.9)	386 (378, 393)	6.0 (1.4, 10.5)
QT (msec)	379 (366, 392)	-8.6 (-14.6, -2.6)	375 (365, 386)	1.5 (4.4, 7.4)
HR (beats/min)	62 (58, 66)	7.8 (4.8, 10.7)	66 (62, 70)	2.5 (0.1, 4.9)
Injection 2				
QTc (msec)	374 (367, 381)	12.8 (6.7, 18.8)	380 (374, 386)	14.7 (10.2, 19.2)
QT (msec)	366 (354, 379)	-7.0 (-14.0, -0.1)	363 (355, 372)	4.2 (-1.9, 10.4)
HR (beats/min)	65 (60, 70)	12.1 (8.3, 15.9)	70 (65, 74)	5.9 (2.7, 9.0)

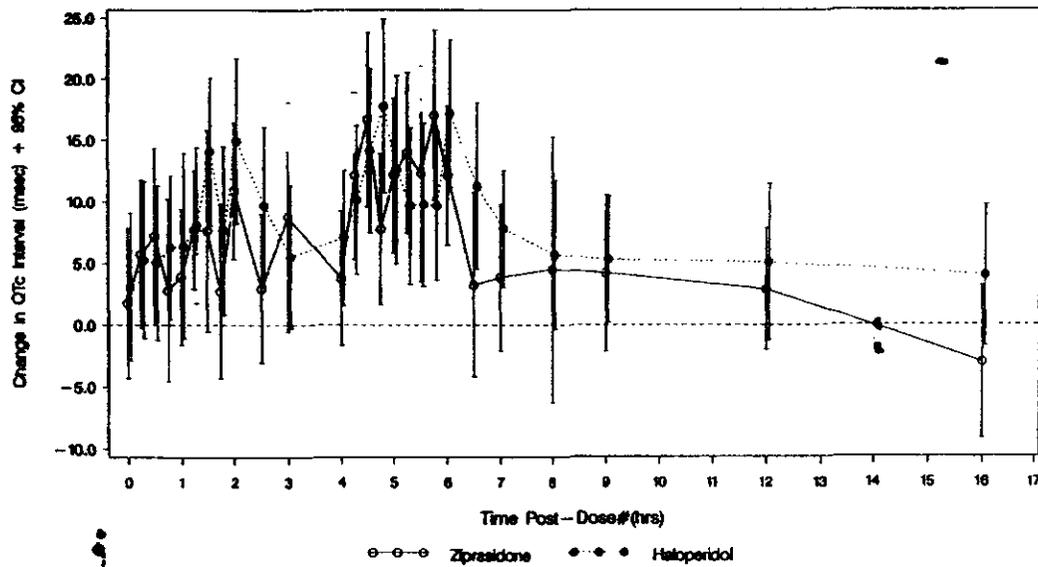
Categorical summary of QTc and QTc changes from baseline after dosing in the two treatment groups at their respective Cmax values among completers.

N=	Injection 1		Injection 2	
	Ziprasidone 25	Haloperidol 24	Ziprasidone 25	Haloperidol 24
With QTc				
>=450 (msec)	0	0	1 (4%)	0
>=480 (msec)	0	0	0	0
>=500 (msec)	0	0	0	0
Change in QTc				
>=30 (msec)	12 (48%)	13 (54%)	18 (72%)	14 (58%)
>=60 (msec)	1 (4%) #	0	1 (4%)	0
>=75 (msec)	0	0	0	0

The patient discontinued after the first injection.

Time-matched changes from baseline in QTc by hours post dose (sponsor's figure 1.2.1) show that, for subjects receiving ziprasidone, the mean change in QTc increased approximately 2-fold between 15 minutes and 2 hours after the first injection (5.7 msec to 10.9 msec). A trend in mean change values towards baseline was evident between 2 and 4 hours post dose. A further prolongation in QTc interval was observed after the second injection. A mean increase in QTc of approximately 12 msec was evident within 15 minutes after the injection; this increase was maintained (range: 12.1 msec to 17.1 msec) to 2 hours post dose with a trend towards baseline evident thereafter. At 8 and 12 hours after the second ziprasidone injection, the mean changes from baseline in QTc were 2.9 msec and -3.0 msec, respectively. Mean changes in QTc after IM haloperidol followed a generally similar pattern.

Figure 1.2.1
 Ziprasidone Protocol 1063
 Time-Matched QTc Interval Changes from Baseline* vs Time Post-Dose by Treatment Group - Completers



*Baseline values come from the day prior to dosing (Day 0).
 #Time post-dose is in reference to the first injection. Injections are given at 0 and 4 hours.
 Source Data: Section 13 Table 18.1. Date of Data Extraction: 04DEC2001. Date of Figure Generation: 05DEC2001.

4.3 Discontinuations and Serious Adverse Events

Of the nine subjects who discontinued five were due to adverse events (ziprasidone (n=3): extrapyramidal syndrome, hypotension and dizziness, and agitation; haloperidol (n=2): extrapyramidal syndrome and abdominal pain [pain started before treatment]). All patients were treated and symptoms resolved. Four subjects discontinued for other reasons. All 9 of these discontinuation occurred during "Period 3" (day 1).

One serious adverse event (haloperidol: depression, increased, severe psychosis) was reported post-therapy. The subject was hospitalized and the event resolved. No deaths were reported in this study.

4.4 Common adverse events

Dizziness (7/31, 23%), anxiety (5/31, 16%), and bruising (2/31, 7%) were higher (>2x) in the ziprasidone group than in the haloperidol group.

The five most common adverse events reported in the ziprasidone group were somnolence (28/31, 90%), dizziness (7/31, 23%), anxiety (5/31, 16%), dry mouth (4/31, 13%), and nausea (4/31, 13%). It is worthy to note that the studied population was not agitated at the time of drug administration.

4.5 Clinical laboratory test abnormalities

Only eight subjects (5 ziprasidone and 3 haloperidol) had blood samples drawn for lab tests during study treatment or within one calendar day after the last dose of study drug. Only one subject (50480060) in the ziprasidone group experienced an elevated (>1.2x ULN) basophil count on day 2.

4.6 Blood pressure and pulse rate

Systolic and diastolic blood pressure and pulse rate were comparable at baseline in the two treatment groups. No subject met the criteria for clinically significant change in pulse rate. Two subjects in the ziprasidone group (2/31, 7%) experience a clinically significant decrease in systolic (BP<90 mmHg and >20 mmHg decrease) and diastolic (BP<50 mmHg and > 15 mmHg decrease) blood pressure post injection. One was discontinued due to "hypotension and dizziness" and the other one was discontinued after the first injection because she refused the second dose of IM ziprasidone.

4.7 Clinical Pharmacology (CP) Reviewer

The aim of Dr. Gobburu's review was to "(1) quantitate the relationship, if any, between [ziprasidone] exposure and QTc and (2) simulate scenarios that allow appreciation of the maximal net effect on QTc with the recommended dosing."

Two subjects in each of the treatment groups had unusually high concentrations. In the ziprasidone group, subject # 50480015 had a plasma level of — ug/L at 4.75 hr post first dose and subject # 50480025 had a plasma level of — ug/L at 1 hr post first dose. These subjects did not have correspondingly high QTc intervals. The reason for these unusually high concentrations was not identified and the sponsor deleted the subjects from further analyses.

Using QT data from the clinical pharmacology study, Dr. Gobburu simulated concentration and QT data, in 2900 subjects, relying on the parameters generated from final pharmacokinetics and pharmacodynamics models. The maximal QTc change in each subject was determined and the various quantiles of this statistic were calculated as shown in the following table.

CP reviewer's table 5: Quantiles of maximal effect for each patient, over a total of 2900 patients, determined for the simulated data. Patients received 20 mg at 0 hr and another 20 mg at 4 hr.

Quantile	Maximal Effect, msec
100 %	44
90 %	18
75 %	12
50 %	7
25 %	2
0 %	-4

The CP reviewer concluded:

1. "The primary conclusion from the current analyses is that the QTc prolongation of ziprasidone is concentration dependent. The between subject variability of

relationship is considerably high (100%). Although the mean (or median) QTc prolongation is about 8 msec, the variability is considerable, as shown in Table 5. It is possible that there are about 10% of the patients who might have QTc prolongation between 18 and 44 msec.

2. Table 5 presents the various quantiles of net maximal QTc effect in 2900 simulated patients who received two ziprasidone doses of 20 mg q4h. Simulations are needed for at least 2 reasons here: (1) the sponsor studied a higher second dose while the label recommended dosing is 20 mg q4h and (2) the study includes only 31 patients thereby the probability of the worst case scenarios may not be estimated as reliably as would be possible via simulations. The medical reviewer should consider the risk of having the presented QTc prolongation for the perceived benefit that the patient might derive from using ziprasidone.
3. The approvable letter raised another issue for the sponsor to address regarding the distribution of Cmax values after IM injection compared to that after oral. The sponsor reported a mean (CV) Cmax value of 182 (33) ug/L after the first dose (20 mg) and 319 (41) ug/L after the second dose (30 mg). Based on the previous OCPB review, the mean (CV) of Cmax values after 80 mg bid (oral) was 202 (35%) ug/L. Based on the simulations conducted in the present review, the mean (CV) of Cmax values after 20 mg q4h (IM) was 208 (33%) ug/L.
4. Separate univariate analyses to determine the mean change in QTc at Tmax and its variability was conducted. The mean (CV) change in QTc (=QTc at Tmax – Baseline) of haloperidol is 15.5 (65%) msec and that of ziprasidone was 13 (104%) msec. The inter-patient variability of haloperidol (65%) is only slightly less than that of ziprasidone (104%).
5. Another important point is the applicability of the findings of the current review to the oral ziprasidone. In general, the fundamental properties of the drug such as the relationship between given concentration and effect will be independent of the mode of administration. Specifically in the case of ziprasidone, the finding about the high variability in the slope parameter from the IM data will be applicable to the oral case as well. This should be an important consideration in the risk/benefit assessment by the medical team.
6. Two subjects (50480015 and 50480025) were dropped due to unusually high ziprasidone concentrations. These subjects did not have correspondingly high QT intervals. The reviewer conducted a separate analysis including the 2 subjects, but without the 2 high concentrations under doubt. The analysis with all the 31 subjects (without the 2 high concentrations) resulted in very similar PK and PD model parameter estimates.
7. The weakness of the analysis is that the metabolites were not tested for relationship with QTc prolongation. Discerning the individual effects of parent and metabolites might not be feasible in the absence of separate administrations of these moieties.”

The CP office final recommendation is that: “overall, ... the sponsor has adequately addressed the issue of QTc prolongation, as raised in the approvable letter dated March 6, 2001”.

5 Sponsor's proposed labeling changes pertinent to QT interval

5.1 Contraindications

"QT Prolongation

Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs [ziprasidone [

[;]

5.2 Warnings

"QT Prolongation and Risk of Sudden Death

A study directly comparing the QT/QTc prolonging effect of oral ziprasidone with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. In the first phase of the trial, ECGs were obtained at the time of maximum plasma concentration when the drug was administered alone. In the second phase of the trial, ECGs were obtained at the time of maximum plasma concentration while the drug was coadministered with an inhibitor of the CYP4503A4 metabolism of the drug.

In the first phase of the study, the mean change in QTc from baseline was calculated for each drug, using a sample based correction that removes the effect of heart rate on the QT interval. The mean increase in QTc from baseline for ziprasidone ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine.

In the second phase of the study, the effect of ziprasidone on QTc length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid).

In placebo controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received Ziprasidone and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and

a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsades de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition.

Torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies. [

A study the QT/QTc prolonging effect of intramuscular ziprasidone with intramuscular haloperidol was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample based correction that removes the effect of head rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 following the first injection and 14.7 following the second injection. In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. [

Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. (see Indications and Usage).

Certain circumstances may increase the risk of the occurrence of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

It is recommended that patients being considered for ziprasidone treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during ziprasidone treatment. Persistently prolonged QTc intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, ziprasidone should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements > 500 msec.

For patients taking ziprasidone who experience symptoms that could indicate the occurrence of torsade de pointes, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, e.g., Holter monitoring may be useful."

6 Sponsor's Conclusions

"This highly controlled study characterized the pharmacokinetics and effect of IM ziprasidone and IM haloperidol on the QTc interval. The magnitude of QTc prolongation in the IM ziprasidone and IM haloperidol groups was comparable at Cmax. For ziprasidone and haloperidol, increases in concentration of study drug coincided with increases in the QTc interval. No subjects has a QTc interval \geq 480 msec. No safety concerns emerged from this study."

7 Reviewer's comments

- In general, the study addressed the concerns laid out in the Approvable Letter. Specifically, this was information on ziprasidone plasma levels achieved at T_{max} for the maximum dose proposed and the duration of the QT_c interval at this T_{max}:

At C_{max}, the mean changes from baseline in QT_c after the first dose are 4.6 msec and 6 msec for ziprasidone and haloperidol, respectively. After the second dose, the mean changes from baseline in QT_c are 12.8 msec and 14.7 msec for ziprasidone and haloperidol, respectively.

The distribution of C_{max} values after the IM injection was similar to that after the oral administration. The CP reviewer stated that “the sponsor reported a mean (CV) C_{max} value of 182 (33) ug/L after the first dose (20 mg) and 319 (41) ug/L after the second dose (30 mg). Based on the previous OCPB review, the mean (CV) of C_{max} values after 80 mg bid (oral) was 202 (35%) ug/L. Based on the simulations conducted in the present review, the mean (CV) of C_{max} values after 20 mg q4h (IM) was 208 (33%) ug/L.”

- It is not clear why very few patients underwent laboratory tests.
- A second subject in the ziprasidone group had a QT_c interval of > 450 and an increase of > 60 msec (454 msec at 1.25 hour after the first injection compared to 378 msec on day 0). This subject went on to discontinue prematurely from the study because she refused the second dose of IM ziprasidone. Adding this patient increases the total percentage of patient that had a change in QT_c of > 60 msec from 4% (1/25) to 8% (2/25). No patient in either treatment group had a measured QT_c duration greater than 480 msec.

8 Recommendations

- The following paragraph should be added to the suggested labeling after the part describing the ziprasidone intramuscular study:

In a clinical trial with intramuscular ziprasidone, the electrocardiograms of 18/25 (72%) patients who received ziprasidone and 14/24 (58%) patients who received haloperidol revealed a change in QT_c interval of more than 30 msec. In addition, the electrocardiograms of 2/25 (8%) patients who received ziprasidone compared to none of the patients who received haloperidol showed a change in QT_c interval from baseline of more than 60 msec. No patient in either treatment group had a measured QT_c duration greater than 480 msec.

- The following sentence should be removed: □

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

/s/

Tarek Hammad
6/3/02 12:02:37 PM
MEDICAL OFFICER

Judith Racoosin
6/11/02 10:35:33 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

Drug: Geodon (ziprasidone) IM
NDA: 20-919
Sponsor: Pfizer
Material Submitted: Response to Approvable Letter
Correspondence Date: 12-21-01
Date Review Completed: 5-31-02

Background:

The NDA for intramuscular ziprasidone (Geodon IM), an atypical antipsychotic agent, received an "approvable" action on 3/6/01. The intended indication for IM ziprasidone is "the treatment of acute agitation in schizophrenic patients who are being considered for treatment with oral ziprasidone but are in need of intramuscular antipsychotic medication for initial control of the agitation". The oral formulation of ziprasidone is known to prolong the QTc interval of the electrocardiogram, an effect that is correlated with the ventricular arrhythmia, torsade de pointes, and sudden death. A clinical pharmacology study designed to measure the effect of oral ziprasidone on the QTc interval showed that the prolongation was about 9-14 msec greater with ziprasidone than with four oral comparator drugs (haloperidol, risperidone, olanzapine, and quetiapine).

The approvable letter for IM ziprasidone laid out the following requests with regard to the effect of the IM formulation on the QTc interval:

1. Empirical data on the effect of IM ziprasidone on the QTc interval at Tmax after a second 20 mg IM dose (4 hours apart).
2. Empirical data on the plasma level at Tmax following a second 20 mg IM dose of ziprasidone (4 hours apart).
3. Comparison of the mean Cmax with maximal IM dosing to that with maximal oral dosing.
4. Comparison of the highest plasma levels following maximal IM dosing to the highest plasma levels following maximal oral dosing.
5. Did an increased number of patients achieve these highest levels following maximal IM dosing compared to maximal oral dosing?

Dr. Tarek Hammad of the Division safety team and Dr. Joga Gobburu of the Office of Clinical Pharmacology and Biopharmaceutics each reviewed the trial (A1281063) submitted by the sponsor to address the above questions. Please see their reviews for the details of study design and study findings.

Study A1281063 was a single-blind controlled parallel multi-center study designed to characterize the effect of the maximal recommended intramuscular dose of ziprasidone on the QTc interval at the observed Cmax. IM Haloperidol was used as a comparator. The study design appeared to be capable of providing the empirical data requested in the approvable letter showing the effect of IM ziprasidone on the QTc interval, and the associated plasma levels of ziprasidone. Note that the IM ziprasidone doses used were

20mg, followed by 30 mg. The second dose is 50% higher than the dose intended for marketing.

Findings:

I will summarize the findings according to the questions laid out above in the background section.

1. The mean changes from baseline following the first and second IM injections of ziprasidone and haloperidol are highlighted in the table below.

Baseline and mean changes from baseline in HR, QT, and QTc after dosing in the two treatment groups at their respective Cmax values among completers.

	Ziprasidone (mean and 95% CI)		Haloperidol (mean and 95% CI)	
	Baseline (BL)	Change from BL at Cmax	BL	Change from BL at Cmax
Injection 1				
QTc (msec)	380 (373, 388)	4.6 (0.4, 8.9)	386 (378, 393)	6.0 (1.4, 10.5)
QT (msec)	379 (366, 392)	-8.6 (-14.6, -2.6)	375 (365, 386)	1.5 (4.4, 7.4)
HR (beats/min)	62 (58, 66)	7.8 (4.8, 10.7)	66 (62, 70)	2.5 (0.1, 4.9)
Injection 2				
QTc (msec)	374 (367, 381)	12.8 (6.7, 18.8)	380 (374, 386)	14.7 (10.2, 19.2)
QT (msec)	366 (354, 379)	-7.0 (-14.0, -0.1)	363 (355, 372)	4.2 (-1.9, 10.4)
HR (beats/min)	65 (60, 70)	12.1 (8.3, 15.9)	70 (65, 74)	5.9 (2.7, 9.0)

A related finding of the biopharmaceutics review, based on the simulation with 2900 patients treated with 20 mg IM ziprasidone followed by a second 20 mg IM dose four hours later, is that the mean (or median) QTc prolongation from baseline, based on that dosing regimen, is about 8 msec. Because the between subject variability of relationship is high (100%), about 10% of the patients treated with this dosing regimen could experience a QTc prolongation from baseline as high as 18- 44 msec.

The outliers using absolute and relative (change from baseline) thresholds are seen in the following table.

Categorical summary of QTc and QTc changes from baseline after dosing in the two treatment groups at their respective Cmax values among completers.

N=	Injection 1		Injection 2	
	Ziprasidone 25	Haloperidol 24	Ziprasidone 25	Haloperidol 24
With QTc				
>=450 (msec)	0	0	1 (4 %)	0
>=480 (msec)	0	0	0	0
>=500 (msec)	0	0	0	0
Change in QTc				
>=30 (msec)	12 (48 %)	13 (54 %)	18 (72 %)	14 (58%)
>=60 (msec)	1 (4 %) #	0	1 (4 %)	0
>=75 (msec)	0	0	0	0

The patient discontinued after the first injection.

2. The empirical data on the plasma levels at Tmax following a second IM dose of ziprasidone and haloperidol are seen in the table below.

QTc Change, Categorical Increases, and Pharmacokinetic Parameters for Ziprasidone and Haloperidol

		Injection 1		Injection 2	
		Ziprasidone	Haloperidol	Ziprasidone	Haloperidol
QTc Change*	N =	25	24	25	24
Mean (95% CI)		4.6 (0.4, 8.9)	6.0 (1.4, 10.5)	12.8 (6.7, 18.8)	14.7 (10.2, 19.2)
Incidence ≥ 50 msec		0	0	0	0
Incidence ≥ 30 msec		12	13	18	14
Incidence ≥ 60 msec		0	0	1	0
Pharmacokinetics	N=	23	22	23	22
Mean Cmax (%CV)		182 (33)	12.6 (43)	319 (41)	17.9 (32)
Mean Tmax (%CV)		1.2 (58)	0.6 (33)	1.1 (45)	1.0 (80)

* Change from Baseline QTc defined as the average of the 3 values surrounding Tmax for each injection; Baseline correction, $QTc = QT/RR^{0.33}$

The primary conclusion from the biopharmaceutics analysis is that the QTc prolongation of ziprasidone is concentration dependent, although the variability is considerable. Based on the simulation conducted by Dr. Gobburu, the mean (CV) of Cmax values after 20 mg q4h (IM) was 208 (33%) ug/L. This simulation was done because the second IM dose of ziprasidone in the study was 30 mg, a dose 50% higher than the intended dose for marketing.

3. Comparison of the mean Cmax with maximal IM dosing to that with maximal oral dosing.

The sponsor did not provide a direct comparison between the mean Cmax for maximal IM dosing and maximal oral dosing. According to the biopharmaceutics reviewer, based on the previous OCPB review, the mean (CV) of Cmax values after 80 mg bid of oral ziprasidone was 202 (35%) ug/L. This is very close to the 208 (33%) ug/L found in the simulation of 20 mg IM ziprasidone followed by a second 20 mg IM dose (as described above).

4. Comparison of the highest plasma levels following maximal IM dosing to the highest plasma levels following maximal oral dosing.

The sponsor did not provide a direct comparison between the highest plasma levels observed following maximal IM dosing and maximal oral dosing. Based on the observation that the coefficient of variability was similar between the maximal oral dosing and the simulated maximal IM dosing (see #3 above), one can infer that the distribution of high plasma levels would be similar between the two dosing routes.

5. Did an increased number of patients achieve these highest levels following maximal IM dosing compared to maximal oral dosing?

The sponsor did not provide a direct comparison of the number of patients experiencing the highest plasma levels following maximal IM dosing and maximal oral dosing. However, based on the observation that the mean and variance of the Cmax of the maximally orally treated and maximally IM treated populations were similar, then the

likelihood of a particular concentration being observed is similar for both of these populations.

Conclusions:

The sponsor has responded adequately to the questions from the approvable letter regarding the effect of maximally dosed IM ziprasidone on the QTc interval duration at C_{max}.

Labeling recommendations:

These recommendations combine the biopharmaceutics recommendations with the safety group's recommendations.

The italicized text represents the sponsor's proposal. The excerpt below starts with the 5th paragraph under the Warnings statement "QT Prolongation and Risk of Sudden Death."

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsades de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses in premarketing studies.

A study evaluating the QT/QTc prolonging effect of intramuscular ziprasidone, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of ziprasidone (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular ziprasidone is 50% higher than the recommended therapeutic dose. The mean change in QTc from baseline was calculated for each drug, using a sample based correction that removes the effect of head rate on the QT interval. The mean increase in QTc from baseline for ziprasidone was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QTc from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection.

3 In this study, no patients had a QTc interval exceeding 500 msec.

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. □

□ Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. (see Indications and Usage).

/S/

Judith A. Racoosin, MD, MPH
Safety Team Leader,
Division of Neuropharmacological
Drug Products

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

/s/

Judith Racoosin
5/31/02 01:14:52 PM
MEDICAL OFFICER

MEMORANDUM

DATE: March 4, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-919

SUBJECT: Action Memo for NDA 20-919, for the use of Geodon IM (ziprasidone mesylate) for the treatment of acute agitation

NDA 20-919, for the use of Geodon IM (ziprasidone mesylate), was submitted by Pfizer, Inc., on 12/17/97. That application was the subject of a Not Approvable letter dated 12/17/98. The primary clinical reason for the action was the finding with the oral ziprasidone formulation of a prolongation of the QTc interval, and the requirement for further characterization of this finding. Importantly, the letter informed the sponsor that the Agency had determined that the sponsor had demonstrated substantial evidence of effectiveness for the proposed indication, "the acute control and short-term management of the agitated psychotic patient". In addition to the clinical deficiency, there were 2 other reasons given for the Not Approvable conclusion: 1) the need for rodent and non-rodent 1 month toxicity studies with the beta-cyclodextrin sulphobutyl ether formulation given IM, and 2) a number of deficiencies related to the manufacture of the sulphobutyl ether beta-cyclodextrin, including an unsatisfactory inspection of its manufacturer. In addition to these reasons for the Not Approvable decision, there were several other pharmacology/toxicology and CMC deficiencies noted.

The sponsor responded to the Not Approvable letter in a submission dated 9/6/00. Subsequent to this re-submission, the NDA for the oral formulation was approved on February 5, 2001. The approval of that application was based on substantial additional work done to further characterize the nature and degree of the QTc prolongation. Briefly, the sponsor performed a clinical pharmacology study in which the effects of a number of newer, "atypical" (risperidone, quetiapine, and olanzapine) and older (thioridazine, haloperidol) anti-psychotic drugs on the QT interval were assessed at each drug's T_{max}, and with maximum metabolic inhibition. This study demonstrated that the QTc interval with ziprasidone was prolonged to a greater degree than with any of these comparator drugs (about 10-15 msec greater than that seen with haloperidol) except thioridazine, which had a substantially longer QTc interval than even ziprasidone. The degree of prolongation with ziprasidone did not increase with maximum metabolic inhibition (achieved by co-administration of ketoconazole), although the plasma levels of ziprasidone did increase by about 30% (the dose of ziprasidone studied was 80 mg BID at steady-state, the maximum proposed recommended dose).

These findings supported the approval of oral ziprasidone, but with restrictive labeling (especially the requirement that prescribers consider alternative treatments because of the observed QTc prolongation), and prominent warnings. Importantly, the letter asked the sponsor to further evaluate the effects of this degree of QTc prolongation, as well as to further characterize the dose response for QTc prolongation, beyond the 80 mg BID dose.

Subsequent to the Not Approvable letter, the division sent the sponsor a letter (4/20/00) that informed them that we had begun to re-think the appropriateness of the indication they had proposed, and which we had previously stated was acceptable, and for which we had further stated that the sponsor had established evidence of effectiveness. This concern related to our view that "acute agitation" had not been adequately defined, and further it was not clear if agitation was a non-specific symptom, which appeared in the context of a number of clinical settings, or whether it was fundamentally different in different clinical settings. For this reason, this issue was discussed at a meeting of the Psychiatric Drugs Advisory Committee on 2/15/01.

At that AC meeting, the committee unanimously agreed that the sponsor had demonstrated effectiveness of ziprasidone IM for the acute treatment of agitation in patients with schizophrenia and schizoaffective disorders (the patients in whom the studies were performed). The committee also concluded that safety had also been established, but the vote was 5-3.

The 9/6/00 re-submission has been reviewed by Dr. Lois Freed, pharmacologist (review dated 3/2/01), and Dr. Tom Laughren, Psychiatric Drugs Team Leader (memo dated 2/28/01). In addition, Dr. Robert Seevers, Chemistry Team Leader, has reviewed several CMC submissions made by the sponsor in response to the deficiencies stated in the Not Approvable letter (reviews dated 11/19/99 [2], and 1/14/00). Dr. Seevers has concluded that the outstanding CMC deficiencies have been addressed. Dr. Freed reiterates the request, made in the Not Approvable letter, for the sponsor to commit to performing a reproductive toxicity study in Phase 4, and, in addition, requests that the sponsor submit toxicokinetic data for the 1 month rat and dog toxicity studies. Dr. Laughren has concluded that the application should be considered Approvable, but that the sponsor must provide additional data to establish the safety of the product.

I agree that the sponsor has demonstrated substantial evidence of effectiveness for a claim related to the acute management of agitation in patients with schizophrenia (while the studies enrolled patients with schizoaffective disorders, there is good reason to limit the indication to patients with schizophrenia; see below), but I also agree with Dr. Laughren that additional questions must be adequately addressed before the application can be approved.

Specifically, there are a number of questions related to the full characterization of the effects of IM ziprasidone on the QTc interval at the maximum dose to be recommended.

The sponsor has provided little empirical data on two important points; namely, the plasma levels achieved at Tmax for the maximum dose proposed (40 mg/day, either as 10 mg q2h x 4, or 20 mg q4h x 2), and the duration of the QTc interval at this Tmax.

Specifically, the sponsor has empirically documented plasma levels after multiple IM doses in only one study (Study 046), in which subjects received various regimens. Of particular interest was the group that received 80 mg/day, given as 20 mg dose every 4 hours. While this study could have given useful information about Cmax at an appropriate regimen, this parameter was not measured.

Instead, the sponsor has submitted (via fax on 2/26/01) the results of simulation studies done to predict Cmax at the maximum proposed regimen.

The results of these simulations suggest that the mean Cmax in 1000 simulated patients after a second dose of 20 mg given 4 hours after the first dose would be about 284 ng/ml. The sponsor concludes that these levels are approximately equal to the Cmax levels seen in the previously described clinical pharmacology study with oral ziprasidone, for which we have empirical QTc data. In this study, the mean Cmax (with metabolic inhibition) was about 224 ng/ml. The sponsor concludes that there is no expected increase in the QTc interval with the maximum recommended dose of IM ziprasidone compared to that for the maximum exposure to oral ziprasidone.

However, the sponsor has submitted little data on the effects on the QTc interval at the Cmax's seen with the maximum recommended dose of IM ziprasidone.

Specifically, the sponsor has presented data from 12-14 patients who had QTc intervals measured at 0-2 hours after what I believe to be multiple doses of 20 mg IM ziprasidone. The mean change from baseline varied from 6.4-9.1 msec (the data from the sponsor's presentation at the 2/15/01 AC meeting and their briefing book for that meeting are slightly different).

Further, we have no direct data that speak to the variability of the Cmax's expected to be seen with IM administration compared to oral administration. In particular, even if we could conclude that the mean Cmax's seen were essentially equivalent between those achieved after the maximum recommended doses of the approved oral form and the IM, we need to assess the risk of much higher Cmax's in any outliers. While the sponsor stated at the AC meeting that the variability of the oral is greater than that of the IM, we have seen no direct comparison of this variability. Clearly, the sponsor's simulations suggest that patients could be exposed to levels of up to 800 ng/ml after IM ziprasidone. The

number of patients who achieved plasma levels greater than 400 ng/ml in the oral ziprasidone development program was 9.

Further, even if we could conclude that the mean Cmax's were not importantly different between the IM and oral formulations, we could not assume that these would result in equivalent durations of the QTc segment, because of the markedly different rates of absorption. While the Cmax after oral administration is reached about 6 hours after dosing, it is reached in about 1 hour or less after dosing with the IM formulation. The data on the effects of this rapid absorption of drug on the QT interval have largely been unaddressed, save for the 12-14 patients described above. It is theoretically possible, for example, as postulated by the sponsor at the AC meeting, that the QTc may be more prolonged at Cmax following oral dosing, if any metabolites formed during first-pass contribute to the QT effect, given that these metabolites might not appear when the drug is given parenterally. Nonetheless, this has not been adequately addressed.

Finally, we have no direct information that addresses the importance, if any, of the duration of QTc prolongation to any potential risk of life-threatening arrhythmias. That is, under oral dosing, plasma levels approximately equal to Cmax may persist for several hours, while plasma levels drop off rapidly with the IM formulation. Whether spending more time at a given prolonged QTc interval confers more risk to a patient (as may be seen with oral dosing) than the relatively brief time that plasma levels are close to Cmax after IM dosing has not been addressed by the sponsor.

Labeling

Dr. Laughren has proposed that IM ziprasidone be indicated for use only in those agitated schizophrenic patients for whom consideration has been given to being treated with oral ziprasidone. This keeps faith with the current indication for oral ziprasidone, which, as noted above, recommends that prescribers consider other treatments first. While there are no other approved treatments for the control of acute agitation, there are other parenteral medications that are currently used for this indication, and I agree that it is prudent to maintain the principle that ziprasidone IM be used only in those patients in whom oral ziprasidone is being considered for long term treatment.

I also agree with Dr. Laughren that IM ziprasidone should not be used in patients currently being treated with oral ziprasidone. I recognize, as does Dr. Laughren, that these 2 conditions will likely restrict the use of IM ziprasidone considerably (that is, it should be used only in those patients for whom oral ziprasidone is being considered, but only in those not currently being treated with it). However, as discussed at the AC meeting, we are very concerned that the use of IM ziprasidone in patients with pre-existing plasma levels of ziprasidone may result in plasma levels that are quite high, with associated risks that are unknown. In

the absence of evidence establishing that plasma levels that might be achieved under these circumstances do not confer additional risk, it is prudent to restrict IM ziprasidone use to patients who are not currently being treated with oral ziprasidone.

For the reasons stated above, I will issue the attached Approvable letter, with the appended draft labeling.

/s/

Russell Katz, M.D.

/s/

Russell Katz
3/6/01 12:13:38 PM
MEDICAL OFFICER

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 28, 2001

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for Geodon IM (ziprasidone IM) for the acute treatment of agitation in schizophrenia

TO: File NDA 20-919
[Note: This overview should be filed with the 9-6-00 resubmission of the NDA in response to the 12-17-98 non-approval letter. The reader is referred to my 12-8-98 memo to the file for a more complete summary of the administrative history and data in support of this application.]

1.0 BACKGROUND

Ziprasidone IM is an intramuscular formulation of the antipsychotic drug ziprasidone that is being proposed for use in the "acute control and short-term management of the agitated psychotic patient." It is noteworthy that NDA 20-825 for the PO formulation of ziprasidone was recently approved (2-5-01) for the treatment of schizophrenia. The approval of the oral formulation was delayed several years because of concerns about the potential for QTc prolongation with this drug. In fact, the labeling makes clear that ziprasidone is an outlier regarding this effect compared to several other recently approved antipsychotic drugs, and suggests that other drugs might be considered before selecting ziprasidone.

Because of unresolved concerns about the safety of ziprasidone at the time we were considering the IM application, a non-approval letter was issued (12-17-98). It is noteworthy that, in the non-approval letter, we indicated that we considered the efficacy data sufficient to support the claim. We noted that safety was our concern. Thus, even though no other drugs were specifically approved for agitation (nor are any such drugs approved at present), we suggested that the availability of intramuscular formulations of other drugs, including other antipsychotic drugs and also various sedating drugs (benzodiazepines and others), argued against the need for this drug to be approved at that time. The non-approval letter also listed pharmacology/toxicology and CMC deficiencies, some of which would need to be addressed prior to approval, and some later.

The NDA was initially resubmitted 3-10-00, however, we issued a 4-20-00 letter noting that the resubmission was not considered complete, since it did not include the 1 month tox studies cited as necessary in the non-approval letter. In addition, we alerted Pfizer that discussions at the 3-9-00 meeting of the PDAC, which focused on psychiatric syndromes in patients with dementia, had raised questions about the entity agitation, in particular how to define it and whether to think of it as a specific or nonspecific symptom. Thus, we noted that even the issue of efficacy may not be as settled as our 12-17-98 letter might have suggested.

We did not take the original NDA to the PDAC, however, the resubmitted application was the subject of a 2-15-01 meeting of this committee.

2.0 CHEMISTRY

To my knowledge, all CMC issues have been resolved at this point.

3.0 PHARMACOLOGY

The requested 1 month tox study data were included in the 9-6-00 resubmission of the NDA, and to my knowledge, all pharmacology/toxicology issues have been resolved at this point.

4.0 BIOPHARMACEUTICS

To my knowledge, all biopharmaceutics issues have been resolved at this point, to the extent that they can be, given the available data. I am persuaded, based on the actual data we have that, for the most part, ziprasidone naive patients dosed with IM ziprasidone at the recommended IM doses do not experience ziprasidone exposures much in excess of those observed with maximal dosing with oral ziprasidone. However, the exposures that will be seen when IM ziprasidone is added to orally dosed patients is unknown, and we have only simulations from the sponsor, received in a package faxed to us only very recently (2-26-01). Reviewing this material will take a considerable effort. In the meantime, I have proposed labeling that recommends against such use.

5.0 CLINICAL DATA

5.1 Efficacy Data

As noted in my 12-8-98 memo, the sponsor presented the results of 2 controlled trials involving the use of ziprasidone IM in the control of agitation in psychotic patients (125 & 126). Both utilized a low (2 mg) ziprasidone IM dose as the control against which a higher ziprasidone IM dose was compared. In each case, the focus was on the control of agitation following the initial ziprasidone IM dose. Although the protocols identified 3 primary outcomes for each study, i.e., (1) AUC for the

Behavioral Assessment Scale (BAS) after the first dose, (2) change from baseline to 4 hours for the CGI-S, and (3) change from baseline to study endpoint for the CGI-S, we decided, prior to looking at the data, that the most critical endpoint would be the AUC for the BAS. The BAS was developed by Pfizer specifically for these 2 trials, and consists of a 7-point scale targeting both agitation and level of consciousness. The 7 items are defined as follows:

- 1 = difficult or unable to rouse;
- 2 = asleep, but responds normally to verbal or physical contact;
- 3 = drowsy, appears sedated;
- 4 = quiet and awake (normal level of activity);
- 5 = signs of overt activity (physical or verbal), calms down with instructions;
- 6 = extremely or continuously active, not requiring restraint;
- 7 = violent, requires restraint.

In summary, both studies were successful in showing superiority of the higher ziprasidone dose (10 mg in study 125 and 20 mg in study 126) over the 2 mg dose in controlling agitation following the initial IM dose, as assessed by the BAS.

5.2 Safety Data

Regarding safety, there were no new findings to suggest a different safety profile for ziprasidone IM compared to that observed for oral ziprasidone. Orthostatic hypotension may occur in some patients, as it does with oral ziprasidone, particularly in nonschizophrenic patients not accustomed to taking antipsychotic agents. A dose dependent increase in QTc was apparent for ziprasidone IM, with a magnitude similar to that observed with oral ziprasidone. However, as discussed later, more work is needed to better explore possible QTc effects with IM ziprasidone.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

A 2-day meeting of the PDAC was held February 14-15, 2001, with two goals: (1) to discuss generally approaches to developing intramuscular formulations of antipsychotic drugs for treating agitation, and (2) to specifically discuss two applications for such products. The general discussion occurred on 2-14-01, and the discussion of the ziprasidone application occurred on 2-15-01.

6.1 Background Information for General Discussion

As part of the background information for the general discussion, the committee was provided with an overview of different possible approaches to developing IM antipsychotic products. One approach to gaining approval for parenteral formulations of these newer agents would be to rely on pharmacokinetic (PK) studies characterizing the PK profile for these parenteral formulations, along with sufficient safety data to provide reassurance of the safety of these formulations. The problem with this approach, from FDA's perspective, is that parenteral formulations are almost certainly not

going to be bioequivalent with the immediate release formulations, i.e., equivalent regarding both rate and extent of absorption. Thus, relying on this approach would necessitate assuming that either rate or extent of absorption is not pertinent to efficacy, and this is not an assumption the agency has been willing to make for other formulations. For example, sustained release formulations have been proposed for a number of psychotropic products, and at the current time, the requirements for approval of these formulations include a demonstration of efficacy based on at least one adequate and well-controlled clinical trial. It should be noted that, at the time the parenteral formulations of the older antipsychotics were approved, there was not a requirement for efficacy data to support such approvals.

Thus, as we have been approached by sponsors of more recently approved antipsychotic drug products seeking to develop parenteral formulations for their products, we have had to confront the issue of how best to develop these formulations. In designing a clinical program, the first question to address is what clinical entity to target in the program. Depending on how this question is answered, two alternative approaches for developing parenteral formulations have emerged.

One approach to targeting a clinical entity is to take the view that the clinical entity being treated with the parenteral formulation is the identical entity for which the antipsychotic drug product has an approved indication, i.e., schizophrenia. In fact, this is consistent with the view of many clinicians who consider the use of parenteral antipsychotic drugs as the only practical way to initiate treatment for some acutely exacerbated schizophrenic patients. Thus, they view the use of an IM antipsychotic agent as the initiation of the treatment of a schizophrenic episode, with the understanding that a switch to oral immediate release medication will occur very quickly. Furthermore, it is understood that the antipsychotic effect will most likely not be achieved until well after the switch to oral medication is made.

A clinical trial to demonstrate the effectiveness of a strategy of initiating treatment with an IM formulation and then rapidly switching to oral medication could be done and would simply be a slight modification of a typical short-term antipsychotic trial. The modification would be that, rather than getting oral medication from day 1, patients would get IM medication for some fixed time period, e.g., the first 2 days, and would then be switched to oral medication. Assessments of antipsychotic effect would still focus on the later time points in the trial, since the expected time frame for antipsychotic response would not be changed. However, this does raise the interesting question of whether or not initiation of treatment with IM medication would hasten the antipsychotic response. This question could also be studied, but would involve a more complex design.

An alternative view is that the use of IM antipsychotic medication is not really intended to treat the psychosis per se, but rather, is intended to have a more general calming effect, related to properties of the drug other than its specific antipsychotic effect. The clinical target in this case might be considered to be the "agitation" that is often observed in exacerbated schizophrenic patients. This approach to gaining approval of IM formulations of these products has the advantage of focusing on a clinical target for which a very rapid response could be expected and, thus, an effect would be fairly easy to demonstrate. This approach is also appealing from the standpoint of what the drugs may actually be used for, i.e., initial rapid control of patients, rather than a longer-term antipsychotic effect.

The question then becomes, "What is agitation?" Dorland's Medical Dictionary defines "agitation" as "exceeding restlessness associated with mental distress." It defines "agitated" as "marked by restlessness and increased activity intermingled with anxiety, fear, and tension." DSM-IV defines "psychomotor agitation" as "Excessive motor activity associated with a feeling of inner tension. The activity is usually nonproductive and repetitious and consists of such behavior as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still." These are fairly general definitions that might apply to patients with very different underlying diagnoses. They are consistent with a definition that appeared in a recent paper in the psychiatric literature, i.e., "motor restlessness such as fidgeting and pacing associated with an inner tension..." (Phenomenology and Treatment of Agitation, Alan Schatzberg, J Clin Psychiat, Monograph on "Phenomenology and Treatment of Aggression Across Disease States," Vol 17, Monograph 2, 1999, pp.12-14).

One distinction worth noting is between what might be considered acute agitation and chronic agitation. Acute agitation might be considered the restlessness associated with an acute illness, e.g., exacerbation of schizophrenia. Chronic agitation might be considered a more chronic pattern of behavior associated with a chronic disease state, e.g., Alzheimer's disease. In fact, there was considerable discussion of the concept of "agitation" at a March 9, 2000 meeting of the PDAC focused on behavioral and psychological symptoms associated with various dementias. The chronic agitation associated with an illness like Alzheimer's disease is generally viewed as including a much broader set of behaviors than usually considered to comprise acute agitation.

At the March 9, 2000 meeting of the PDAC, there was no general consensus regarding agitation, either how to define it, or how to think of it in terms of it being either a disease specific entity or a nonspecific symptom. Some members and guests considered agitation of Alzheimer's disease a syndrome distinct to that illness, while others viewed it as an entity that might be considered nonspecific and occurring in a similar form in association with different disease states. In either case, there were widely varying views on how to define the entity. Thus, no agreement was reached at the March 9th meeting on whether or not and how to develop drug treatments for "agitation" in association with Alzheimer's disease.

The committee was reminded that two types of clinical entities are considered appropriate targets for new claims. Specific diseases or syndromes are the usual focus of a drug claim, e.g., congestive heart failure or rheumatoid arthritis. However, nonspecific signs or symptoms not unique to a single disease or syndrome, e.g., pain or fever, may also be the focus for a claim. Antipyretics and analgesics are approved for these nonspecific symptoms on the basis of studies involving different "models" for each such symptom, e.g., headache pain and dental pain as different pain models. The basis for accepting this nonspecific approach to indications is the view that, while the disease states leading to these nonspecific symptoms may differ markedly, the symptoms themselves are: (1) universally defined, in whatever disease context they occur; (2) readily measured, using commonly accepted assessment methods; (3) ideally have a well understood pathophysiological basis; (4) and respond similarly to drug treatment for that symptom, quite apart from the diverse disease states that may lead to the nonspecific symptom. Of course, we do not understand any psychiatric illnesses at a pathophysiological level, and this would not be an absolute requirement for a nonspecific symptom; however, this is a reasonable goal to strive for in this instance, since an understanding of mechanism may help to establish such a symptom as really independent of the underlying specific disease state in which it

happens to occur. Critical to this approach to gaining a new claim is the concept of pseudospecificity. In this context, since the essence of this type of claim is that the symptom is nonspecific, i.e., to any one disease, it is essential that efficacy be demonstrated in several different disease models. To attempt to obtain a claim for a nonspecific symptom in a single disease model would, by definition, be pseudospecific, since such a claim would give the impression that the symptom is specific to that disease.

In considering new claims, whether for a specific disease/syndrome or a nonspecific sign/symptom, the committee was reminded that similar criteria are used by FDA to evaluate the proposed clinical entity as an appropriate target for a new claim. The proposed clinical entity must be accepted in the relevant clinical/academic community, it must be operationally definable, and it must identify a reasonably homogeneous patient group. The latter two criteria are important to ensure the validity of the clinical trials supporting the claim and to make it possible to inform clinicians in labeling about the use of the proposed treatment.

6.2 Committee Discussion of Specific Questions

Following a presentation of background information, the committee was asked to discuss several questions pertinent to developing parenteral formulations of antipsychotic drugs for IM use. Following are the questions and a summary of my impression of committee member's views on these issues:

Question: Are effectiveness data needed to support the approval of a parenteral formulation of an antipsychotic for IM use, or is it sufficient to rely on the efficacy data available for the orally administered immediate release formulation?

Response: The committee seemed to be unanimous in the view that efficacy data would be needed to support the approval of any such products.

Question: If effectiveness data are needed, what should be the clinical target that is the focus of the required effectiveness studies?

-In particular, should the focus be on schizophrenia, the approved indication for the oral formulation, or on some other clinical findings present during an acute episode of illness that are deemed to require the use of IM medication?

Response: There was essentially no support among committee members for focusing effectiveness trials for IM antipsychotic products on schizophrenia per se.

Question: If schizophrenia is considered to be the appropriate clinical target for the development of IM formulations of antipsychotic drug products, what study designs would be optimal to support a claim for these products?

Response: As noted, there was agreement that schizophrenia is not an appropriate target for IM antipsychotic product development programs.

Question: Is "agitation" an acceptable clinical target for the development of IM antipsychotic drug products?

- If so, how should "agitation" be defined?
- What outcome measures are optimal for the assessment of "agitation?"
- What study designs are optimal for the study of "agitation?"

Response: There seemed to be general agreement that agitation, however that might be defined, was the appropriate target for these programs.

-There was a fair amount of discussion about what characterizes "agitation," however, no attempt was made to try to define this in a standard way. There was an attempt to try to identify features of agitation that might appropriately lead to the use of IM antipsychotic products, e.g., "threatening behavior," "escalating behavior," "urgently distressing behavior," "self-exhausting behavior that threatened the well-being of a patient," or "behavior that impeded a needed diagnostic assessment of a patient." There seemed to a general view that clinicians "know agitation when they see it."

-There was some discussion of outcome measures, but no consensus on which are optimal.
-There seemed to be general agreement that very short-term trials, i.e., even single dose as was the case for the two development programs to be discussed in this meeting, were appropriate, given the short-term nature of IM treatment.

Question: Is it worthwhile distinguishing between what might be considered "acute agitation" and "chronic agitation?"

Response: There did seem to be agreement that the type of chronic, persistent agitation that might be seen in a patient with dementia can reasonably be distinguished from the acute agitation that occurs in patients with exacerbating illnesses and requires intervention with IM medication.

Question: Is "agitation" a phenomenon that is specific to different disease states or can this be considered a nonspecific symptom that occurs in identical form in association with different disease states?

- If "agitation" can be considered a nonspecific symptom, is it necessary to study it in different disease models in order to gain a claim?
- If so, in what disease models should it be studied?

Response: There was extensive discussion of this issue, and ultimately committee members were asked to individually respond to this question. There was essentially unanimous agreement that these products should not be granted broad claims for "agitation," but rather, that the claims should be tied fairly closely to specific diagnoses. There were several reasons supporting this view, one being a general agreement that we do not yet understand the pathophysiology of agitation. There was particular concern about agitation in psychiatric and non-psychiatric settings, and about the different types of agitation not studied in these programs. These concerns were partly based on possible differences in efficacy, but also on different safety profiles, e.g., the use of these products in patients naive to antipsychotic products. In any case, there was broad agreement that we are not yet ready to consider

agitation a nonspecific symptom in the same sense that we consider pain and fever to be nonspecific symptoms.

6.3 Discussion of Ziprasidone IM Application

Since the discussion of this application occurred on the second day of the meeting, following first the general discussion and then the specific discussion of the olanzapine IM application, both on the first day, the committee had already largely solidified its position on some general principles, in particular, the principle that the claims for agitation should be tied to the specific diagnoses in which a drug was studied. Thus, there was no objection in principle to the ziprasidone application, which was more limited in scope than the olanzapine program, in that it focused largely on agitation in association with schizophrenia, and to a somewhat lesser extent with schizoaffective disorder.

After discussion of the application, the committee voted unanimously that the efficacy of ziprasidone IM in the treatment of agitation associated with schizophrenia and schizoaffective disorders had been demonstrated. There was not a unanimous opinion regarding the safety of IM ziprasidone, however, the vote was overall in favor of the safety of this drug (5 for, 3 against).

There were several issues that received particular attention during the committee deliberations:

-What plasma exposure for ziprasidone might be expected for the highest recommended dose and how does this compare with the exposures seen for the highest recommended oral dose?

-There was initially confusion on this point at the PDAC meeting, since a Pfizer representative suggested that average C_{max}'s after two 20 mg doses are in the 350-400 ng/ml range, i.e., levels that were not generally observed with maximal oral dosing. However, they corrected this with information that the levels after two 20 mg doses are in the 250 ng/ml vicinity. They did predict, however, that with combined oral and IM dosing, levels around 400 ng/ml might easily be reached.

-Comment: The committee was concerned about the lack of experience at the higher exposures that might be seen with combined dosing and generally seemed to feel that such use could not be recommended.

-What diagnostic groups were studied?

-Since Pfizer intended to support a claim for agitation in psychotic patients, they decided to permit broad entry criteria, including patients with any of the following DSM-IV diagnoses for studies 125 and 126: schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, schizophreniform disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, or psychotic disorder not otherwise specified. Despite the broad entry criteria in terms of diagnoses, roughly half the patients were schizophrenic, a third were schizoaffective, and most of the rest were bipolar. There were only a few patients meeting other diagnostic criteria. At the meeting, Pfizer provided data for schizophrenic and schizoaffective patients separately, suggesting that an effect was demonstrated in both

subgroups. There clearly were not enough of any other subgroups to reveal whether or not there was an effect in other subgroups.

-Comment: The committee seemed to view this sample as sufficient for supporting a claim for agitation in patients with schizophrenia and schizoaffective disorder.

-What clinical entity was studied?

-Patients had to be "acutely agitated," and presumably in need of IM medication, in the judgement of the investigator. The only attempt to further define agitation was an added requirement that patients have a score of ≥ 3 on 3 of 4 PANSS agitation items (anxiety, tension, hostility, and excitement). It was noted that patients with the most severe agitation were excluded since they could not give consent (thus, there were no patients with 7's on the BAS, and very few 6's).

-Comment: The committee was sympathetic to the impossibility of including the most severely agitated patients, and seemed satisfied with the relatively imprecise characterization of "agitation."

-Were patients excessively sedated?

-There was discussion of this issue since item 1 of the BAS is characterized as "difficult or unable to arouse," and a small but not insignificant proportion of patients (roughly 10%) were given this classification following treatment with IM ziprasidone. However, this term may have been used somewhat differently than characterized, since only 4% of patients with this classification were missing vital signs assessments at the time of this rating, and this assessment including the requirement to stand for orthostatic measurements. Furthermore, it was pointed out that sound sleep is often an acceptable outcome in a patient who has not slept for several days due to exacerbating psychotic illness.

-Comment: The committee seemed satisfied with this explanation.

-What should be the recommended dose?

-Although there was no direct comparison of the 10 and 20 mg doses, there was indirect evidence of a somewhat greater effect for the 20 mg compared to the 10 mg dose. The 10 mg dose was superior to placebo on the BARS AUC at 2 hours, but not on the CGI severity at 4 hours and 24 hours. However, the 20 mg dose was superior to placebo on all three outcomes. Furthermore, while the curves for placebo improvement on the BARS were overlapping for the two studies, the 20 mg data were superior to the 10 mg data for the first 2 hours for which intensive data monitoring occurred. Finally, a responder analysis also favored 20 mg over 10 mg.

-Comment: The committee seemed to agree that both the 10 and 20 mg doses were shown to be effective, but also that there was some evidence at least suggestive of a somewhat greater effect for the 20 mg dose.

7.0 LABELING

There are several labeling issues that merit comment:

-Indication: The sponsor proposed labeling targeting agitation in patients with both schizophrenia and schizoaffective disorder, and the PDAC seemed to agree with this choice. However, given the essentially second-line status for this drug, and the limitation of its use to schizophrenia, I think at this time it is important to also limit the IM formulation to agitation in schizophrenia. In addition, given the uncertainties regarding the risks associated with the QTc prolongation seen with ziprasidone generally, and ziprasidone IM in particular, I feel this product should be further targeted to schizophrenic patients who are being considered for chronic treatment with the oral formulation, i.e., patients considered candidates for oral ziprasidone therapy who are in need of short-term IM medication for acute control of agitation. Furthermore, given the lack of experience in adding IM ziprasidone to steady state levels associated with chronic oral dosing, and the prediction that such a combination might well lead to plasma level exposures well in excess of those for which we currently have experience with oral dosing, I consider it appropriate to further limit the use of this product to patients not already taking oral ziprasidone orally. Thus, I have proposed labeling which significantly limits the use of IM ziprasidone in this way.

-Pharmacokinetics: We have deleted speculation about the metabolism and elimination of IM ziprasidone, since this has not been systematically examined. We have not incorporated any information from the simulations received only recently (2-26-01), but upon further review, there may be some information that might be added to labeling based on these simulations.

-Description of Clinical Trials: In keeping with the more narrow indication, I have proposed a description of the clinical trials that mentions only the patients with schizophrenia. Support for this choice comes from a subgroup analysis showing that even within the schizophrenic subgroup the higher ziprasidone doses are statistically significant favored over the 2 mg dose. I have also deleted all safety information from the clinical trials description section, since this section of labeling is ordinarily limited to efficacy findings.

-Warnings: In the sponsor's proposed labeling, the only mention of QTc effects with ziprasidone IM is a reassuring statement that none of 523 patients exposed to this formulation had a QTc interval exceeding 500 msec. However, given the fact that ECG's were obtained mostly at random times after dosing, this finding is not very reassuring, given the rapid rise and fall in plasma levels with IM administration. In fact, relatively few patients had ECGs recorded within 2 hours of dosing, the time when peak effects would be expected (e.g., only n=14 at 20 mg IM had ECGs during this interval). Furthermore, there is the question of rate of rise of plasma concentration and QTc effect; ideally the sponsor would have looked at this question with frequent ECG assessments during the first 2 hours after dosing. While I am reasonably persuaded, based on the plasma level data for the population

exposed to ziprasidone IM, that the exposures overall fell within the exposure range for the oral formulation experience, there is not sufficient information to address the question of rate of rise and QTc effects, nor is there sufficient information to address the question of outliers in terms of plasma level exposure. More work is needed before we can adequately draft this section regarding QTc risks for ziprasidone IM.

-Adverse Reactions: I have made a number of changes to this section, and I have asked that the sponsor replace the common events table with one based solely on the pool of studies 125 and 126, since these are most similar in design.

-Dosage and Administration: The sponsor has proposed a dose of 10 or 20 mg, without further qualification, thus leaving it up to the judgement of clinicians to decide which dose to use in which patient. I believe that both doses were shown to work, and there is only indirect evidence to suggest a somewhat greater benefit for the 20 mg dose compared to the 10 mg dose. Both doses were also acceptably safe. Thus, I don't object to the somewhat ambiguous advice.

8.0 FOREIGN REGULATORY ACTIONS

To my knowledge, ziprasidone IM is marketed only in Sweden at this time.

9.0 APPROVABLE LETTER

A draft approvable action letter is included in the package.

The letter includes a request for the sponsor to conduct several additional studies to better characterize the QTc effects of IM ziprasidone and ziprasidone in general. As noted above, the difficulty with the existing database is that few patients actually had ECG assessments at the critical times following IM administration, and the possible effects of rapid rise of plasma level has not been examined at all. Furthermore, they have not looked at the QTc effects of adding IM to patients already on oral dosing, nor have they generally explored the dose/response for QTc effects even for oral ziprasidone, a suggestion we also made in the approval letter for the oral formulation. Thus, we have asked the sponsor to design studies to address these questions.

10.0 CONCLUSIONS AND RECOMMENDATIONS

In my view, Pfizer has submitted sufficient clinical data to support the conclusion that ziprasidone IM is approvable for the treatment of acute agitation in patients with schizophrenia. This is a somewhat narrower indication than that sought by the sponsor, and as I've indicated, I think the indication should be further restricted to patients being considered for oral therapy, but who are not already on oral

therapy. I think this very limited indication is justified given the remaining questions about IM ziprasidone and the fact that other treatments are available for this indication. Several other antipsychotic drugs are available in intramuscular formulations, as are benzodiazepines and other sedative hypnotic drugs. While none of these drugs is specifically approved for agitation associated with schizophrenia, they are, nevertheless, widely used for this indication and represent a reasonable alternative. As noted, additional work is needed to clarify the QTc effects of IM ziprasidone before this application can be approved. Consequently, I recommend that we issue the attached approvable letter with our proposed labeling and requests for additional studies.

cc:

Orig NDA 20-919 (Zeldox IM)

HFD-120

HFD-120/TLaughren/RKatz/RGlass/SHardeman

DOC: MEMZIPIM.AE1

/s/

Thomas Laughren
2/28/01 10:41:09 AM
MEDICAL OFFICER

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_____ § 552(b)(5) Draft Labeling

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MEMORANDUM

DATE: December 11, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-919

SUBJECT: Supervisory Review of NDA 20-919, Zeldox IM for use in the management of the agitated psychotic patient

On December 17, 1997, Pfizer, Inc. submitted NDA 20-919 for Zeldox IM for the "acute control and short-term management of the agitated psychotic patient". The submission contains the results of 2 adequate and well controlled, as well as additional safety information. Critically, though, the sponsor had previously submitted an NDA for oral Zeldox for use in psychotic patients that was turned down (Not Approvable letter dated 6/17/98) because of a signal of QTc prolongation, which has yet to be adequately characterized. In fact, in the one study in the IM NDA that appeared to monitor the EKG near the Tmax of ziprasidone, this signal also emerged.

This application has been reviewed by Dr. Glass, medical reviewer (review dated 11/13/98), Dr. Wang, statistician (review dated 10/26/98), Dr. Al-Habet, Biopharmaceutics (review dated 5/22/98), Drs. Freed and Fitzgerald, pharmacology (reviews dated 10/1/98 and 12/4 and 12/9/98, respectively), Drs. SeEVERS and Klein, chemistry (reviews dated 11/30/98 and 12/8/98, respectively), and finally Dr. Laughren, Team Leader, Psychiatric Drug Products, (review dated 12/8/98).

The review team has concluded that Zeldox has been found to be effective for the proposed indication, and I agree. However, as discussed by Dr. Laughren, the safety concerns raised by the NDA for the oral product apply to this product as well. Indeed, the signal has been seen in the one study of the IM product that could reasonably have been expected to detect it. Therefore, it is critical that the deficiencies that precluded approval of the NDA for the oral product be adequately addressed before approval can be granted for this NDA. In addition, there are several pharmacology and CMC deficiencies.

For this reason, I agree with the review team that the attached Not Approvable letter should be issued to the sponsor.

^ /s/

Russell Katz, M.D.

Cc:
NDA 20-919
HFD-120
HFD-120/Katz/Laughren/Hardeman

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA 20-919

Sponsor: Pfizer Inc.

User Fee Due Date: December 17, 1998

Drug Name

Generic Name: Ziprasidone Mesylate

Trade Name: Zeldox IM

Drug Characterization

Pharmacologic Category: Serotonin and Dopamine Antagonist

Proposed Indication: Acute Control and short-term management of the
agitated psychotic patient

NDA Classification: 3S

Dosage Forms: IM for injection; 20 mg ziprasidone/mL

Reviewer Information

Clinical Reviewer: Roberta L. Glass, M.D.

Review Completion Date: November 13, 1998

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1.0 Material Utilized in Review

1.1 Material from NDA/IND

This NDA submission was presented in a combination of hard copy and electronic format. Case report forms were submitted in electronic format only. There were no electronic data sets provided for this review.

The documents most frequently referred to for the purposes of this review were the following:

Integrated summary of efficacy
Integrated summary of safety
Study reports for trials 125 and 126
Literature summary

Also considered were Pfizer's commercial IND 34,629/NDA 20-825 (ziprasidone po for psychotic disorders) C

Case report forms were examined for the following subjects: 125-795-0071 and 126-063-80121.

1.2 Related Reviews, Consults, etc.

The Division of Cardio-Renal Drug Products was consulted for issues concerning ziprasidone's cardiovascular adverse events, review by Sughok K. Chun, M.D. (HFD-110:10/23/98), and by Charles J. Ganley, M.D. (HFD-110: 11/18/98 and 1/6/98). Also referred to were the following documents: 1) Clinical Pharmacology and Biopharmaceutics Review by Sayed Al-Habet, Ph.D. (HFD-860: 5/22/98), 2) Statistical Review and Evaluation by Sue-Jane Wang, Ph.D. (HFD 710 & 715), 3) Summary and Evaluation of Pharmacology and Toxicology by Lois M. Freed, Ph.D. (HFD:120: draft), 4) CDER correspondence of nonapprovable letter to Pfizer for NDA 20-825 by Robert Temple, M.D. (HFD-101: 6/17/98) 5) Memorandum Re: Pfizer NDA 20-825 by Paul Leber, M.D. (HFD-120: 6/1/98), 6) Memorandum Re: Pfizer NDA 20-825 by Thomas P. Laughren, M.D. (HFD-120: 5/14/98), and 7) Review and Evaluation of Clinical Data of Ziprasidone HCL:NDA 20-825 by Roberta L. Glass, M.D. (HFD-120: 4/30/98).

1.3 Other Resources

Dr. Andrew Mosholder provided excellent mentoring during the review process.

2.0 Background

2.1 Indication

Of the currently nine antipsychotic medications available in the intramuscular form for the indication of acute agitation, all are considered to be traditional dopamine antagonist agents. There have been few efforts of drug development for an intramuscular formulation of the more recently marketed 'atypical' antipsychotic agents (i.e. antipsychotics possessing both serotonin type 2 and dopamine receptor antagonist properties). It has been suggested that these 'atypical' agents may reduce the incidence of EPS, result in less risk of the development of tardive dyskinesia, and may be more effective in treating the negative symptoms of schizophrenia.

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

Pfizer submitted NDA 20-825 for the oral formulation of ziprasidone HCl with the indication for the treatment of psychotic disorders in March, 1997. A nonapprovable letter was sent to Pfizer for NDA 20-825 on June 17, 1998 indicating that ziprasidone's ability to prolong the QTc interval presented a risk of potentially fatal ventricular arrhythmias which did not outweigh the benefits of ziprasidone compared to

already marketed antipsychotics. Also of note was the high sudden death rate observed within the NDA data base.

This current NDA 20-919 for the intramuscular formulation of ziprasidone was submitted on December 18, 1997. The proposed labeling incorporates the previously submitted labeling of the oral formulation which was not approved.

This sponsor also has the active IND

According to a teleconference of July 21, 1998 with Dr. Ritrovato from Pfizer, all clinical studies of ziprasidone have been done under Pfizer's sponsorship.

2.3 Administrative History

The original commercial IND for intramuscular ziprasidone was filed on October 30, 1995. It was determined, based on human pharmacokinetic data, that the IM and PO formulation of ziprasidone were not bioequivalent. DNDP sent a letter to the sponsor in March, 1996 suggesting approaches to establish efficacy such as focusing on the indication of agitation and restlessness in acutely psychotic patients. DNDP sent a letter (7/10/96) to the sponsor regarding the lack of placebo control in study 128-125, which was proposed to be a pivotal study, and the need to show a between group difference or a dose response relationship; it was also suggested that the sponsor consider adding an active control group such as lorazepam. In a facsimile of December 19, 1996, Dr. David Hoberman, FDA statistician, communicated that no correction for multiple comparisons for the two pivotal studies (125 & 126) was acceptable if the randomization lists were completely separate, and if investigators were not identical between the two studies.

A pre-NDA meeting was held on August 13, 1997, during which the sponsor discussed their concerns regarding labeling for the indication of short-term management of agitated psychotic patients. Approaches of presenting efficacy and safety data were also discussed.

In a facsimile of August 25, 1997, Dr. Lois Freed, pharmacologist, recommended that the sponsor conduct one month rat and dog studies using the IM excipient, sulphobutylether beta-cyclodextrin (SBECD) rather than only the intravenous formulation; in addition, it was recommended that the NDA include multiple dose toxicokinetic data for IM ziprasidone.

During a meeting on August 14, 1997, FDA chemistry reviewers and the sponsor discussed that NDA stability data would be required for the excipient, SBECD, because it has not been previously available commercially.

2.4 Proposed Labeling

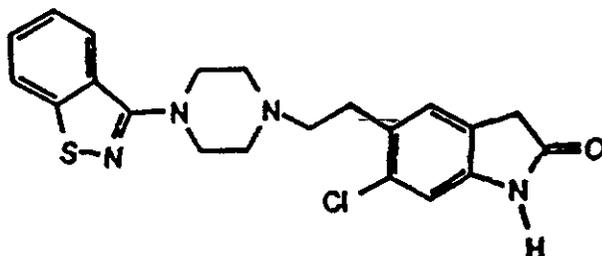
The dosing instructions in the draft labeling recommend an initial dose of 10 to 20 mg, with subsequent doses of 10 mg to be administered every 2 hours, or 20 mg to be administered every 4 hours. The labeling states that the recommended maximum dosage is 80 mg/day, and that use for more than 3 consecutive days has not been studied.

2.5 Foreign Marketing

According to a teleconference of 7/21/98 with Dr. Charles Ritrovato from Pfizer, ziprasidone is not marketed anywhere in the world.

3.0 Chemistry

The chemical structure for the free base of ziprasidone is:



The chemical structure for the vehicle, beta-cyclodextrin sulfobutyl ether sodium (SBECD) is:

4.0 Animal Pharmacology and Toxicology

Renal tubule epithelial vacuolation was observed in animal toxicology studies using the intravenous formulation of Sulphobutylether Beta-Cyclodextrin (SBECD); the sponsor states that these changes were reversible following cessation of treatment. There were also dose related incidence and severity of foamy macrophages in the liver and lungs.

Similar renal tubular vacuolation was observed in animal studies of the intravenous formulation of ziprasidone. Also increased heart rates was observed in a 2 week dog study. Rabbit studies provided evidence for discomfort at the site of injection of ziprasidone tartrate, but not with ziprasidone mesylate.

5.0 Description of Clinical Data Sources

5.1 Primary Source Data (Development Program)

Appendix 5.1.1.1 lists the cumulative number of subjects in the integrated safety data base. The cut-off date for the safety information was July 31, 1997. The integrated safety data base includes the Phase I study 046 which studies patients with the diagnosis of schizophrenia, schizoaffective or schizotypal personality disorder (not with an acute exacerbation for at least 6 months prior to participation). There were a total of 523 subjects in the integrated safety data base.

Please refer to Appendix 5.1.1.2 for a listing of all studies. The integrated safety data base includes one Phase I study (046), 5 Phase II/III (121, 125, 126, 306, 120), and two extension studies (127E and 306E).

The safety data submitted also includes 4 clinical studies testing the excipient Sulphobutylether Beta-Cyclodextrin (SBECD) which are not integrated in the safety data base for ziprasidone IM. The number of healthy subjects exposed to the excipient is 48. There are no subjects days exposure calculated. Please see Appendix 5.1.1.3 for listing of all Phase I studies utilizing the excipient SBECD.

5.1.1 Study Type and Design/Patient Enumeration

5.1.2 Demographics

Please refer to Appendix 5.1.2.1 for a demographic profile of all Phase I studies.

Appendix 5.1.2.2 contains the demographic profile for the Phase I studies for SBECD.

The demographic profile for subjects in the integrated safety data base (including Phase I study 046 and all Phase II/III studies) is listed in Appendix 5.1.2.3. For clarification of the sponsor's categorization, "other ziprasidone" refers to all ziprasidone treatment groups except the ziprasidone 2mg group; "combined ziprasidone" refers to all ziprasidone treatment groups including the ziprasidone 2mg groups.

The majority of subjects included in the integrated safety data base are Caucasian males 19 to 76 years old.

5.1.3 Extent of Exposure (dose/duration)

The modal daily dose and duration for Phase I studies for ziprasidone IM are shown in Appendix 5.1.3.1. All subjects were exposed to a low daily dose (≤ 20 mg ziprasidone IM). Appendix 5.1.3.2 summarizes the available information regarding modal daily dose of SBECD in phase I studies.

The modal daily dose for Phase II/III studies (also including phase I study 046) are shown in Appendix 5.1.3.3. This table shows that the majority of subjects were exposed to doses between 5 to 40 mg ziprasidone IM daily for a mean duration of 2 days. There have been 369 subjects (70.6%) within this pool who were exposed to daily doses ranging from 5-60 mg ziprasidone IM; 69 subjects (13.2%) were exposed to daily doses > 60 mg, and 85 subjects (16.3%) exposed to daily doses < 5 mg. The mean exposure time was 2 days while 245 subjects (46.8%) were exposed to ziprasidone IM for 3 days. The proposed labeling recommends that the initial dose be 10-20 mg and the maximum daily dose be 80 mg ziprasidone IM, and that treatment beyond 3 days was not studied.

The following table summarizes the person time in the ziprasidone IM safety data base:

Subject-years exposure in ziprasidone safety data base*

ORIGINAL NDA	ZIPRASIDONE	HALOPERIDOL	PLACEBO
N=	523	142	6
Subject-days exposure*	1144	371	18

Includes phase I study 046 which included subjects with diagnosis of schizophrenia, schizoaffective or schizotypal personality disorder, but did not have acute exacerbation for at least 6 months.

Appendix 5.1.3.2 summarized the exposure of IV SBECD in Phase I studies.

5.2 Secondary Source Data

5.2.1 Other Studies

There were no other studies conducted.

5.2.2 Postmarketing Experience

As of July 21, 1998, ziprasidone IM is not marketed in any country as per a teleconference with Dr. Ritrovato at Pfizer.

5.2.3 Literature

According to a teleconference of July 21, 1998 with Dr. Ritrovato from Pfizer, all clinical studies have been done under Pfizer's sponsorship and are included in the current NDA submission.

The Sponsor included approximately 100 published papers and abstracts (NDA Vol. 54-57) that contained some information regarding ziprasidone. The literature search encompassed the years of 1966 through 1996. The literature search was conducted by David Larson, Ph.D. who has been employed by Pfizer since 1971.

A review of the sponsor's literature search did not reveal any unexpected safety findings.

6.0 Human Pharmacokinetic Considerations

For complete details, please refer to the biopharmaceutics review.

Ziprasidone mesylate IM demonstrated an absolute bioavailability of 100%. Single IM doses to healthy male subjects revealed a terminal half-life of approximately 2.9 hours (ranging 2.1 to 3.8 hours). After multiple dose administration in schizophrenic subjects for three days, the terminal half-life ranged from 6.7 to 13.4 hours, suggesting that half life was longer after multiple dosing.

The maximum concentration was achieved in approximately 0.6 hours after injection (ranging from 0.17 to 1.5 hours). Systemic clearance after a single IM dose of 5-20 mg in healthy volunteers was 4.9 ml/min/kg (ranging 4-6 ml/min/kg). In the range of 5-40 mg, the AUC and Cmax were observed to increase in a dose related manner.

There were no metabolites identified for ziprasidone mesylate IM. For oral ziprasidone HCl, the major metabolites were ziprasidone-sulfoxide and ziprasidone-sulfone; both demonstrated a low affinity to D₂ and 5HT_{2A} receptors. For oral ziprasidone, in vitro studies of human liver microsomes suggest that ziprasidone is a cytochrome P450 3A4 substrate mainly for the metabolic processes of sulfur oxidation and N-dealkylation.

Also of note is that ziprasidone mesylate IM was not tested on patients with hepatic or renal impairment. This becomes a note of concern since the cyclodextrin excipient is cleared by renal filtration. The sponsor included a mention of this precaution under the special populations section.

7.0 Review of Efficacy

7.1 Background

Pfizer reports that they have two well controlled studies testing the effectiveness of ziprasidone in treating acute agitation in subjects who have psychotic disorders. In lieu of a placebo control, the sponsor used a low dose (2 mg ziprasidone IM) control group making comparisons with a higher dose ziprasidone group to support claims of efficacy. This review will discuss the following studies which were randomized, double blind, fixed dose, flexible schedule, multicentered trials in subjects diagnosed with psychotic disorders:

Study 125, n=117 total, comparing 2 mg ziprasidone IM and 10 mg ziprasidone IM in a flexible dose schedule with a maximum of 4 doses in the 24 hour study period.

Study 126, n=79 total, comparing 2 mg ziprasidone IM and 20 mg ziprasidone IM in a flexible dose schedule with a maximum of 4 doses in the 24 hour study period.

7.2 Review of individual studies

7.2.1 Study 125

Investigators/Location

This study was conducted in 17 centers in the United States. Please refer to Appendix 7.2.1.1 for the sponsor's list of investigators and sites. Ten additional sites (585, 599, 663, 697, 707, 767, 774, 786, 784, 785) were terminated prior to randomization of any subjects; the sponsor did not provide reasons for closing these sites.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone IM in treating subjects with a psychotic disorder and acute agitation.

Population

Subjects chosen for this study were physically healthy males and females aged 18 years and older with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, schizophreniform disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder or psychotic disorder, NOS. Females of childbearing potential were required to use medically accepted forms of contraception during the study. Baseline scores (obtained within 4 hours of first double blind dose administration) were required to be ≥ 3 (mild) in at least three of the following items of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS): anxiety, tension, hostility, and excitement. The protocol allowed investigator discretion for a positive benzodiazepine or cannabinoids result in the urine drug screen; otherwise, it was required to be negative. Excluded from this study were patients with bipolar disorder without psychotic features, mental retardation, substance-induced psychotic disorder, psychoactive substance abuse/dependence within the preceding 2 months of the study, history of alcohol abuse, use of clozapine within 12 weeks prior to screening, and a high risk for suicide or homicide. Concurrent medications allowed during the double-blind trial period included benzotropine (prn EPS), propranolol (prn EPS), lorazepam (prn agitation or insomnia) and temazepam (prn insomnia). Also allowed was chronic use (at least 2 months prior to study) of antihypertensives, diuretics, oral hypoglycemics, and hormone replacements (not insulin). Medications which required clearance from the sponsor's clinical monitor included psychotropic drugs (other than allowed as above), anorexics, antianginal agents, antiarrhythmics, antihistamines (terfenadine, astemizole), anticoagulants, steroids, theophylline, tryptophan, diuretics, H₂ blockers, cisapride, anti-infectives and all over the counter medications. Use of antiemetics was prohibited.

Design

This was a randomized, double-blind inpatient trial comparing two dose regimens of ziprasidone (2 mg vs. 10 mg ziprasidone IM). Screening included ECG, CBC, urinalysis, routine labs, urine drug screen, beta-HCG (for women), hepatitis battery, and lithium levels. ECGs and physical exams were repeated at baseline and at study endpoint (at least six hours after last dose); CBC, urinalysis and routine labs were repeated at study endpoint only. Vital signs were to be monitored at screening, just prior to dosing and 30 and 60 minutes post dosing. Serum samples to determine pharmacokinetic properties would be collected at study endpoint only. Baseline data was to be collected within four hours prior to administration of the first dose of double blind medication. Baseline assessments included the Behavioural Assessment Scale (BAS), Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), Nurses Observation Scale for Inpatient Evaluation (NOSIE), Simpson-Angus Rating Scale (SARS), Barnes Akathisia Scale, AIMS and ECG. Each patient's chart was to be reviewed to assess appropriateness for the study. After subjects were randomly assigned to either the 2 mg ziprasidone IM group or the 10 mg IM group, they would receive an initial dose with

successive doses administered at least 2 hours apart. In the 24 hour period of the study, patients could receive a maximum of four doses (8 mg ziprasidone IM for the 2mg group, and 40 mg ziprasidone IM for the 10 mg group). Investigators could choose to halt or administer less frequent treatments when a patient's agitation appeared to resolve.

The Behavioural Assessment Scale (BAS) was to be measured at the following times: 1) screening, 2) just prior to dose administration, 3) 15, 30, 45, 60, 90 minutes, and 2 hours after dose administration, and then hourly until either the next IM dose or termination. The CGI-S, CGI-I, NOSIE, SABS, and Barnes Akathisia Scale were to be administered at screening, baseline (up to 4 hours prior to dose administration), 4 hours after the first dose and at study endpoint. Study endpoint is defined as: 1) the longer of either 6 hours after last dose or at the end of the 24 hour period, or 2) the time of early termination.

Analysis Plan

There were three primary efficacy variables defined in the protocol: 1) the area under the curve (AUC) for measurements of the Behavioural Assessment Scale (BAS) from 0 to 2 hours after the first dose, 2) changes from baseline to 4 hours of the CGI-S score, and 3) changes from baseline to study endpoint of the CGI-S. The protocol states that linear models were to be used for analysis of the AUC with log transformations if required by data distribution. Linear models would also be used to analyze the CGI-S, but in case of violations of linear model assumptions, methods of categorical data analysis were to be utilized. Rank transformation may be used for change from baseline scores if required by the data distribution. Interaction effects of center and treatment were also to be analyzed.

In order to detect a difference of 1 point in the mean change from baseline of the CGI-S between the two treatment groups, the sponsor estimated a sample size of 50 subjects per group to provide 80 % power (alpha=0.05, two tailed).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 143 patients screened to enter the study, 117 patients were randomized to one of the two treatment group and received at least one IM injection. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report itemizes reasons for discontinuation from the two treatment groups:

Discontinuations from Study Ziprasidone Protocol 125		
Number (%) of Subjects	Ziprasidone 2mg 54	Ziprasidone 10mg 63
Discontinuations		
Related to Study Drug	1 (1.9)	2 (3.2)
Adverse event	1 (1.9)	2 (3.2)
Not Related to Study Drug	1 (1.9)	0
Protocol violation	1 (1.9)	0
Total	2 (3.8)	2 (3.2)

The dropout rates for the treatment group taking ziprasidone 10 mg IM and the group taking 2 mg IM were almost identical at less than 4%.

Appendix 7.2.1.2 displays the number of subjects who received one, two, three or four injections within the 24 hour period of the study. Within the twenty-four hour period, one injection was used to treat 24.1% (13 of 54) of the 2mg IM group, while 36.5% (23 of 63) of the 10mg IM group received only one injection. The

rates of subjects receiving two and three injections were similar for both groups. Four injections (the maximum allowed) were administered to 24.1% (13 of 54) in the 2 mg IM group and 14.3% (9 of 63) in the 10 mg IM group.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with the mean age of approximately 40 years old. The mean age of the female patients was similar to the males. There did not appear to be imbalances in the treatment groups. Appendix 7.2.1.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the CGI-S and the BAS (see below) were slightly lower in the 2 mg ziprasidone IM group but are comparable to the 10 mg ziprasidone IM group. The sponsor did not provide any statistical comparisons of the baseline values.

Mean Baseline Values of Primary Efficacy Variables -Study 125

MEAN SCORE	ZIPRASIDONE IM 2 MG GROUP	ZIPRASIDONE IM 10 MG GROUP
CGI-S	4.24	4.37
BAS	4.65	4.81

Concomitant Medications

In both groups, lorazepam was used by approximately 10% of the patients during the study. Please refer to the following table for select concomitant medication use:

Selected concomitant medication used in Study 125

	Ziprasidone IM 2 mg (n=54)	Ziprasidone IM 10 mg (n=63)
Lorazepam	5	6
Temazepine	3	3
Benztropine	8	6
Beta-Blocker	3	0
Antidepressant	0	1

Lorazepam was used by

Efficacy Results

Please refer to Appendix Tables for results of the primary outcome measures (CGI-S at 4 hours, CGI-S at endpoint, and AUC of BAS at 2 hours). When compared to the 2 mg ziprasidone IM group at a 95 % confidence interval, the 10 mg ziprasidone IM group demonstrated a statistically significant difference in the AUC of the BAS (0 to 2 hours). However, there was no statistical significance observed between the 2 and 10 mg ziprasidone IM groups when comparing mean changes from baseline of the CGI-S scores at 4 hours and at study endpoint. The sponsor also submitted an analysis of a subgroup of subjects with BAS scores ≥ 5 which had similar efficacy results to the total sample tested (please refer to Miscellaneous Issues for further discussion of BAS).

Miscellaneous Issues

This Behavioural Assessment Scale was developed by Pfizer to assess the effects of this IM medication. Because it is a new scale, there is no literature establishing it as a standardized rating scale. This BAS appears to be an instrument which combines two subscales—one assessing degree of agitation and one assessing levels of consciousness:

Behavioural Assessment Scale (BAS):

- 1 = difficult or unable to rouse;
- 2 = asleep, but responds normally to verbal or physical contact;
- 3 = drowsy, appears sedated;
- 4 = quiet and awake (normal level of activity);
- 5 = signs of overt activity (physical or verbal), calms down with instructions;
- 6 = extremely or continuously active, not requiring restraint;
- 7 = violent, requires restraint

There was no required baseline scoring of the BAS in the inclusion criteria. The mean BAS score presented by the sponsor was 4.65. According to the efficacy tables, it appears that approximated 70% (45 of 63 subjects) of the subjects had baseline scores of ≥ 5 while the remainder had BAS scores less than 5. It is questionable if a BAS score of 5 (indicating that a person is likely to respond to instruction) or lower is typical of patients for whom this IM medication would be indicated as IM medication is usually reserved for patients who are too agitated to follow directions to swallow a pill.

When viewing the psychiatric inclusion criteria further, it is noted that the baseline scores for the PANSS were required to be ≥ 3 (mild) in at least three of the following items of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS): anxiety, tension, hostility, and excitement as follows:

PANNS:

Anxiety: 3 (mild): Expresses some worry, over-concern, or subjective restlessness, but no somatic and behavioral consequences are reported or evidenced.

Tension: 3 (mild): posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.

Hostility: 3 (mild): Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions, and occasional irritability.

Excitement: 3 (mild) tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.

Again, it is questionable if a patient whose profile fits a PANNS score of 3 (mild) in the above items would be representative of subjects who clinically requires an intramuscular injection of an antipsychotic as opposed to the less invasive treatment of oral medication.

Conclusions:

Because this study demonstrated statistical significance in only one of the three primary efficacy variables, it merely provides fair evidence for the effectiveness of ziprasidone IM treating agitation in psychotic psychiatric patients.

7.2.2 Study 126

Investigators/Location

This study was conducted in 18 centers in the United States. Please refer to Appendix 7.2.1.2 for the sponsor's list of investigators and sites. Two additional sites (777 and 793) were terminated prior to randomization of any subjects; the sponsor did not provide reasons for closing these sites.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone IM in treating subjects with a psychotic disorder and acute agitation.

Population

Please refer to Study 125 which had the same entrance criteria. Concurrent medications were similar to those used in Study 125.

Design

This was a randomized, double-blind inpatient trial comparing two dose regimens of ziprasidone (2 mg vs. 20 mg ziprasidone IM). The details of this study's design were similar to Study 125 (please refer to Study 125 for more information).

Once chosen for the study, subjects were to be randomized to one of two treatment groups: 1) 2 mg ziprasidone IM, or 2) 20 mg ziprasidone IM. After the initial dosing of 2 mg or 20 mg ziprasidone IM, repeat dosing was to have been administered at least 4 hours apart. The maximum allowed dose in the 24 hour period of the study was 8 mg for the 2 mg ziprasidone IM group, and 80 mg for the 20 mg ziprasidone IM group. Investigators could choose to halt or administer less frequent treatments when a patient's agitation appeared to resolve.

Assessment scales included a Behavioural Assessment Scale (BAS), PANSS, CGI, NOSIE, Simpson-Angus Scale, Barnes Akathisia Scale, and AIMS. The schedule of assessment was similar to Study 125 (Please see Study 125 for further details regarding the use of these instruments).

Analysis Plan

The primary efficacy variables were listed as: 1) the area under the curve (AUC) for the Behavioural Assessment Scale (BAS) from 0 to 4 hours after the first IM dose, 2) change from baseline to 4 hours of CGI-S score, and 3) change from baseline to study endpoint of the CGI-S. The protocol states that linear models including center and treatment were to be utilized for the analysis of the AUC with log transformations if required by data distribution. Linear models were also to be attempted to analyze the CGI-S, but in case of violations of linear model assumptions, methods of categorical data analysis were to be applied. Rank transformation would be used for change from baseline scores if required by the data distribution. Interaction effects of center and treatment were also to be analyzed.

In order to detect a difference of 1.5 points in the mean change from baseline of the CGI-S between the two treatment groups, the sponsor estimated a sample size of 30 subjects per group to provide 80 % power ($\alpha=0.05$, two tailed).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 99 subjects screened to enter the study, 79 were randomized to one of the two treatment groups. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following table from the sponsor's study report summarizes the discontinuation rate:

Discontinuations from Study Ziprasidone Protocol 126		
Number of Subjects	Ziprasidone 2mg 38	Ziprasidone 20mg 41
Discontinuations		
Related to Study Drug	1	0
Lack of efficacy	1	0
Not Related to Study Drug	1	3
Adverse event	1	0
Subject defaulted	0	3
Total	2 (5.3%)	3 (7.3%)

The dropout rate for the treatment group taking ziprasidone 20 mg IM was slightly higher than for the group taking ziprasidone 2 mg IM, but by only one patient.

Appendix 7.2.2.2 displays the number of subjects who received one, two, three or four injections within the 24 hour period of the study. Within this twenty-four hour period, one injection was used to treat 26.3% (10 of 38 patients) of the 2mg IM group, while 41.5% (17 of 41) of the 20mg IM group received only one injection. For the administration of subsequent dosing (i.e. 2, 3 or 4 injections), the 20 mg IM group had a slightly lower rate than the 2mg IM ziprasidone group.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with the mean age of approximately 40 years old. The mean age of the female patients was similar to the males. There did not appear to be imbalances in the treatment groups. Appendix 7.2.2.3 shows the breakdown of demographics by treatment group.

The 2 mg ziprasidone IM group and the 10 mg ziprasidone IM group had comparable scores for the mean baseline values of the CGI-S and the BAS as can be seen in the following table:

Mean Baseline Values of Primary Efficacy Variables - Study 126

MEAN SCORE	ZIPRASIDONE IM 2 MG GROUP	ZIPRASIDONE IM 20 MG GROUP
CGI-S	4.74	4.63
BAS	5.00	4.98

Concomitant Medications

During the study, lorazepam was used at a higher rate in the ziprasidone 20 mg IM group (15%) than the ziprasidone 2 mg IM group (8%). Please refer to the following table for select concomitant medication use:

Selected concomitant medication used in Study 126

	Ziprasidone IM 2 mg (n=38)	Ziprasidone IM 20 mg (n=41)
Lorazepam	3	6
Temazepine	0	1
Benzotropine	3	3
Beta-Blocker	3	0
Antipsychotic	0	1

Efficacy Results

Please refer to Appendix Tables for results of the primary outcome. When compared to the 2 mg ziprasidone IM group at a 95 % confidence interval, the 20 mg ziprasidone IM group demonstrated a statistically significant difference in the AUC of the BAS (0 to 4 hours), the mean changes from baseline

of the CGI-S scores at 4 hours and at study endpoint.

Miscellaneous Issues

Please refer to Study 125 (Miscellaneous Issues) for a discussion about the BAS scale and the psychiatric entrance requirement.

Conclusions

This study demonstrated statistical significance in the three defined efficacy variables when comparing the 20 mg ziprasidone IM treatment group with the 2 mg ziprasidone IM treatment group. Therefore, these results provide evidence that ziprasidone IM is effective in treating agitation in psychotic psychiatric patients.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

When exploring how demographic characteristics may have affected the efficacy data, the sponsor claims to have found no significant effect on treatment based on age, gender, or race. The p-values are not significant for the interaction effects of age (<55 years or ≥ 55 years), gender, race (Caucasian or African American) and any of the efficacy variables tested (AUC of BAS 0-2 hours, AUC of BAS 0-4 hours, CGI-S).

7.3.2 Choice of dose

In study 126, ziprasidone IM was shown to be efficacious when comparing the higher dose treatment group (20 mg ziprasidone IM) to the lower dose treatment group (2 mg ziprasidone IM). However, in study 125, the higher dose treatment group (10 mg vs 2 mg ziprasidone IM) demonstrated a statistically significant difference in one of three primary efficacy variables. These results could provide support that the higher dose of ziprasidone 20 IM may demonstrate a better efficacy profile.

The sponsor has recommended that the initial intramuscular dose of ziprasidone be 10 to 20 mg. It further states that subsequent doses of 10 mg may be administered as often as every 2 hours, or 20 mg every 4 hours as needed with a maximum recommended daily dose of 80 mg. This information accurately reflects the findings from these efficacy studies.

7.3.3. Duration of Treatment

A greater percent of patients in the higher dose treatment groups, compared to the low dose ziprasidone 2mg IM group, were administered only one injection in the 24 hour studies in both studies 125 and 126. It appears that the higher dose group (20 mg ziprasidone IM) in study 126 had a slightly higher percent of subjects receiving only one injection than the higher dose group in study 125 (10 mg ziprasidone IM). After the first injection, all treatment groups in both studies had comparable rates of subsequent injections.

As stated above, the proposed labeling offers a dosing schedule with 80 mg ziprasidone as the maximum recommended daily dosing. The labeling further states that use of ziprasidone IM greater than 3 days has not been tested. These recommendations reflect the guidelines used in the clinical trials of ziprasidone IM.

7.4 Conclusions regarding efficacy data

Ziprasidone IM has been clearly proven to be effective in the treatment of agitation in psychotic patients in one well controlled study which compared the dose of 20 mg ziprasidone IM to a low dose (2 mg) ziprasidone IM. Results of a second well controlled trial comparing the dose of 10 mg ziprasidone IM with a low dose (2mg) ziprasidone control group provided some support for the efficacy of ziprasidone IM at this dose.

Because of the sedative properties of ziprasidone IM, it may not be surprising that patients appear less psychotic in the 20 mg ziprasidone IM group of study 126 (i.e. significant improvement of CGI scores compared to the low dose group) than the 10 mg ziprasidone IM group of study 125. If effectiveness for an IM treatment of agitation is best reflected by the parameter of AUC of the BAS, then the presented data has proven ziprasidone to be efficacious in the treatment of acute agitation in patients who have psychotic disorders.

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

The sponsor submitted the integrated safety data base for all Phase II/III studies for review. This data base also included one Phase I study (046) which included subjects diagnosed with a psychotic disorder. The main focus of the safety review was on the integrated safety data base to identify significant adverse events. Cardiovascular safety issues were explored in depth by cardiology consultant, Dr. Chun (HFD-110), who reviewed three Phase I studies (033, 038, 046) and one Phase III study (121).

The determination of common adverse events presented some difficulty in this review as there were no placebo controlled studies. As a substitute for placebo controlled studies, the sponsor submitted two well controlled studies (125 and 126) which used a low dose (2 mg/dose; maximum qid) ziprasidone IM group as a control group to be compared to a higher dose ziprasidone group. The higher dose group for study 125 was 10 mg ziprasidone IM group (maximum qid), and study 126 used a 20 mg ziprasidone IM group (maximum qid) to compare with the low dose (2 mg) ziprasidone IM group. Therefore, observations could only be made regarding the dose response when comparing the low and high doses in each of these studies. Alternative strategies for review would be to pool the 2 mg IM control groups into the denominator of all ziprasidone treatment groups; however, this method may dilute safety data within the therapeutic dosage range.

In the ISS, the sponsor chose to submit tables which pooled together the three studies which they termed "fixed dose" studies. These included the two controlled studies (125 and 126) and study 121, an open label study testing 5, 10, & 20 mg (qid x 3 days) ziprasidone IM with a haloperidol treatment arm. The pooling of this data presented many unbalances given the different designs and duration of the studies (both studies 125 and 126 were 24 hours and study 121 was a three day study). The sponsor used this pooling to determine common adverse events for the proposed labeling comparing the ziprasidone treatment groups with haloperidol groups. This is discussed further in sections 8.1.5.3 and 8.1.5.4.

Although the ISS includes safety data pooling together patients who received IM treatment and subsequent oral treatment of ziprasidone, this review will focus primarily on the safety data of the IM treatment. It is noted that the adverse events were collected up to 24 hours after the last dose of IM medications and that some patients may have been receiving oral ziprasidone during some of that time period.

8.1.1 Deaths

There were no deaths reported as of the data cutoff date of July 31, 1998. However in the submission of 5/18/98, the sponsor reported one death (48 y.o. female: PID 127E-7190004) which occurred 74 days after discontinuing treatment with oral ziprasidone (100 mg bid x 162 days). No further details were provided.

8.1.2 Other Serious Adverse Events

In the Integrated Summary of Safety (ISS) the sponsor states that they applied the same definition for a serious adverse event that is used by FDA (i.e. any drug experience that is fatal or life-threatening, is permanently disabling, requires hospitalization, or is a congenital anomaly, cancer, or overdose). Serious adverse events were submitted as listings itemized by subjects and COSTART body system/preferred term.

Four of the five serious adverse events occurring during the phase I/II/III ziprasidone IM trials were listed as psychiatric events which may have been manifestations of the psychiatric disease under study. The following table summarizes the only serious adverse event reported during the phase I/II/III ziprasidone IM trials which was considered to be attributed to treatment with ziprasidone IM:

Serious adverse events IM dosing Phase I/II/III

SUBJECT #	AGE/SEX	MEAN DOSE (MG)	# OF INJECTIONS/TREATMENT (DAYS)	SERIOUS ADVERSE EVENT/ COMMENTS
125-7950071	67/M	2	1	Hypertensive episode 220/100 (sitting) 7 ½ hours after IM injection. Treated with captopril and clonidine. Subject had history of hypertension.

Please refer to Appendix 8.1.2 for serious adverse events which occurred during the extension studies in which patients were treated with oral ziprasidone.

8.1.3 Dropouts

8.1.3.1 Overall Profile of Dropouts

The primary integrated database included 99 (19%) of the total 523 patients who prematurely discontinued treatment in the Phase II/III trials from ziprasidone IM treatment groups. The sponsor's table below provides reasons for discontinuations:

Number (%) of Subjects	Ziprasidone 2mg* 92	Other Ziprasidone 431	Combined Ziprasidone 523	Haloperidol 142
Discontinuations				
Adverse event	6 (6.5)	17 (3.9)	23 (4.4)	2 (1.4)
Insufficient clinical response	6 (6.5)	14 (3.2)	20 (3.8)	3 (2.1)
Other	11 (12.0)	45 (10.4)	56 (10.7)	13 (9.2)
Total	23 (25.0)	76 (17.6)	99 (18.9)	18 (12.7)

(CONTINUED)
* Subjects randomized to "2mg maximum Q1D" group in protocols 125,126
Other reasons for discontinuation may include failure to meet randomization criteria, lost to follow-up, protocol violation, withdrawn consent, etc.
Protocols: 046,120,121,125,126,127C,306,306C
Date of Table Generation: 06/01/97

Number (%) of Subjects	Placebo 6
Discontinuations	
Adverse event	0
Insufficient clinical response	0
Other	0
Total	0

NOTE: "Other Ziprasidone" refers to all ziprasidone doses other than the ziprasidone 2 mg IM dose groups; "Combined Ziprasidone" includes all ziprasidone IM treatment groups.

It appears from the table above that the highest withdrawal rate for insufficient efficacy was seen in the 2 mg ziprasidone IM group, the low dose control group. However, please note that the above table, which was prepared by the sponsor, does not provide an accurate profile of the discontinuations. In the ISS text (p.22 and 35), the sponsor makes an attempt to explain the inconsistencies in their tables by stating that three subjects in the 2 mg ziprasidone IM group and four subjects in the "other ziprasidone" IM groups may have been counted as withdrawals for adverse events but latter considered to withdraw due to an insufficient clinical response. However, even with these corrections, there is still a discrepancy amongst the sponsors tables when compared with the table of line listings of withdrawals. It is possible that the

sponsor confused the number of events with the number of subjects who discontinued when making calculations for the above table.

8.1.3.2 Adverse Events Associated with Dropout

The following table was also included in the ISS and presents a count of discontinuations that is consistent with the table of line listings of withdrawals in the safety data base:

Discontinuations Due to Adverse Events During Intramuscular Dosing in Phase III Studies					
2 mg Ziprasidone 2 subjects discontinued		Other Ziprasidone 9 subjects discontinued		Haloperidol 1 subject discontinued	
Body System	Preferred Term	Body System	Preferred Term	Body System	Preferred Term
Cardiovascular	Hypertension	Body as a Whole	Suicide gesture	Nervous	Dystonia Extrapyramidal syndrome
Nervous	Agitation Psychosis	Cardiovascular	Hypertension Migraine Tachycardia		
Urogenital	Priapism	Nervous	Agitation Akathisia (2 cases) Personality disorder Psychosis Somnolence		
		Digestive	Nausea Diarrhea		
		Respiratory	Respiratory tract infection		
		Urogenital	Urinary tract infection		

Using figures from the table above, the rates of withdrawals from the entire safety data base are the following:

Rates for withdrawal for adverse events in the integrated safety data base for ziprasidone IM				
	2 mg ziprasidone IM n=92	2.5-20 mg ziprasidone IM n=431	all ziprasidone IM n=523	Haloperidol n=142
# withdrawals	2 (2.2%)	8 (1.9%)	10 (1.9)	1 (0.7%)

It appears that the 2mg ziprasidone IM group, which was used as a low dose control group, demonstrated the highest rate of withdrawal for adverse events. This observation suggests that the low dose of 2 mg ziprasidone was not a true placebo.

Of note in the adverse events listed above is Subject 126-6380212, a 50 y.o. male patient with schizophrenia who experienced priapism after two doses of 2 mg ziprasidone IM. This patient was subsequently treated with epinephrine, cephalexin and a needle aspiration of blood from the corpora cavernosa. According to the case report form, this subject had 2 prior episodes of priapism (3 and 6 months prior to taking ziprasidone IM) and had one more episode one week after discontinuing ziprasidone IM requiring a surgical (Winters) procedure. The sponsor and the investigator attributed this episode of priapism to the subject's prior treatment with prolixin decanoate. The subject's prior treatment with prolixin decanoate are as follows:

16 days prior to start of trial: 25 mg IM prolixin decanoate
 14 days prior " " : 75 mg " "
 7 days prior " " : 75 mg " "

It is noted that the labeling for prolixin decanoate does not mention priapism as a warning or precaution. Although this subject's schedule for prolixin decanoate may have been on the higher end of dosing, the labeling allows for individual variation of treatment that is not inconsistent with this subject's dosing.

8.1.4 Other Search Strategies

None.

8.1.5 Common Adverse Events

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

Pfizer did not provide their working definition of an adverse event in the Integrated Summary of Safety. All adverse events presented were classified by organ system using COSTART terminology. The sponsor stated that adverse events were collected by either direct observation, by the investigator or by patients volunteering this information. This method may result in an under representation of adverse events, because the schizophrenic population may not be able to spontaneously volunteer and articulate their discomfort.

The ISS mentions that adverse events were collected up to 24 hours after the last dose of IM medications and that some patients may have been receiving oral ziprasidone during some of that time period.

8.1.5.2 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

In the ISS, the sponsor chose to submit tables which pooled together the three studies which they termed "fixed dose" studies. These included the two controlled studies (125 and 126) and study 121, an open label study with a haloperidol treatment arm (see section 8.1 for dosing schedules). The pooling of this data presented many unbalances given the different designs and duration of the studies (both studies 125 and 126 were 24 hours and study 121 was a three day study).

Appendix 8.1.5.2 delineates the adverse events occurring in 1% of patients taking 5-20 mg ziprasidone IM from the "fixed dose" studies (121, 125 and 126). In the 1% table for the proposed labeling, the sponsor established a comparison of ziprasidone IM and haloperidol by utilizing the columns of "Other Ziprasidone" and "Haloperidol" from Appendix 8.1.5.2.

Appendix 8.1.5.3 is extracted from the sponsor's proposed labeling and lists all adverse events occurring in the primary safety data base in the original submission. This list merges all adverse events in the oral and IM ziprasidone NDA data bases that have not been reported in the 1% tables or else where in the proposed labeling.

8.1.5.3 Identifying Common and Drug-Related Adverse Events

Because of the lack of a placebo-controlled study, the traditional approach to identify a common event as occurring at least 5% in the treatment group and twice as frequently in the treatment group compared to placebo cannot be strictly applied. In the proposed labeling, the sponsor chose to define commonly observed events in this data base as occurring $\geq 5\%$ in the ziprasidone group from fixed dose studies (from studies 121, 125, & 126) and twice as frequently than in the haloperidol group (study 121). Using this approach, the sponsor identified injection site pain, nausea and dizziness as common events when comparing ziprasidone with haloperidol using the sponsor's criteria. However this approach may be inconsistent with the format of most labeling which identifies common adverse events as those that occur in the study drug groups compared to the incidence in placebo groups.

An alternative approach, if one were to assume that the low dose ziprasidone simulates a placebo group, would be to use this same pooled data from fixed dose studies (121, 125 and 126) and identify a common adverse event as one occurring in at least 5% of the higher dose group (5-20 mg ziprasidone IM) and more than twice as frequently in the higher dose group than in the low dose 2 mg ziprasidone IM control group. From this perspective, the drug related adverse events fulfilling this criteria were tachycardia, headache (of note, Subject 121-7590150 discontinued due to exacerbation of a migraine headache), dyspepsia, nausea, vomiting, agitation, akathisia, anxiety, dizziness, and insomnia.

8.1.5.4 Additional Analyses and Explorations

Dose Response

A dose relationship for several adverse events was established when the sponsor applied the Mantel-Haenszel test to the pooled data from the fixed dose studies (121, 125, 126) for doses of 2, 5, 10 and 20 mg ziprasidone IM. The sponsor's analysis showed a statistically significant dose relationship ($p \leq 0.05$) with the following adverse events: **postural hypotension, akathisia, nausea, constipation, increased salivation, and insomnia.**

Demographic Analyses

The sponsor did not include statistical comparison of the interaction effect of gender, age, or race for the pool of fixed dose ziprasidone studies (121, 125, and 126). Please see Appendix 8.1.5.4 for the sponsor's summary tables of comparisons of groups by gender, age and race. From observation, the most consistent finding was that female patients have more digestive system adverse events than males. Also from this data, it appears that the age group > 55 were more sensitive to cardiovascular and digestive adverse events at low doses than the younger age group; however, the population sample is not large enough to make definitive conclusions. There were no consistent findings comparing races.

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing in the Development Program

The Integrated Summary of Safety (ISS) states that routine laboratory tests for all studies included complete blood count, electrolytes, serum hepatic and renal function. The final samples were collected at either six hours after the last dose administration or at the end of the twenty-four hour period (whichever was longer) or at early termination. The frequency of laboratory testing varied amongst the studies; the ISS merely states that routine laboratory tests were collected at baseline and repeated during and/or at the end of treatment.

8.1.6.2 Selection of Studies and analyses for Overall Drug-control comparisons

This section will discuss trends observed in the entire safety data base. Also reviewed are the two controlled studies 125 and 126 which utilized the low dose (2 mg) ziprasidone IM control group to help assess the effects of higher doses of ziprasidone.

8.1.6.3 Standard Analyses and Explorations of Laboratory Data

8.1.6.3.1 Analyses focused on Measures of Central Tendency

Please see Appendix 8.1.6.3.1 for the sponsor's table of the median change from baseline to last observation of laboratory values for all Phase II/III studies. The sponsor did not perform any statistical analysis of comparisons of any treatment group. Inspection shows that the triglycerides levels were elevated by 8% in all ziprasidone treatment groups when comparing median change from baseline to last observation. The low dose 2 mg ziprasidone IM group had a mean change of 4% in cholesterol levels while the higher ziprasidone groups showed a mean change of 1% from baseline.

Mean triglycerides were also noted to be elevated in all ziprasidone IM treatment groups in the controlled studies 125 and 126. In study 125, the median change from baseline to last observation of triglycerides increased by 17% in the ziprasidone 2mg IM treatment group and increased by 35% in the ziprasidone 10 mg IM treatment group. In study 126, triglycerides were noted to increase by 9% in the ziprasidone 2 mg IM group and by 33.6% for the ziprasidone 20 mg dose.

8.1.6.3.2 Analyses focused on Outliers

The sponsor used an elaborate system of assessing abnormal laboratory results. Different normal reference ranges were used for patients who had normal baseline values versus abnormal baseline values.

Appendix 8.1.6.3.2a contains the sponsor's laboratory reference ranges used to determine whether the baseline value was normal or abnormal; baseline values were then compared to post baseline values (it is unclear from the ISS if the post baseline values were the worst laboratory value found during the study). The sponsor applied different criteria for subjects who began the study with abnormal laboratory values. Clinical significance was determined using the values of column "A" and "B" Appendix 8.1.6.3.2b (extracted from review of NDA 20-825); for subjects with normal baseline values, the worst value was required to be outside the range specified in column "A." Meanwhile, for subjects with an abnormal baseline value, it was required that their post baseline lab value fulfill criteria of both column "A" and "B" in order to be considered of clinical significance and be included in the number of subjects with laboratory abnormalities.

Please refer to Appendix 8.1.6.3.2c for the incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies. Laboratory abnormalities were observed in 16 % (14 patients of 90) of the 2 mg ziprasidone IM group and 19 % (78 of 403) of the higher dose IM ziprasidone treatment groups. Of note are the following incidents of clinically significant laboratory test abnormalities:

Adverse Event	Ziprasidone IM 2 mg n=90	Other ziprasidone IM doses n=403
↑ Eosinophils	2 (2%)	6 (1.5%)
↑ SGOT	1 (1)	0
↑ Potassium	1 (1)	5 (1)
↓ Phosphorus	0	2 (1)
↑ Phosphorus	1 (1)	6 (1.5)
↑ Triglycerides	4 (4)	24 (6)
↑ Urine glucose	1 (1)	8 (2)
↑ Urine WBC	5 (6)	12 (3)
↑ Urine RBC	2 (2)	6 (1.5)

The incidence of elevated triglycerides for study 125 showed an abnormality in 21% (11 of 53) of the 2 mg ziprasidone IM group and 23 % (14 of 62) of the 10 mg ziprasidone groups. Study 126 revealed that 13 % (5 of 38) of subjects in the 2 mg ziprasidone IM group had an elevated triglycerides while there was an incidence of 23% (9 of 40) who had abnormal changes in triglycerides compared to baseline. The results from studies 125 and 126 suggest that there is a dose effect of elevated triglycerides for administration of ziprasidone.

Also of note in the ziprasidone groups are the elevated urine WBC and RBC count. The haloperidol groups demonstrated an elevated urine WBC in 7% (7 of 94) of subjects in the integrated safety data base; elevated urine RBCs were not observed in the in the haloperidol group.

Proteinuria was observed in 25 % (4 of 16) of patients tested. Of note is subject 120-0747002 whose baseline value was 26.4 mg/day which elevated to 486.5 mg/day after three days of IM ziprasidone treatment. Other renal functions for this patient at the time were within normal limits; there is no follow up information provided for this patient.

Elevated bilirubin was noted in a 50 y.o. patient (046-05570029) who received 10 mg ziprasidone IM q 2 hours for 3 days. Baseline values were 0.6 mg/dl (NL: 0-1.3) and on day 4, his bilirubin was elevated to 2 mg/dl; his levels normalized by day 11.

8.1.6.4 Dropouts for Laboratory Abnormalities

There were no dropouts for laboratory abnormalities.

8.1.6.5 Additional Analyses and Explorations

Study 121, a Phase III open label 3 day fixed IM dose study, included renal function tests (urinary microalbumin, NAG:creatinine ratio, total protein, β 2-microglobulin) which were conducted at screening and Day 4 (i.e. within 24 hours of discontinuing IM medication). Appendix 8.1.6.4 summarizes these results which show comparable percentage of incidence across the ziprasidone and haloperidol treatment group. The sponsor reports that there were no clinically significant changes noted during the study.

8.1.7 Vital Signs

8.1.7.1 Extent of Vital Sign Testing in the Development Program

The ISS does not specify which vital signs were compared to baseline; the final vital sign monitoring was taken at least 6 hours after the final dose was administered. The sponsor analyzed changes in standing or sitting systolic or diastolic blood pressure and sitting or standing heart rate, and weight gain or loss. Please refer to Appendix 8.1.7.3.1 for vital sign parameters used to determine clinical significance. There is no data comparing changes of supine and standing vital signs; therefore, orthostatic changes could not be adequately assessed.

8.1.7.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The focus of this section will be trends observed in the integrated Phase II/III safety data base, study 121, (a phase III open label study of 20-80 mg/d ziprasidone IM x 3 days with one arm including treatment with haloperidol), studies 033 & 038 (both Phase I studies with normal subjects), and study 046 (Phase I studies with schizophrenic/schizoaffective patients).

8.1.7.3 Analyses and Explorations of Vital Sign Data

8.1.7.3.1 Phase I Studies

As part of the review process, Sughok K. Chun, M.D., cardiology consultant at FDA (review of 11/4/98) did an in depth review of vital signs in studies 033, 038 and 046. In study 033 (single dosing 5-20 mg ziprasidone IM in healthy males), standing blood pressure was unable to be recorded in three (of eleven) subjects because of dizziness upon standing; another subject (033-708-0001) experienced a one minute syncopal episode three hours after a 5 mg dose of ziprasidone IM requiring treatment of oxygen for 16 minutes. In study 038 (single dose study 5-20 mg ziprasidone IM in healthy males), four (of six) subjects taking 10 mg ziprasidone IM and six (of six) subjects taking 20 mg ziprasidone IM were unable to stand up for 0.5 to 2.0 hours after dosing. Dr. Chun concluded that severe orthostatic hypotension, most likely due to a decrease of systolic blood pressure and increase in heart rate, was observed in healthy males when exposed to ziprasidone IM.

In study 046 (multiple dosing 20-80 mg/d x 3 days in patients with schizophrenia or schizoaffective disorder), Dr. Chun noted an increase in heart rate (>120 bpm) at the following rates: placebo:16.7%; ziprasidone IM 20 mg/d:33.3%; ziprasidone IM 40 mg/d:57.1%; and, ziprasidone IM 80 mg/d:16.7%. Otherwise, mean changes from baseline for vital signs were not felt to be clinically significant in study 046. (Please refer to Appendix 8.1.7.3.1 and Dr. Chun's review for further details)

8.1.7.3.2 Phase II/III Studies

In her review of study 121 (a phase III open label study of 20-80 mg/d ziprasidone IM x 3 days with one arm including treatment with haloperidol), Dr. Chun reports that a "postural drop of systolic blood pressure

of 10-20 mmHg with significant increase of standing heart rate and diastolic blood pressure" was observed in most cases after each dosing, especially after doses of 10 and 20 mg ziprasidone IM. The following table (extracted from Dr. Chun's review) summarizes the incidences of clinically significant changes from baseline in the fixed dose studies (121, 125 and 126):

Subjects with clinically significant changes in BP/HR in studies 125, 125 and 121
(Table extracted from Cardiology Consult:10/23/98)

	Z 2mg QID		Z5,10, 20mg-QID		Combined ZIPR		Haloperidol	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
StandSBP decrease	90	2 (2.2)	300	25 (8.3)	390	27 (6.7)	92	8 (8.7)
StandDBP increase	90	2 (2.2)	300	23 (7.7)	390	25 (6.4)	92	3 (3.3)
SitSBP decrease	92	1 (1.1)	303	10 (3.3)	395	11 (2.8)	94	3 (3.2)
SitDBP increase	92	0 (0.0)	303	19 (6.3)	395	19 (4.8)	94	5 (5.3)
StandHR increase	89	2 (2.2)	300	61(20.3)	389	63(16.2)	92	15(16.3)
SitHR increase	92	0 (0.0)	303	23 (7.6)	395	23 (5.8)	94	9 (9.6)

BP/HR measurements : Study 121 – BL 0, 30 & 60 min after IM dose;

Studies 125 & 126 – BL 0, 30 & 60 min after each dose and end point

Dr. Chun notes that the incidence of significant decreases of standing and sitting systolic blood pressure and the increase of standing heart rate and diastolic blood pressure are similar amongst the higher dose ziprasidone IM (5, 10, 20 mg) and the haloperidol group.

In the integrated safety data base, the following vital sign parameters occur with a greater incidence in the higher dose ziprasidone groups compared to the low dose (2mg) ziprasidone groups: 1) a decrease in standing and sitting systolic blood pressure, 2) an increase in standing and sitting diastolic blood pressure, and 3) an increase in standing and sitting heart rate (see Appendix 8.1.7.3.2). The incidence of increased heart rate was observed in 18.4% (76 of 412) of patients in the higher dose ziprasidone IM group, compared to 2.2% (2 of 89) of the ziprasidone IM group and 13 % (17 of 131) of the haloperidol group.

8.1.7.3.3 Dropouts for Vital Sign Abnormalities

The following table summarizes all patients who withdrew due to vital sign abnormalities:

Subjects who discontinued due to vital sign abnormalities

Subject ID #	Age/Sex	Mean dose/ duration (Ziprasidone Rx group)	Reason for d/c	Outcome/comments
121-5650217	M/36	70 mg/ 2 days (20 mg qid)	tachycardia	Heart beat: At baseline: 92 bpm Maximum : 136 bpm (30 min. after 2 nd injection):
125-7950071	M/67	2 mg/ 1 day (2 mg group)	hypertension	Baseline: 125/85 mmHg (sitting) Time after 1 st injection: 2.5 hrs: 140/92 3 hrs: 170/100 7 hrs: 200/100 8 hrs: 220/100
306-3540106	F/55	30 mg/ 2 days (10 mg qid)	hypertension	Baseline: 130/70 (sitting) 1 hr after 6 th injection: 170/120

8.1.8 ECGs

8.1.8.1 Extent of ECG testing in the development program

ECGs were recorded in all Phase II/III trials. The tracing were read on site for most of the studies and then re-read at a central site at Premier Research Worldwide which the sponsor states was blinded to the study drug group. The local and centrally read ECGs were included in the study report of studies 046 and 306. However, the study report for study 120 contains only the on site ECG reading. The ECGs for studies-121, 125, 126 and 127E were only read once at the central site. Only centrally read ECG data was included in the sponsor's integrated safety tables.

8.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

This section will discuss observations seen in study 121 (a Phase III open label study with a haloperidol treatment arm) as well as ECG tracing in study 046 (a Phase I open label study in psychiatric patients).

8.1.8.3 Analyses and Explorations of ECG Data

8.1.8.3.1 Individual Studies (046 and 121)

A review of all of the protocols of the studies in this NDA data base revealed that most ECGs were recorded at trough levels of ziprasidone (e.g. 6-24 hours after administration of the study drug). Study 046 (multiple dose study, 20-80 mg/d x 3 days in stable psychotic patients) obtained ECGs at baseline, 1 hour after the first dose (at approximate C_{max}), and on day 4, approximately 18 hours after the last dose of day 3. Referring to results seen in Appendix 8.1.7.1 (and summarized below), Dr. Chun, cardiology consultant, concludes that this data demonstrates a trend of QT prolongation:

Summary of QTc Mean changes from baseline (Study 046)

	Ziprasidone IM (mg/day)			Placebo (n=6)
	20 (n=6)	40 (n=6)	80 (n=6)	
QTc: Day 2 1 hr post 4 th dose	4 msec	11 msec	13 msec	5
QTc: Day 4 18 hrs after last dose of day 3	-4 msec	22 msec	19 msec	1

It appears that there is a dose dependent relationship when viewing the QTc trends at the reading during day 2 recorded at the approximate t_{max}.

For Study 046, Dr. Chun also concluded that there were no significant changes in the PR or QRS duration as a result of exposure to ziprasidone IM (see Appendix 8.1.8.3a).

Appendix 8.1.8.3b (submission 10/19/98) summarizes QTc changes observed in study 121 (a phase III open label study of 20-80 mg/d ziprasidone IM x 3 days with one arm including treatment with haloperidol). There is a discrepancy in the timing of the ECGs as presented in the submission of 10/19/98 (requested by Dr. Chun) and in the original NDA submission of 12/18/97. In the study protocol and study report for study 121, the only ECGs scheduled to be conducted were at screening, day 4 (prior to oral ziprasidone) and at day 7; however, the submission of 10/19/98 suggests that there was an additional ECG performed on day 1, one hour post dosing of the first IM dose. From her review of study 121, Dr. Chun concludes that that most ECG abnormalities and the number of clinically significant changes in QTc interval observed were "small and comparable across all treatment groups...most of the abnormal ECG finding during IM treatment were flattening T wave, and/or right axis deviations and/or nonspecific ST/T abnormalities."

8.1.8.3.2 Analyses focused on Outliers

The number of clinically significant QTc interval changes in the entire safety data base is summarized in the following table from the sponsor's ISS:

QTc Interval	Number (%) of Subjects with a Clinically Significant Change in QTc Interval During IM or IM Plus Oral Treatment					
	2 mg Ziprasidone		Other Ziprasidone		Haloperidol	
	IM	IM Plus Oral	IM	IM Plus Oral	IM	IM Plus Oral
≥ 450 msec	8(8.7)	10(10.9)	22(5.2)	39(9.2)	12(9.3)	16(11.7)
≥ 480 msec	0	0	2(0.5)	3(0.7)	0	0
≥ 500 msec	0	0	1(0.2)	1(0.2)	0	0
Increase in QTc Interval						
≥ 50 msec	0	0	7(1.7)	13(3.1)	4(3.1)	7(5.2)
≥ 75 msec	0	0	1(0.2)	2(0.5)	0	0
≥ 100 msec	0	0	0	0	0	0
≥ 20%	0	0	0	1(0.2)	0	0

The following table from the sponsor's ISS summarizes details of the four subjects whose QTc interval changes were ≥ 480 msec had a change of ≥ 75 msec:

Clinically Significant ECG Readings					
Subject ID	Study drug randomization group	Baseline	Most abnormal QTc interval	QTc change from Baseline	Day of Abnormality
QTc of ≥ 480 msec					
121 05810008	Ziprasidone, 20 mg	444 msec	484 msec	40 msec	4 (IM dosing)
127E0701003	Ziprasidone, 20 mg	426 msec	490 msec	64 msec	7 (oral dosing)
121 05900362	Ziprasidone, 5 mg	420 msec	504 msec	84 msec	4 (IM dosing)
QTc Increase of ≥ 75 msec					
306E03740017	Ziprasidone	331 msec	414 msec	83 msec	42 (oral dosing)
121 05900362	Ziprasidone, 5 mg	420 msec	504 msec	84 msec	4 (IM dosing)

8.1.8.3.3 Dropouts for ECG Abnormalities

There were no dropouts for ECG.

8.1.9 Special Studies

8.1.9.1 Sulphobutylether Beta-Cyclodextrin (SBECD)- the excipient

Sulphobutylether Beta-Cyclodextrin (SBECD) is a novel excipient not currently used in any marketed formulation.

SBECD is also being studied to be an excipient in the drug development of an IV formulation, which is still in early phases of drug development. The sponsor included safety data obtained from the work-up of SBECD as an excipient to this IV formulation. There were 4 studies with data of SBECD administered alone: 1) Study 225 (SBECD alone n=10), a single blind placebo controlled IV study with doses of 25 mg/kg to 200 mg/kg, 2) Studies 226 (SBECD alone: n=9), 227 (SBECD alone: n=9), and 230 (SBECD alone: n= 21), studies in which SBECD IV was used as the placebo control compared to SBECD in combination with the active IV formulation.

The sponsor calculated that each milliliter of the ziprasidone IM formulation contains 20 mg ziprasidone, 294 mg SBECD and 4.7 mg of methanesulfonate. If patients were to be receiving 20 mg ziprasidone IM qid for each dose with a maximum of 4 doses in one day, they could potentially be exposed to 1176 mg daily of SBECD. Assuming that subjects range 50-70 kg, the exposure could be determined to be ranging from 17 to 24 mg/kg/day which appears to be comparable to dosing exposure in the phase I studies of IV formulation.

Pharmacokinetic data has shown that SBECD is eliminated by the kidney. Adverse events in the submitted in these studies included abnormal vision, dizziness, headache, mild elevation in AST, and rash. The study report for study 150-230 also mentions two subjects with hematuria during exposure to SBECD, but with normal baseline.

No studies were conducted that tested the IM form of SBECD (without the ziprasidone IM formulation) and its behavior at a muscular injection site.

8.1.9.2 Extrapyramidal Symptoms

Extrapyramidal Symptoms (EPS) will not be reviewed in depth for ziprasidone IM as there is sufficient evidence from the review of the oral formulation that ziprasidone has the potential to cause EPS (see review NDA-20-825:4/30/98). Of note, four patients in the ziprasidone IM data base discontinued due to symptoms of EPS: 1) Subject 121-5980101 withdrew on the first day of treatment with ziprasidone IM (10 mg qid) because of akathisia, sedation and increased psychosis and 2) Subject 125-6530077 withdrew on the first day of treatment with ziprasidone IM (10 mg qid) after 2 injections due to akathisia, diarrhea and nausea, 3) Subject 121-5980101 experienced acute dystonia on the first and second day of treatment with ziprasidone IM (10 mg qd and 5 mg qd respectively), and withdrew because of laryngospasm on the third day just after starting oral ziprasidone 40 mg qd, and 4) Subject 121-5980101 withdrew on the first day of treatment with ziprasidone IM (10 mg qid) because of akathisia, sedation and increased psychosis.

8.1.10 Withdrawal Phenomena/Abuse Potential

The sponsor did not study the abuse potential nor the effects of sudden or gradual discontinuation of ziprasidone IM treatment.

8.1.11 Human Reproduction Data

The sponsor did not address this topic in the Integrated Summary of Safety, and this information was not located in this submission.

8.1.12 Overdose Experience

There was no report regarding overdose of ziprasidone IM in the ISS.

8.2 Adequacy of Patient Exposure and Safety Assessments

8.2.1 Adequacy of Clinical Experience

The clinical data of this NDA is based on a relatively small subject exposure of the adult population for a new molecular entity. The labeling proposed is combined with the previously proposed labeling for the oral formulation of ziprasidone. However, the oral formulation was not approved for commercial marketing because of cardiovascular safety issues. Therefore, the current ziprasidone intramuscular exposure of the adult population appears to be insufficient to merit marketing with its own labeling. There was no pediatric exposure of ziprasidone IM reported in this NDA submission.

The sponsor submitted more than one adequate and well controlled study to support the efficacy claims of ziprasidone IM.

8.2.2 Adequacy of Animal and/or In Vitro Testing

Toxicity studies were not adequately performed using the intramuscular formulation of ziprasidone; preclinical studies were performed using the IV and oral formulations without adequate pharmacokinetic data to generalize results to the IM formulation of ziprasidone. Also, reproductive studies and

genotoxicity studies were not performed using the entire formulation of ziprasidone IM which would include, according to the proposed labeling, the excipient Sulphobutylether Beta-Cyclodextrin (SBECD), methanesulfonic acid and ziprasidone. For further details, please refer to Dr. Freed's Pharmacology Review.

8.2.3 Adequacy of Routine Clinical Testing

This submission was of adequate quality to be submitted for review. Of concern, though, is that most of the ECG recordings obtained in this data base were performed without regard for timing. There were few ECG readings/QTc measurement done at times of peak concentrations of ziprasidone IM.

Ziprasidone IM was not tested on patients with hepatic or renal impairment. This becomes a note of concern because the cyclodextrin excipient is cleared by renal filtration. The sponsor included a mention of this precaution under the special populations section in the proposed labeling.

There was also a methodological flaw in the collection of the vital signs. Most of the vital signs recorded were done with sitting blood pressure rather than blood pressures recorded in the supine position; this does not allow for the most accurate assessment of orthostatic effects of ziprasidone. Also, in looking at the median changes from baseline of vital signs, the sponsor used observations that could have been recorded up to twenty-four hours after the last dose of study treatment; this may provide less accurate comparisons than could have been made if these measurements were recorded sooner given the half-life of this drug ($t_{1/2}$ was approximately 3 hours).

The elaborate system used by the sponsor for reporting clinical significance of laboratory values set up many restrictions that may not have captured laboratory abnormalities of interest. The criteria for a change from baseline for a baseline-abnormal subject appears extreme, and changes that may be concerning would not be picked up using this system. It would perhaps be more helpful to identify changes from baseline and use that as the criteria. It is curious that there were a significant number of subjects who had an abnormal baseline to merit different criterion; however, their laboratory values were not so abnormal that they were excluded from enrolling in the study. Also of note is that the last laboratory value was performed up to 24 hours after the last administration of IM ziprasidone, some subjects may no longer have had appreciable plasma concentrations when the tests were performed, and the maximum effect of the study drug may not have been appreciated.

8.2.4 Adequacy of Metabolic Workup

A metabolic profile of ziprasidone IM was not performed. It is unknown if the combination of the ingredients in the entire formulation of ziprasidone IM (SBECD, methanesulfonic acid and ziprasidone) would generate metabolites that were not identified in the metabolic work up of oral ziprasidone.

8.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by New Drug; Recommendations for Further Study

Because of ziprasidone's potential to prolong the QTc interval, it would be helpful to assess ECG monitoring more closely with a Holter monitor or a series of ECGs to assess QTc changes during concentration peaks.

8.2.6 Assessment of Quality and Completeness of Data

No electronic data sets were made available as part of the electronic submission, and all data was assessed from the grouping done by the sponsor's tables. Therefore, the laboratory abnormalities were determined by the sponsor's fixed criterion.

Some topic presentations within the NDA submission presented inconsistent data. The sponsor included several tables of the rate of discontinuations that were not consistent (see Section 8.1.3.1). Also, there were inconsistencies in the submission of the timing of cardiovascular data study 121 (see Section 8.1.8.3.), and

Dr. Chun, cardiology consultant noted paradoxical blood pressure data in study 033 (see Cardiology Consultant Review).

8.3 Summary of Selected Drug-Related Adverse Events

8.3.1 QTc prolongation

Ziprasidone IM has been shown to prolong the QTc interval in study 046, a multiple dose study in stable psychotic patients (See Section 8.1.8.3, p.21). This potential to prolong the QTc has been established in the oral formulation of ziprasidone. It is important to mention that most of the ECG work up for this NDA data base was done with little regard for the timing of the ECG or the effect of ziprasidone on the QTc at peak concentration. Drug induced QTc prolongation may be correlated with the development of ventricular arrhythmia, syncope, and sudden death.

Clinically significant QTc prolongation was noted in two patients while taking ziprasidone IM: 1) Subject 590-0362 had a QTc > 500 with an 84 msec change from baseline, and 2) Subject 121-5900362 had a 40 msec change from baseline (See section 8.8.3.2, p. 21).

Based on the findings which suggest that ziprasidone IM and oral ziprasidone prolong the QTc interval, Dr. S. Chun, FDA cardiology consultant (HFD-110), agreed with Dr. C. Ganley, FDA cardiology consultant for oral ziprasidone, that there may be the usual risks of ventricular arrhythmia, syncope, and sudden death observed with drugs which prolong the QT interval. It was recommended that the labeling clearly reflect this risk and that it may be necessary to consider this drug as a second line therapy if approved.

8.3.2 Orthostatic Hypotension/Syncope

Because ziprasidone demonstrates alpha adrenergic properties, it is not unexpected that orthostatic hypotension and syncope were observed as adverse events in this data base (see Section 8.1.7.3, p.19). It is noted that the most severe cases of orthostatic hypotension were observed in the Phase I studies in subjects who were naïve to neuroleptic exposure. However, in this NDA data base, there was also a significant incidence of decreases in systolic blood pressure, and increases in standing heart rates/diastolic blood pressure which suggests that ziprasidone IM also causes postural hypotension in patients previously exposed to neuroleptics.

It is also noted that there was a dose response relationship of postural hypotension observed (see Section 8.1.5.4, p. 16).

8.3.3 Tachycardia

Increases in standing and sitting heart rates were observed with a higher incidence in the higher dose ziprasidone IM groups (5-80 mg/day) compared with the low dose ziprasidone IM group (2mg/dose) in the integrated safety data base and in study 121, a phase III open label study of 20-80 mg/d ziprasidone IM (see Section 8.1.7.3.2, p.19).

One patient (subject #121-565-0217) discontinued due to an episode of tachycardia occurring within 30 minutes after the second injection of ziprasidone IM(see Section 8.1.7.3.3, p.20).

8.3.4 Priapism

One 50 y.o. male diagnosed with schizophrenia was noted to experience priapism after two doses of 2 mg ziprasidone IM (see Section 8.1.3.2, p.15). Although this subject's history suggests that he had a pre-disposition to priapism, there appears to be temporal relationship between the onset of symptoms of the reported episode and the administration of the second dose of ziprasidone. This event would merit a cautionary statement in labeling.

8.3.5 Elevated Triglycerides

Triglyceride levels were noted to be elevated in the median change from baseline to last observation of laboratory values for all Phase II/III studies (see Section 8.1.6.3.1, p. 17). In the two low dose ziprasidone IM controlled studies (studies 125 and 126), triglycerides were elevated from baseline to last observation. Results also suggested a dose response relationship in the two controlled studies 125 and 126, because the higher doses demonstrated higher elevations than the low dose groups (see Section 8.1.6.3.1, p. 17).

8.3.6 Extrapyramidal Symptoms (EPS)

Extrapyramidal Symptoms (EPS) was not reviewed in depth for ziprasidone IM as there is sufficient evidence from the review of the oral formulation that ziprasidone has the potential to cause EPS (see review NDA-20-825:4/30/98). There were four subjects who withdrew because of symptoms of EPS (see Section 8.1.9.2, p.23).

Akathisia was noted to have a dose response relationship (see Section 8.1.5.4, p.17).

9.0 Labeling

If approved, the sponsor's labeling will require considerable revision, especially in light of the fact that the proposed labeling is based entirely on the oral formulation, which was not approved for marketing. Please see section 8.3 for important concerns that will need to be addressed in future proposed labeling.

10.0 Conclusions

A nonapprovable letter was sent to Pfizer for NDA 20-825 on June 17, 1998 indicating that ziprasidone's ability to prolong the QTc interval presented a risk of potentially fatal ventricular arrhythmias which did not outweigh the benefits of ziprasidone compared to already marketed antipsychotics. Also of note was the high sudden death rate observed within the NDA data base.

The current submission of ziprasidone IM suggests that this formulation also has the potential for QTc prolongation. As with the ziprasidone oral NDA submission, the ziprasidone IM NDA submission had most of the ECGs performed at trough levels. During the one study done according to protocol, a dose dependent relation of QTc prolongation was observed when the QTc was measured at the approximate time of maximum concentration. It is important that the sponsor adequately characterize ziprasidone's effect on the QT interval by Holter monitor or multiple ECGs, encompassing a time period that would capture the individual variation of maximal concentrations that would be observed amongst patients in a clinical setting.

More understanding and research (using consistent methodology) are needed to clarify this issue for ziprasidone. There is evidence that, like the oral formulation, the intramuscular formulation of ziprasidone has the ability to prolong the QTc in a dose dependent manner within the therapeutic dosing range.

11.0 Recommendations

Ziprasidone IM has been shown to be effective for the indication of agitation in psychotic psychiatric patients.

However, it is important to note that the entire proposed labeling for ziprasidone IM is integrated with and based on the proposed labeling for the oral formulation, which is not approved for marketing. The exposure of adult population for this current submission is too small to merit marketing ziprasidone IM as a new molecular entity. The issue of approval for this new molecular entity becomes even more complicated when considering that the extent of the QTc prolongation of ziprasidone is not well characterized for both the oral and the intramuscular formulation; thus the risk for syncope, ventricular arrhythmias, and sudden unexpected death remains unknown. Therefore, it is recommended that the intramuscular formulation of ziprasidone not be approved at this time.

/S/ - 11/13/98

Roberta L. Glass, M.D.
Medical Officer, Division of Neuropharmacological Drug Products

NDA 20-919
Div File
HFD-120:Laughren/Hardeman/Mosholder/Glass

12-8-98

I agree that this NDA
should not be approved
at this time. See memo
to file for more detailed
comments.

/S/ (M)
TL, PAP

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Appendix 5.1.1.1 Summary of all trials in integrated safety data base (from sponsor's submission 12/18/97)

Table N.2.1
Safety Database: Summary of All Studies Included in the Submission Page 1 of 1.

	Studies Included in the Subject Count	Ziprasidone 2mg*	Other Ziprasidone	Combined Ziprasidone	Haloperidol	Placebo
Phase II/III Studies						
Fixed Dosing						
One day IM dosing	125, 126	92	104	196		
IM and oral dosing; haloperidol-controlled	121		206	206	100	
Flexible Dosing						
IM and oral dosing; haloperidol-controlled	306		90	90	42	
IM and oral dosing	120		12	12		
Patient pharmacokinetic study	846		19	19		6
Oral Extension Studies	127E, 306E	55 (55)	97 (97)	152 (152)	4 (4)	
Grand Total		92	431	523	142	6

* Subjects randomized to "2mg maximum QID" group in protocols 125,126
Numbers in brackets represent the number of subjects included in the non-bracketed number whose participation was in a continuation study under the same treatment as the parent study and are also counted in the parent study category for that treatment. These subjects are counted only once in totals and subtotals.

Appendix 5.1.1.2 Table of all Phase I/II/III studies (from sponsor's submission 12/18/97)

Summaries of Important Information from Completed Studies in the Ziprasidone Intramuscular Clinical Program	
Phase I Studies	
128-033-nonUS	Investigator blind, randomized, parallel, placebo-controlled, IM trial; healthy men; single dose; (ziprasidone: 5 mg, n=5; 10 mg, n=5; 20 mg, n=6; placebo: n=5); tartrate salt.
128-037-US	Open, randomized, 3-way crossover, oral/IM/IV trial; healthy men (n=13); single dose; ziprasidone doses (5 mg IM; 5 mg IV; 20 mg oral); mesylate salt.
128-038-US	Investigator blind, randomized, parallel, placebo-controlled, IM trial; healthy men; single dose; (ziprasidone: 5 mg, n=6; 10 mg, n=6; 20 mg, n=6; placebo, n=6); mesylate salt.
128-046-US	Investigator blind, randomized, parallel, placebo-controlled, IM trial; 20 men and 5 women with psychotic disease; multiple dose; (ziprasidone: 20 mg daily, n=6; 40 mg daily, n=7; 80 mg daily, n=6; placebo: n=6); mesylate salt.
Phase II/III Studies	
128-120-nonUS	Open-label, flexible-dose, IM (3 days) and oral (2 days) in 12 men with psychosis (ziprasidone IM 2.5-20 mg BID-QID; ziprasidone oral 20-60 mg BID).
128-121-US and Canada	Open, randomized, parallel, haloperidol-controlled, IM (3 days) and oral (4 days) trial; 271 men and 35 women with psychotic disorder (ziprasidone IM 5 mg QID, n=69; 10 mg QID, n=71; 20 mg QID, n=68; haloperidol IM up to 10 mg BID to QID, n=100); (ziprasidone oral 40-200 mg daily, BID schedule; haloperidol oral flexible daily dose, BID schedule).
128-125-US	Double-blind, randomized, parallel, IM, 24-hour study in 81 men and 36 women with acute agitation and psychotic disorder (ziprasidone IM 2 mg up to QID, n=54; 10 mg up to QID, n=63)
128-126-US	Double-blind, randomized, parallel, IM, 24-hour study in 62 men and 17 women with acute agitation and psychotic disorder (ziprasidone IM 2 mg up to QID, n=38; 20 mg up to QID, n=41)
128-306-nonUS	Open, randomized, parallel, flexible-dose, IM and oral study in 123 men and 9 women with acute agitation and psychotic disorder (ziprasidone: n=90; IM 5-20 mg/injection up to 4x/day; oral, 40-100 mg BID) (haloperidol: n=42; IM 2.5-10 mg up to 4x/day; oral, 5-40 mg BID); 1-3 days IM; oral to total 7 days study treatment.

Appendix 5.1.1.3 Table of trials testing the excipient SBECD (from sponsor's submission 12/18/98)

Number of Subjects Treated in Studies with Sulphobutylether Beta-Cyclodextrin					
Study	Treatment	Study Design IV Dosing	Number of Subjects		SBECD IV Clinical Database
			per Group		SBECD
150-225 Single-Blind	SBECD	Single, escalating doses of 25, 50, 100 and 200 mg/kg SBECD and a single random dose of placebo during 5 study periods.	10		10
150-226 Single-Blind	SBECD	Single dose of 50 or 100 mg/kg SBECD.	50 mg/kg	3	8
			100 mg/kg	5	
150-227 Open-Radiolabel	SBECD	IV infusion over 1 hour of 100 mg/kg SBECD on day 1 followed 12 hours later by IV infusion of 100 mg/kg SBECD. 50 mg/kg SBECD IV infusion BID on days 2-9. Single 50 mg/kg SBECD IV infusion on day 10.	9		9
150-230 Double-Blind	SBECD	Cohort 1: 96 mg/kg SBECD IV BID on day 1 and 48 mg/kg IV BID days 2-7. 96 mg/kg SBECD IV BID on day 21 and 80 mg/kg IV BID on days 22-27. Cohort 2: 96 mg/kg SBECD IV BID on day 1 and 64 mg/kg IV BID days 2-7.	Cohort 1	14	14
			Cohort 2	7	7
SUBJECT TOTAL					48

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Appendix 5.1.2.1 Demographics of subjects exposed to ziprasidone in Phase I clinical trials (from sponsor's submission of 8/23/98)

Demographic Characteristics for Ziprasidone studies 033, 037 and 038				
	Ziprasidone 5mg IM	Ziprasidone 10mg IM	Ziprasidone 20mgIM	Placebo
	Male	Male	Male	Male
Number of Subjects	24	11	12	11
Age (years):				
18-25	10	1	6	3
26-35	11	7	3	2
36-45	2	3	3	6
Mean age (years)	27.2	31.3	28.2	33.5
Age range	19 - 42	22 - 45	18 - 43	20 - 44
Race:				
Asian	0	0	0	0
Black	0	0	0	0
White	21	11	11	11
Other	1	0	0	0
Mean weight (kg)	76.9	77.8	77.8	73.9
Weight range	63 - 97	72 - 87	72 - 86	63 - 83

Appendix 5.1.2.2 Demographics of subjects exposed to the excipient Sulphobutylether Beta-Cyclodextrin (SBECD) clinical trials (from sponsor's submission of 8/23/98)

Demographic Characteristics for SBECD Studies 150-225, 150-226, 150-227 and 150-230					
Study Number	150-225	150-226	150-227	150-230	Total
Number of SBECD Subjects	10	8	9	21	48
Age (years)					
<18	0	0	0	0	0
18 - 24	3	3	0	14	20
25 - 34	3	1	0	7	11
35 - 44	3	4	9	0	16
≥ 45	1	0	0	0	1
Age range (years)	22 - 45	22 - 44	35 - 44	18 - 34	18 - 45
mean	32	31	39	24	31.5
Race					
White	10	8	9	20	47
Other				1	1
Weight range (kg)	54.0 - 81.6	33.5 - 87.0	53.6 - 81.9	59.6 - 92.8	59.6 - 92.8
mean	72.3	73.0	75.2	73.5	73.5
Sex					
Male	10	8	9	21	48
Female	0	0	0	0	0

Appendix 5.1.2.3 Demographics of subjects exposed to ziprasidone in Phase II/III clinical trials (from sponsor's submission of 12/18/97)

Demographic Characteristics All Phase II/III Studies									
	Ziprasidone 2mg*			Other Ziprasidone			Combined Ziprasidone		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	60	24	92	369	62	431	437	86	523
Age (years):									
18-54 years	64	22	86	343	52	395	407	74	481
>=55 years	4	2	6	26	10	36	30	12	42
Mean age (years)	37.3	42.0	38.6	37.5	42.1	38.2	37.5	42.1	38.2
Age range	18-67	24-71	18-71	19-76	21-66	19-76	18-76	21-71	18-76
Race:									
Asian	2	1	3	6	0	6	8	1	9
Black	15	5	20	94	17	111	109	22	131
Caucasian	44	18	62	239	43	282	283	61	344
Other	7	0	7	30	2	32	37	2	39
Mean weight (kg)	82.2	81.0		80.4	77.8		80.7	78.1	
Weight range	53-127	51-104		42-154	41-113		42-154	41-113	

(CONTINUED)
 * Subjects randomized to "2mg maximum QID" group in protocols 125,126
 Protocols: 046,120,121,125,126,127E,306,306E
 Date of Table Generation: 04OCT97

Demographic Characteristics All Phase II/III Studies						
	Haloperidol			Placebo		
	Male	Female	Total	Male	Female	Total
Number of Subjects	127	15	142	5	1	6
Age (years):						
18-54 years	122	14	136	5	1	6
>=55 years	5	1	6	0	0	0
Mean age (years)	36.3	45.0	37.2	42.8	41.0	42.5
Age range	19-62	37-57	19-62	40-48	41-41	40-48
Race:						
Asian	4	0	4	0	0	0
Black	35	2	37	0	1	1
Caucasian	79	13	92	5	0	5
Other	9	0	9	0	0	0
Mean weight (kg)	80.9	83.1		93.6	55.8	
Weight range	46-134	48-130		81-139	56-56	

* Subjects randomized to "2mg maximum QID" group in protocols 125,126
 Protocols: 046,120,121,125,126,127E,306,306E
 Date of Table Generation: 04OCT97

Appendix 5.1.3.1 Modal daily dose of ziprasidone IM in phase I studies (from sponsor's submission 8/3/98)

Modal Daily Dose and Duration of Ziprasidone Treatment for studies 033, 037 & 038						
	Modal Total Daily Dose Per Subject					Total of IM subjects (%)
	5mg IM	10mg IM	20mg IM	5mg IV	20mg Oral	
Number of Subjects with Treatment Duration						
<=1 day	24	11	12	11	12	47 (100.0)
2 - 7 days	0	0	0	0	0	0 (0.0)
8 - 14 days	0	0	0	0	0	0 (0.0)
Number of Subjects (%)	24 (51.1)	11 (23.4)	12 (25.6)	11 (NA)	12 (NA)	47 (100.0)
Mean Duration	1	1	1	1	1	1
Range	1 - 1	1 - 1	1 - 1	1 - 1	1 - 1	1 - 1

Studies 033, 037 and 038 were all single dose phase I studies in normal healthy male volunteers. Study 037 was a 3-way crossover study with an I.V. and P.O. leg, as well as an I.M. leg. The totals in this table only include the data from IM dosing leg of protocol 037. Study 033 used a research formulation (ziprasidone tartrate) while studies 037 and 038 used the commercial formulation (ziprasidone mesylate).

Appendix 5.1.3.2 Modal daily dose of SBECD in phase I studies (from sponsor's submission 8/3/98)

Modal Daily Dose and Duration of SBECD treatment for studies 150-225, 150-226, 150-227 & 150-230							
	Modal Total Daily Dose Per Subject (IV dose per body weight)						Total (%)
	25mg/kg	50mg/kg	86 - 100mg/kg	128 mg/kg	160mg/kg	200 mg/kg	
Number of Subjects with Treatment Duration							
<=1 day	10	13	15	0	0	10	48 (52.2)
2 - 7 days	0	0	14	7	14	0	35 (38.3)
8 - 14 days	0	0	9	0	0	0	9 (9.3)
Number of Subjects (%)	10 (10.9)	13 (14.1)	38 (41.3)	7 (7.6)	14 (15.2)	10 (10.9)	92 (100.0)
Mean Duration	1	1	5	7	7	1	4
Range	1 - 1	1 - 1	1 - 10	7 - 7	7 - 7	1 - 1	1 - 10

Subjects in study 230 were dosed with a 96mg/kg BID loading dose followed by 48mg/kg, 64mg/kg or 80mg/kg. The 48mg/kg group (96mg/kg total daily dose per body weight) has been combined with the 120mg/kg data from studies 226 and 227.

Appendix 5.1.3.3 Mean daily dose of ziprasidone IM in phase II/III studies (from sponsor's submission 12/18/97)

Mean Daily Dose of Intramuscular Ziprasidone All Phase II/III Studies					
	Mean Daily IM Dose Per Subject				Total (%)
	<5mg	>=5 to <40mg	>=40 to <60mg	>=60mg	
Number of Subjects with Treatment Duration					
1 day	40	107	10	0	157 (30.0)
2 days	45	63	6	2	116 (22.2)
3 days	0	105	73	67	245 (46.8)
>3 days	0	3	2	0	5 (1.0)
Number of Subjects (%)	85 (16.3)	278 (53.2)	91 (17.4)	69 (13.2)	523 (100.0)
Mean Duration	2	2	3	3	2
Range	1-2	1-4	1-4	2-3	1-4
Protocols: 046,120,121,125,126,127E,306,306E Date of Table Generation: 25NOV97					

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Appendix 7.2.1.1 INVESTIGATORS AND STUDY CENTERS
 (FROM SPONSOR'S PROTOCOL Study 125)

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
Center 514		
Michael Kronig, M.D.	/	Hillside Hospital A Division of Long Island Jewish Medical Center 75-59 263rd Street Glen Oaks, NY 11004
Center 534		
Steven Targum, M.D.	/	Crozer-Chester Medical Center One President's Boulevard Old Main Upland, PA 19013 and Crozer-Chester Medical Center Community Division 2900 West 9th Street Chester, PA 19013
Center 542		
Alan Buffenstein, M.D.	/	The Queens Medical Center 1301 Punchbowl Street Honolulu, HI 96813-2499
Center 576		
Jeffrey Apter, M.D.	/	Princeton Biomedical Research 256 Bunn Drive Suite 6 Princeton, NJ 08540 and Princeton Biomedical Research 809 River Avenue Axelrad Building Lakewood, NJ 08701 and Princeton House 905 Herrontown Road Princeton, NJ 08540 and Mule Road Professional Building 871 Route 37 West Suite E-8 Toms River, NJ 08755

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Center 585

Ari Kiev, M.D.

Stony Lodge Hospital
Croton Dam Road
Ossining, NY 10510

Center 589

Robert Riesenberg, M.D.

Dekalb Medical Center
2701 North Decatur Road
Decatur, GA 30033

and

Biobehavioral Associates
625 Dekalb Industrial Way
Decatur, GA 30033

Center 595

Dan Zimbroff, M.D.

Behavioral Medicine Center
Loma Linda University Medical
Center
1710 Barton Road
Redlands, CA 92373

and

Pacific Clinical Research
1317 West Foothill Boulevard
Suite 140
Upland, CA 91786

Center 599

David Garver, M.D.

Dallas Veterans Affairs
Medical Center
4500 South Lancaster Road
Dallas, TX 75216

Center 633

Larry Davis, M.D.

Richland Memorial Hospital
800 East Locust Street
Olney, IL 62450

and

Davis Clinic PC
902 East Locust Street
Olney, IL 62450

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Center 653

James Chou, M.D.

Bellevue Hospital Center
462 First Avenue 21W13
New York, NY 10016

Center 663

Jambur Ananth, M.D.

Harbor-University of California
Los Angeles Medical Center
1000 West Carson Street
Building 1-South
Box 497
Torrance, CA 90509-2910

Center 686

Arthur Freeman, III, M.D.

Department of Psychiatry
Louisiana State University Medical
Center
1501 Kings Highway
Shreveport, LA 71130-3932

Center 697

Wayne Fenton, M.D.

CPC Health/Chestnut Lodge Hospital
500 West Montgomery Avenue
Rockville, MD 20850

and

ASCO Healthcare Incorporated
9036 Junction Drive
Annapolis Junction, MD 20701-1152

Center 705

James Hartford, M.D.

Hartford Research Group
3120 Burnet Avenue
Suite 103
Cincinnati, OH 45229

and

The Christ Hospital
2139 Auburn Avenue
Cincinnati, OH 45219

Center 707

Luisito Roxas, M.D.

Saint Alexius Medical Center
900 East Broadway
Bismarck, ND 58501

Center 719

David Brown, M.D.

Charter Hospital of Austin
8402 Cross Park Drive
Austin, TX 78754

and

Charter Hospital of Austin
4411 Medical Parkway
Austin, TX 78756

Center 755

George Grossberg, M.D.

Saint Louis University Medical Center
1221 South Grand Boulevard
St. Louis, MO 63014

Center 765

Scott West, M.D.

Psychiatric Institute of Florida
341 North Maitland Avenue
Suite 260
Maitland, FL 32751

and

University Behavioral Center
2500 Discovery Drive
Orlando, FL 32802

Center 767

James Miller, Jr., M.D.

Clinical Studies Melbourne
1360 Samo Road
Suite B
Melbourne, FL 32935

and

Circles of Care
400 East Sheridan Road
Melbourne, FL 32901

Center 774

Richard Steinbook, M.D.

Jackson Memorial Medical Center
1611 Northwest 12th Avenue
MH Institute Room 112b
Miami, FL 33136

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128-125

Center 780

Ileana Berman, M.D.

Taunton State Hospital/
Southeastern Area of Massachusetts
60 Hodges Avenue
Taunton, MA 02780

Center 782

Michael Lesem, M.D.

Claghorn-Lesem Research Clinic
Incorporated
6750 West Loop South
Suite 1050
Bellaire, TX 77401

and

West Oaks Hospital
6500 Homewood
Houston, TX 77074

Center 784

Shuja Haque, M.D.

Veterans Affairs Medical Center
2 South 4646 John R
Detroit, MI 48201

Center 785

Graig Johnson, M.D.

Northside Hospital Behavioral Medicine
Unit
1000 Johnson Ferry Road Northeast
Atlanta, GA 30342

and

The Promedica Research Center
3758 Lavista Road
Suite 100
Tucker, GA 30084

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128-125

Center 786

Arifulla Khan, M.D.

Northwest Clinical Reseach Center
Hambleton Professional Building
10126 Northeast 132nd Street
Suite B
Kirkland, WA 98034

and

Overlake Hospital
1035 116th Avenue, Northeast
Northeast Bellevue, WA 98004

Center 789

John Zajecka, M.D.

Women's Board Depression
Treatment and Research Center
Rush-Presbyterian-Saint Luke's
Medical Center
1725 West Harrison Street
Suite 995
Chicago, IL 60612

Center 795

Ronald Brenner, M.D.

Saint John's Episcopal Hospital
South Shore
327 Beach 19th Street
Far Rockaway, NY 11691

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Appendix 7.2.1.2 (from sponsor's submission)

Total Number of Injections by Timepoint - All Subjects, Observed Cases
Ziprasidone Protocol 125

Treatment Group	Hours Post First Dose	Number (%)* of Subjects with 1, 2, 3, or 4 Injections				Mode (Mean)
		1	2	3	4	
Ziprasidone 2 mg	0-2	54 (100.0)				1.0 (1.0)
	0-4	40 (74.1)	14 (25.9)			1.0 (1.3)
	0-6	26 (48.1)	27 (50.0)	1 (1.9)		2.0 (1.5)
	0-8	21 (38.9)	31 (57.4)	2 (3.7)		2.0 (1.6)
	0-10	20 (37.0)	27 (50.0)	6 (11.1)	1 (1.9)	2.0 (1.8)
	0-12	20 (37.0)	26 (48.1)	6 (11.1)	2 (3.7)	2.0 (1.8)
	0-16	16 (29.6)	22 (40.7)	14 (25.9)	2 (3.7)	2.0 (2.0)
	0-20	14 (25.9)	17 (31.5)	15 (27.8)	8 (14.8)	2.0 (2.3)
	0-24	13 (24.1)	18 (33.3)	10 (18.5)	13 (24.1)	2.0 (2.4)
	Final		13 (24.1)	18 (33.3)	10 (18.5)	13 (24.1)
Ziprasidone 10 mg	0-2	59 (93.7)	4 (6.3)			1.0 (1.1)
	0-4	54 (85.7)	8 (12.7)	1 (1.6)		1.0 (1.2)
	0-6	44 (69.8)	18 (28.6)	1 (1.6)		1.0 (1.3)
	0-8	40 (63.5)	21 (33.3)	2 (3.2)		1.0 (1.4)
	0-10	35 (55.6)	22 (34.9)	5 (7.9)	1 (1.6)	1.0 (1.6)
	0-12	32 (50.8)	21 (33.3)	9 (14.3)	1 (1.6)	1.0 (1.7)
	0-16	28 (44.4)	21 (33.3)	11 (17.5)	3 (4.8)	1.0 (1.8)
	0-20	24 (38.1)	21 (33.3)	10 (15.9)	8 (12.7)	1.0 (2.0)
	0-24	23 (36.5)	21 (33.3)	10 (15.9)	9 (14.3)	1.0 (2.1)
	Final		23 (36.5)	21 (33.3)	10 (15.9)	9 (14.3)

*Number of subjects out of total number in the study with 1, 2, 3, or 4 injections in each interval.
Source Data: Appendix V Table 6. Date of Data Extraction: 16SEP97. Date of Table Generation: 16SEP97.

Appendix 7.2.1.3 (from sponsor's submission)

Demographic Characteristics
Ziprasidone Protocol 125

	Ziprasidone 2mg			Ziprasidone 10mg		
	Male	Female	Total	Male	Female	Total
Number of Subjects	38	16	54	43	20	63
Age (years):						
18-44	31	9	40	28	17	45
45-64	5	6	11	13	3	16
> 64	2	1	3	2	0	2
Mean age (years)	36.8	41.8	38.3	40.3	39.3	40.0
Age range	18-67	24-71	18-71	20-76	22-60	20-76
Race:						
ASIAN	1	1	2	0	0	0
BLACK	11	3	14	9	7	16
OTHER	5	0	5	6	1	7
WHITE	21	12	33	28	12	40
Mean weight (kg)	84.5	83.2		85.4	79.0	
Weight range	59-127	63-104		57-123	51-113	

Source Data: APPENDIX V TABLE 2 Date of Data Extraction: 03SEP97 Date of Table Generation: 03SEP97

EFFICACY OUTCOME MEASURES FOR STUDY 125
(adapted from sponsor's electronic submission)

Study Summary of Outcomes* for Protocol 125 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	10 mg
AUC of BAS 0-2	Mean	8.30	7.57
	p-value		<0.001
	N	54	62
CGI Severity at Hour 4	Mean baseline	4.24	4.37
	Mean change	-0.74	-0.76
	% change	-17.47	-17.45
	p-value		0.870
	N	54	63
CGI Severity at Last Obs.	Mean baseline	4.24	4.37
	Mean change	-0.50	-0.71
	% change	-11.79	-16.36
	p-value		0.214
	N	54	63
AUC of BAS 0-4	Mean	15.88	13.47
	p-value		<0.001
	N	45	55
BAS Score at Hour 2 (LOCF)+	Mean baseline	4.65	4.81
	Mean change	-0.78	-1.63
	% change	-16.73	-33.89
	p-value		<0.001
	N	54	62
Responder Rate++	# responders	11	28
	% responders	21.15	45.16
	p-value		0.013
	N	52	62

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
 +BAS score at hour 2 is the the last assessment taken up to 2 hours post first injection.
 ++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
 **PANSS Agitation Items Score equals the sum of Items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
 Source Data: Protocol 125. Date of Table Generation: 200CT97.

Study Summary of Outcomes* for Protocol 125 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	10 mg
CGI Improvement	Mean	3.09	2.89
	p-value		0.109
	N	54	63
PANSS Total	Mean baseline	89.38	90.00
	Mean change	-12.30	-13.55
	% change	-13.76	-15.05
	p-value		0.379
	N	53	62
PANSS Agitation**	Mean baseline	14.93	15.03
	Mean change	-3.35	-4.02
	% change	-22.46	-26.72
	p-value		0.162
	N	54	62
NOSIE	Mean baseline	37.63	37.98
	Mean change	-4.28	-5.41
	% change	-11.37	-14.25
	p-value		0.349
	N	54	63

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
 +BAS score at hour 2 is the the last assessment taken up to 2 hours post first injection.
 ++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
 **PANSS Agitation Items Score equals the sum of Items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
 Source Data: Protocol 125. Date of Table Generation: 200CT97.

Appendix 7.2.2.1 INVESTIGATORS AND STUDY CENTERS
 (FROM SPONSOR'S PROTOCOL Study 126)

PRINCIPAL INVESTIGATORS	SUBINVESTIGATORS	STUDY SITES
Center 509 Thomas Posever, M.D.	/	Bay Cove Mental Health Center Inpatient Wards Lemuel Shattuck Hospital 170 Morton Street Boston, MA 02130
Center 529 Steven Potkin, M.D.	/	University of California Irvine Medical Center 101 The City Drive South Route 88 Orange, CA 92868-3298
Center 557 Sheldon Preskorn, M.D.	/	Psychiatric Research Institute 1100 North Saint Francis Suite 200 Wichita, KS 67214
Center 578 Alice Chenault, M.D.		Huntsville Research Associates 2336A Whitesburg Drive Huntsville, AL 35801
		and
		Huntsville Hospital 101 Sivley Road Huntsville, AL 35801

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128-126

Center 581

David Daniel, M.D.

Washington Clinical Research
Center
6404-P Seven Corners Place
Falls Church, VA 22044

and

Columbia/Dominion Hospital
2960 Sleepy Hollow Road
Falls Church, VA 22044

and

Columbia/Arlington Hospital
1701 North George Mason Drive
Arlington, VA 22205

and

Vencor Hospital-Arlington
601 South Carlin Springs Road
Arlington, VA 22204

Center 587

Charles Merideth, M.D.

Affiliated Research Institute
8880 Rio San Diego Drive
Suite 1090
San Diego, CA 92108

and

Harborview Medical Center
120 Elm Street
San Diego, CA 92101

and

Villa View Community Hospital
5550 University Avenue
San Diego, CA 92105

Center 602

John Carman, M.D.

Carman Research
4015 South Cobb Drive Southeast
Suite 245
Smyrna, GA 30080

and

Ridgeview Institute
3995 South Cobb Drive Southeast
Smyrna, GA 30080

128-126

Center 616

Herbert Meltzer, M.D.

Vanderbilt University Medical
Center
Psychiatric Hospital At
Vanderbilt
1601 23rd Avenue South
Suite 306
Nashville, TN 37212

and

The Village At Vanderbilt
1500 21st Avenue South
Suite 200
Nashville, TN 37212

Center 638

Douglas Levinson, M.D.

Allegheny University of The
Health Sciences
MCP-Hahnemann School of
Medicine
3200 Henry Avenue
Philadelphia, PA 19129

Center 659

Gregory Oxenkrug, M.D.

Saint Elizabeth's Medical Center
Department of Psychiatry
736 Cambridge Street
Brighton, MA 02135

Center 669

Robert Horne, M.D.

Lake Mead Hospital
1409 East Lake Mead Boulevard
North Las Vegas, NV 89030

Center 681

Mary Knesevich, M.D.

Saint Paul Medical Center at
Southwestern Medical Center
5905 Harry Hines
Dallas, TX 75235

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128-126

Center 696

Robert Levine, M.D.

Robert Levine, M.D.
1236 Park Avenue
New York, NY 10128

and

Gracie Square Hospital
421 East 75th Street
New York, NY 10021

Center 701

Daniel Van Kammen, M.D.

Veterans Affairs Medical Center
7180 Highland Drive
Pittsburgh, PA 15206-1297

Center 703

Richard Jaffe, M.D.

Belmont Center For
Comprehensive Treatment
4200 Monument Road
Philadelphia, PA 19131

Center 777

Marc Hertzman, M.D.
Lawrence Adler, M.D.

Crain Towers
1600 Crain Highway Southwest
Suite 410
Glen Burnie, MD 21061

and

Taylor Health System
4100 College Avenue
Ellicott City, MD 21041-0396

Center 791

Anne Eden Evins, M.D.

Erich Lindemann Mental Health
Center
25 Staniford Street
Boston, MA 02114

Center 792

Anthony Rothschild, M.D.

University of Massachusetts
Medical Center
Department of Psychiatry-S7
802 55 Lake Avenue North
Worcester, MA 01655

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128-126

Center 793

Franca Centorino, M.D.
Carlos Zarate, Jr., M.D.

Mclean Hospital
115 Mill Street
Belmont, MA 02178

Center 794

Neal Cutler, M.D.
Phillip Tigel, M.D.

California Clinical Trials
Medical Group
8500 Wilshire Boulevard
7th Floor
Beverly Hills, CA 90211

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Appendix 7.2.2.2
(from Sponsor's Submission)

Total Number of Injections by Timepoint - All Subjects, Observed Cases
Ziprasidone Protocol 126

Treatment Group	Hours Post First Dose	Number (%)* of Subjects with 1, 2, 3, or 4 Injections				Mode (Mean)
		1	2	3	4	
Ziprasidone 2 mg	0-2	38 (100.0)				1.0 (1.0)
	0-4	38 (100.0)				1.0 (1.0)
	0-6	27 (71.1)	11 (28.9)			1.0 (1.3)
	0-8	22 (57.9)	15 (39.5)	1 (2.6)		1.0 (1.4)
	0-10	19 (50.0)	14 (36.8)	5 (13.2)		1.0 (1.6)
	0-12	19 (50.0)	12 (31.6)	7 (18.4)		1.0 (1.7)
	0-16	17 (44.7)	12 (31.6)	9 (23.7)		1.0 (1.8)
	0-20	13 (34.2)	14 (36.8)	8 (21.1)	3 (7.9)	2.0 (2.0)
	0-24	10 (26.3)	16 (42.1)	8 (21.1)	4 (10.5)	2.0 (2.2)
	Final	10 (26.3)	16 (42.1)	8 (21.1)	4 (10.5)	2.0 (2.2)
Ziprasidone 20 mg	0-2	41 (100.0)				1.0 (1.0)
	0-4	41 (100.0)				1.0 (1.0)
	0-6	34 (82.9)	7 (17.1)			1.0 (1.2)
	0-8	32 (78.0)	9 (22.0)			1.0 (1.2)
	0-10	27 (65.9)	13 (31.7)	1 (2.4)		1.0 (1.4)
	0-12	25 (61.0)	13 (31.7)	3 (7.3)		1.0 (1.5)
	0-16	19 (46.3)	18 (43.9)	3 (7.3)	1 (2.4)	1.0 (1.7)
	0-20	17 (41.5)	16 (39.0)	5 (12.2)	3 (7.3)	1.0 (1.9)
	0-24	17 (41.5)	15 (36.6)	6 (14.6)	3 (7.3)	1.0 (1.9)
	Final	17 (41.5)	15 (36.6)	6 (14.6)	3 (7.3)	1.0 (1.9)

*Number of subjects out of total number in the study with 1, 2, 3, or 4 injections in each interval.
Source Data: Appendix V Table 6. Date of Data Extraction: 23SEP97. Date of Table Generation: 23SEP97.

Appendix 7.2.2.3
(from Sponsor's Submission)

Demographic Characteristics
Ziprasidone Protocol 126

	Ziprasidone 2mg			Ziprasidone 20mg		
	Male	Female	Total	Male	Female	Total
Number of Subjects	30	8	38	32	9	41
Age (years):						
18-44	22	6	28	23	6	29
45-64	8	2	10	9	3	12
Mean age (years)	38.1	42.5	39.0	39.8	39.9	39.9
Age range	20-62	32-54	20-62	23-60	29-57	23-60
Race:						
ASIAN	1	0	1	2	0	2
BLACK	4	2	6	1	3	4
OTHER	2	0	2	4	1	5
WHITE	23	6	29	25	5	30
Mean weight (kg)	79.2	76.4		85.4	83.8	
Weight range	53-111	51-95		59-117	67-100	

Source Data: APPENDIX V TABLE 2 Date of Data Extraction: 03SEP97 Date of Table Generation: 04SEP97

EFFICACY OUTCOME MEASURES FOR STUDY 126
(adapted from sponsor's electronic submission)

Study Summary of Outcomes* for Protocol 126 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	20 mg
AUC of BAS 0-4	Mean	15.73	12.23
	p-value		<0.001
	N	38	40
CGI Severity at Hour 4	Mean baseline	4.74	4.63
	Mean change	-1.16	-1.88
	% change	-24.44	-40.54
	p-value		0.008
	N	38	40
CGI Severity at Last Obs.	Mean baseline	4.74	4.63
	Mean change	-0.92	-1.58
	% change	-19.44	-34.05
	p-value		0.004
	N	38	40
AUC of BAS 0-2	Mean	8.48	6.95
	p-value		<0.001
	N	37	40
BAS Score at Hour 4 (LOCF)+	Mean baseline	5.00	4.98
	Mean change	-1.17	-2.17
	% change	-23.42	-43.63
	p-value		<0.001
	N	38	41
Responder Rate++	# responders	10	26
	% responders	26.32	65.00
	p-value		0.001
	N	38	40

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
 +BAS score at hour 4 is the the last assessment taken up to 4 hours post first injection.
 ++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
 **PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
 Source Data: Protocol 126. Date of Table Generation: 20OCT97.

Study Summary of Outcomes* for Protocol 126 - All Subjects, Observed Cases

		Ziprasidone	
		2 mg	20 mg
CGI Improvement	Mean	3.32	2.38
	p-value		<0.001
	N	38	40
PANSS Total	Mean baseline	84.00	86.65
	Mean change	-12.08	-18.30
	% change	-14.38	-21.12
	p-value		0.074
	N	38	40
PANSS Agitation**	Mean baseline	14.29	14.88
	Mean change	-4.03	-5.70
	% change	-28.18	-38.32
	p-value		0.102
	N	38	40
NOSIE	Mean baseline	34.71	35.90
	Mean change	-2.29	-4.70
	% change	-6.60	-13.09
	p-value		0.323
	N	38	40

*Data based on last visit, unless otherwise specified, except for AUC, which is based on 0-2 hours or 0-4 hours post first injection.
 +BAS score at hour 4 is the the last assessment taken up to 4 hours post first injection.
 ++Defined as a decrease from baseline of 2 points or more on the Behavioural Assessment Scale at 90 minutes post first dose.
 **PANSS Agitation Items Score equals the sum of items P4 (Excitement), P7 (Hostility), G2 (Anxiety) and G4 (Tension).
 Source Data: Protocol 126. Date of Table Generation: 20OCT97.

Appendix 8.1.2 Serious adverse events occurring in the extension studies in which subjects were treated with oral ziprasidone

Serious events from extension studies with oral ziprasidone

SUBJECT #	AGE/ SEX	MEAN DOSE (MG/D)	DURATION OF TREATMENT (DAYS)	SERIOUS ADVERSE EVENT/ COMMENTS
127E-5810001	43/F		49 days	Overdose of 640 mg resulting in moderate sedation
127E-7190005	49/F	77	78	Ankle fracture
127E-7950002	65/M	77	29	Seizure
121-5810002	49/F	35	26	Erosive duodenitis
121-7550287	28/M	70	28	Dystonia
127E-5950013	34/M	137	47	Bradycardia
127E-6690008	46/M	144	43	Rib fractures, pneumothorax
127E-5950013	35/M	160	45	Bradycardia
127E-5950016	24/M	120	34	Asthma exacerbation
127E-7010003	53/M	120	6	Cardiomegaly, congestive heart failure & pneumonia
127E-7950002	65/M	40	5	Seizure with loss of consciousness
306E-3740017	26/M	80	42	Tonic clonic seizure

*Appears This Way
On Original*

Appendix 8.1.5.2 (From sponsor's Electronic Submission)

Incidence Rates for Treatment-Emergent Adverse Events Reported for at Least 1% of Ziprasidone-Treated Subjects Randomized to Receive 5-20 mg per Dose Fixed-Ziprasidone-Dose Phase II/III Studies Intramuscular dosing

	Ziprasidone 2mg*	Other Ziprasidone	Combined Ziprasidone	Haloperidol
Number of Subjects: Evaluable for Adverse Events	92	310	402	100
% With Adverse Events				
BODY AS A WHOLE				
ABDOMINAL PAIN		1.6	1.2	1.0
APPL/INJ/INCISION/INSERTION SITE PAIN	8.7	9.4	9.2	2.0
ASTHENIA	2.2	2.6	2.5	
HEADACHE	3.3	14.5	11.9	8.0
PAIN		1.6	1.2	2.0
CARDIOVASCULAR				
HYPERTENSION	2.2	3.9	3.5	1.0
HYPOTENSION		1.3	1.0	
POSTURAL HYPOTENSION		2.9	2.2	
TACHYCARDIA		4.8	3.7	6.0
DIGESTIVE				
CONSTIPATION		3.2	2.5	
DRY MOUTH	1.1	2.6	2.2	2.0
DYSPEPSIA	1.1	5.8	4.7	5.0
INCREASED SALIVATION		1.9	1.5	3.0
NAUSEA	4.3	14.5	12.2	3.0
VOMITING		7.7	6.0	5.0
NERVOUS				
ABNORMAL DREAMS		1.3	1.0	
AGITATION	2.2	5.8	5.0	9.0
AKATHISIA		5.5	4.2	21.0
ANXIETY	2.2	10.3	8.5	13.0
DIZZINESS	3.3	13.2	10.9	
DYSTONIA		2.9	2.2	10.0
EXTRAPYRAMIDAL SYNDROME	2.2	1.3	1.5	15.0
HYPERTONIA	1.1	1.3	1.2	11.0
INSOMNIA	3.3	10.3	8.7	12.0
SOMNOLENCE	7.6	9.4	9.0	8.0
SPEECH DISORDER		1.3	1.0	1.0
TREMOR		2.6	2.0	3.0
RESPIRATORY				
RESPIRATORY TRACT INFECTION		1.9	1.5	1.0
RHINITIS	1.1	1.6	1.5	1.0
SPECIAL SENSES				
ABNORMAL VISION		2.3	1.7	1.0

* Subjects randomized to "2mg maximum QID" group in protocols 125,126. The incidence rate in this group for adverse events occurring at the 1% level in "Other Ziprasidone" is displayed for comparison.
 Only adverse events occurring in at least 1% of ziprasidone subjects in the "Other Ziprasidone" dose groups are included in this table.
 Subjects with multiple occurrences of the same adverse event are counted only once for that adverse event.
 Only adverse events occurring while on study treatment or within the one day after the last day of study treatment were included in this table.
 Protocols: 121,125,126
 Date of Table Generation: 080C(9/)

Appears This Way
On Original

Appendix 8.1.5.3

(Selected from sponsor's proposed labeling)

Other Adverse Events Observed During the Premarketing Evaluation of Ziprasidone

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with ziprasidone at multiple doses > 4 mg/day within the database of 2163 patients or in additional studies of ziprasidone intramuscular at doses of 5 mg (n=431). All reported events are included except those already listed in Table 1, Table 2 or elsewhere in labeling, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole Frequent: abdominal pain, back pain, fever, flu syndrome, headache, pain, suicidal ideation: Infrequent: abscess, accidental fall, accidental overdose, allergic reaction, cellulitis, chills, bacterial infection, face edema, fever, flu syndrome, fungal infection, infection, injection site complication, injection site reaction, intentional overdose, lab test abnormal, malaise, neoplasm, pelvic pain photosensitivity reaction, suicide attempt, suicide gesture: Rare: abdomen enlarged, hangover effect.

Cardiovascular System Frequent: hypertension, hypotension: Infrequent: angina pectoris, arrhythmia, bradycardia, electrocardiogram abnormal, hemorrhage, migraine, pallor, palpitation, syncope, vasodilation. Rare: peripheral vascular disorder, QT interval prolonged, retinal vascular disorder.

Digestive System Frequent: tooth disorder, vomiting: Infrequent: cheilitis, duodenal ulcer, dysphagia, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, gingivitis, increased appetite, liver function tests abnormal, oral moniliasis, rectal disorder, rectal hemorrhage, tongue edema, tooth caries: Rare: eructation, fecal incontinence, gum hemorrhage, stomach ulcer.

Hemic and Lymphatic System Infrequent: anemia, ecchymosis, eosinophilia, leukocytosis, leukopenia: Rare: iron deficiency anemia, thrombocytopenia.

Metabolic and Nutritional Disorders Frequent: weight gain, weight loss: Infrequent: albuminuria, dehydration, edema, hyperglycemia, peripheral edema, SGOT increased, SGPT increased, thirst: Rare: bilirubinemia, hypercholesteremia.

Musculoskeletal System Infrequent: arthrosis, bone pain, joint disorder, leg cramps, myasthenia, tenosynovitis.

Nervous System Frequent: agitation, delusions, depression, dyskinesia, hallucinations, hostility, insomnia, manic reaction, myoclonus, nervousness, paranoid reaction, paresthesia, personality disorder, psychosis, schizophrenic reaction, speech disorder, tardive dyskinesia, thinking abnormal, twitching: Infrequent: abnormal dreams, abnormal gait, akinesia, amnesia, apathy, aphasia, ataxia, catatonic reaction, choreoathetosis, cogwheel rigidity, confusion, convulsion, delirium, dementia, depersonalization, drug dependence, dysarthria, emotional lability, euphoria, grand mal convulsion, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido decreased, libido increased, neurosis, oculogyric crisis, paralysis, sleep disorder, stupor, vertigo, withdrawal syndrome: Rare: diplopia, incoordination, neuropathy, nystagmus.

Respiratory System Frequent: bronchitis, dyspnea, pharyngitis: Infrequent: asthma, epistaxis, hiccup, laryngismus, pneumonia, respiratory distress syndrome, sinusitis: Rare: pneumothorax, voice alteration.

Skin and Appendages Frequent: pruritus: Infrequent: acne, alopecia, contact dermatitis, dry

skin, furunculosis, eczema, exfoliative dermatitis, herpes simplex, maculopapular rash, psoriasis, seborrhea, skin disorder, skin hypertrophy, skin ulcer, sweating, urticaria, vesiculobullous rash:
Rare: furunculosis, lichenoid dermatitis, pustular rash.

Special Senses Infrequent: blepharitis, conjunctivitis, deafness, dry eyes, ear disorder, ear pain,

eye pain, otitis externa, otitis media, retinal disorder, taste perversion, tinnitus: Rare: abnormality of accommodation, mydriasis.

Urogenital System Infrequent: abnormal ejaculation, amenorrhea, cystitis, dysmenorrhea, dysuria, gynecomastia, hematuria, impotence, leukorrhea, menorrhagia, metrorrhagia, penile erection, polyuria, urinary frequency, urinary retention, urinary tract disorder, urinary tract infection, vaginitis: Rare: anorgasmia, breast pain, kidney pain, nephritis, pyelonephritis, uterine fibroids enlarged.

Appears This Way
On Original

Appendix 8.1.5.4 Summary tables comparisons of gender, age and race (from sponsor's ISS)

Incidence of Treatment-Emergent Adverse Events by Gender				
	2 mg Ziprasidone		Other Ziprasidone	
	Males n=68	Females n=24	Males n=259	Females n=51
Nervous	17.6	16.7	45.6	31.4
Body as a Whole	16.2	12.5	26.6	35.3
Digestive	8.8	12.5	27.4	35.3
Cardiovascular	2.9	4.2	13.1	9.8

Incidence of Treatment-Emergent Adverse Events by Age				
	2 mg Ziprasidone		Other Ziprasidone	
	18-54 years n=86	≥ 55 years n=6	18-54 years n=280	≥ 55 years n=30
Nervous	17.4	16.7	42.9	46.7
Body as a Whole	16.3	0	28.9	20.0
Digestive	9.3	16.7	28.6	30.0
Cardiovascular	2.3	16.7	12.1	16.7

Incidence of Treatment-Emergent Adverse Events by Race				
	2 mg Ziprasidone		Other Ziprasidone	
	Caucasian n=62	Black n=20	Caucasian n=207	Black n=72
Nervous	14.5	15.0	45.9	44.4
Body as a Whole	17.7	5.0	29.0	31.9
Digestive	9.7	5.0	26.1	38.9
Cardiovascular	1.6	0	11.1	13.9

Appears This Way
On Original

Appendix 8.1.6.3.1 Median change from Baseline to Last Observation for Laboratory Test Data
 All Phase II/III Studies (adapted from sponsor's submission of 12/18/97)

Laboratory Test Data: Median Change from Baseline to Last Observation
 - All Phase II/III Studies - Intramuscular Dosing

GROUP	PARAMETER	UNITS	Ziprasidone 2mg**			Other Ziprasidone			Combined Ziprasidone			Haloperidol	Placebo				
			N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE	N	BASELINE MEDIAN	CHANGE FROM BASELINE
HEMATOLOGY	Hemoglobin (HGB)	G/DL	84	15	0.1	389	15	0	473	15	0	120	14.9	0.1	6	15.4	-0.1
	Hematocrit (HCT)	%	84	45	0	386	44	0	470	44	0	120	44	0	6	45	-1
	RBC Count	MILL/CMM	84	4.7	0	382	4.7	0	466	4.7	0	116	4.7	0	6	4.7	-0.1
	Platelets	THOU/CMM	80	222	7	377	222	4	457	222	4	115	214	5	6	244	14
	WBC Count	THOU/CMM	81	7.5	0.4	386	7.2	0.5	467	7.2	0.5	120	7.2	0	6	8.1	-0.2
	Eosinophils (%)	%	81	6	0	372	6	0	453	6	0	120	5	0	6	9	-1
LIVER FUNCTION	Neutrophils (abs)	THOU/CMM	81	4.96	0.45	369	4.62	0.68	450	4.73	0.56	119	4.73	0	6	4.96	-0.23
	Total Bilirubin	MG/DL	88	0.5	0	393	0.5	0	481	0.5	0	121	0.5	0	6	0.5	0.1
	Total Protein	G/DL	88	7.2	0	382	7.2	0	470	7.2	0	121	7.2	0	6	6.7	0.2
	Serum Albumin	G/DL	87	4.2	0	381	4	0	468	4	0	121	4	0	6	3.8	0.3
	Serum Globulin	G/DL	88	3.2	0	379	3.2	0	467	3.2	0	121	3.2	0	6	3	0
	SGOT(AST)	IU/L	88	24	0	394	24	0	482	24	0	121	25	12	6	35	2
	SGPT(ALT)	IU/L	88	29	1	394	29	1	482	29	1	121	28	5	6	59	14
	LDH	IU/L	88	186	1	315	179	2	403	180	2	95	179	21	6	158	8
RENAL FUNCTION	Alk. Phosphatase	IU/L	88	66	1	394	70	0	482	70	0	121	68	2	6	56	1
	Blood Urea Nitrogen	MG/DL	88	11	1	349	12	0	437	12	0	101	12	1	6	11	-1
ELECTROLYTES	Serum Creatinine	MG/DL	88	1	0	394	1	0	482	1	0	121	1	0	6	0.9	0
	Uric Acid	MG/DL	88	5.8	-0.3	317	5.8	-0.2	405	5.8	-0.3	95	5.8	-0.1	6	5	0
	Sodium	MEQ/L	88	140	0	392	140	0	480	140	0	121	140	0	6	138	1
	Potassium	MEQ/L	88	4.3	0	390	4.3	0	478	4.3	0	121	4.2	0	6	4.2	-0.1
	Chloride	MEQ/L	88	102	0	393	102	-1	481	102	-1	121	102	0	6	102	1
	Calcium	MG/DL	88	9.4	0	393	9.4	0	481	9.4	0	121	9.4	0	6	9.3	-0.2
	Phosphorus	MG/DL	88	4.1	0.1	380	3.7	0.1	468	3.8	0.1	121	3.8	0	6	3.8	0.3
	Glucose, Random	MG/DL	88	84	2	380	87	1	468	85	1	121	86	3	6	101	4
	Cholesterol	MG/DL	88	159	6	316	159	1	404	159	2	95	163	0	6	168	16
	Triglycerides	MG/DL	88	130	11	316	129	10	404	129	10	95	176	5	6	140	8
URINE	Specific Gravity		88	1.018	0	312	1.02	0	400	1.02	0	94	1.02	0	6	1.018	0.002
	Urine pH		87	5	0	314	5	0	401	5	0	94	5	0	6	5	0
	Protein (qual)		70	0	0	101	0	0	171	0	0	94	0	0	6	0	0
	Protein (quant)	MG/DAY					26.4	460.1	1	26.4	460.1				6	0	0
Urine Glucose													1	20			

Based on Laboratory Test Results:

1. Converted to Standard Reporting Units

2. Adjusted to a Common Set Upper and Lower Reference Limits

** Subjects randomized to '2mg maximum QID' in protocols 125,126

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or the one day after the last day of study treatment were included in this table.

Includes protocols 046, 120, 121, 125, 126, 127E, 306, 306E

Date of Table Generation: 15OCT97

Appendix 8.1.6.3.2a Sponsor's Laboratory Reference Ranges to Determine Baseline Abnormality
(from sponsor's submission 12/18/97)

1.2 Pfizer-Defined External Reference Ranges for Normalization of Laboratory Test Data			
Clinical Laboratory Test	Standard Units	Reference Range	
		LLN	ULN
Hemoglobin	G/DL	13.800	17.20
Hematocrit	%	41.000	50.00
Red Blood Cells	MILL/CMM	4.400	5.80
Platelets	THOU/CMM	130.000	400.00
White Blood Cells	THOU/CMM	3.800	10.80
Eosinophils (%)	%	0.000	7.00
Erythrocyte Sedimentation Rate	MM/H	0.000	15.00
Prothrombin Time Quick	SEC	10.900	12.70
Total Bilirubin	MG/DL	0.000	1.30
Direct Bilirubin	MG/DL	0.000	0.40
Protein (total)	G/DL	6.000	8.50
Albumin	G/DL	3.200	5.00
Globulin	G/DL	2.200	4.20
Aspartate Aminotransferase (GOT)	IU/L	0.000	42.00
Alanine Aminotransferase (GPT)	IU/L	0.000	48.00
Lactate Dehydrogenase	IU/L	0.000	250.00
Alkaline Phosphatase	IU/L	20.000	125.00
Blood Urea Nitrogen	MG/DL	7.000	25.00
Creatinine	MG/DL	0.700	1.40
Urate	MG/DL	4.000	8.50
Sodium	MEQ/L	135.000	148.00
Potassium	MEQ/L	3.500	5.30
Chloride	MEQ/L	95.000	108.00
Bicarbonate	MEQ/L	19.000	31.00
Calcium	MG/DL	8.500	10.30
Phosphate	MG/DL	2.500	4.50
Cholesterol	MG/DL	0.000	200.00
Triglycerides	MG/DL	0.000	200.00
Glucose (fasting)	MG/DL	70.000	115.00
Glucose (random)	MG/DL	70.000	115.00
Urine Specific Gravity		1.001	1.04
Urine pH		4.600	8.00
Urine Protein		0.000	0.00
Urine Glucose		0.000	0.00
Urine WBC	/HPF	0.000	5.00
Urine RBC	/HPF	0.000	3.00
Urine Ketones		0.000	0.00
Urine Granular Casts	/LPF	0.000	0.00
Urine Hyaline Casts	/LPF	0.000	0.00
Urine Bilirubin		0.000	0.00
Cholesterol (LDL)	MG/DL	0.000	129.00
Cholesterol (HDL)	MG/DL	45.000	999.00
Thyroxine (T4)	MCG/DL	4.500	12.50
Magnesium	MG/DL	1.700	2.50
Prolactin	NG/ML	0.000	20.00
Urine Calcium	MG/DAY	50.000	400.00
Urine Glucose (24 Hr) Quantitative	MG/DAY	0.000	300.00
Urine (24hr) Protein	MG/DAY	25.000	75.00
TSH	MCIU/ML	0.400	5.50
Urine WBC Cast	/LPF	0.000	0.00
Urine (24 hr) Creatinine	MG/DAY	800.000	2400.00
Urine RBC Casts	/LPF	0.000	0.00
Neutrophils (Abs)	THOU/CMM	1.800	8.00

Appendix 8.1.6.3.2b Incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies (extracted from review of Pfizer's NDA 20-825 for ziprasidone po).

Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Column "A"	Column "B"
					Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
1	Hemoglobin (HGB)	G/DL	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
2	Hematocrit (HCT)	%	HEMATOLOGY	> 1.0 x ULN	>20% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>20% Decrease from baseline	< 90% of baseline
3	RBC Count	MILL/CMM	HEMATOLOGY	> 1.0 x ULN	>25% Decrease from baseline	< 75% of baseline
				< 1.0 x LLN	>25% Decrease from baseline	< 90% of baseline
5	Platelets	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 700	> 120% of baseline
				< 1.0 x LLN	< 75	< 80% of baseline
7	WBC Count	THOU/CMM	HEMATOLOGY	> 1.0 x ULN	> 17.5	> 125% of baseline
				< 1.0 x LLN	< 2.5	< 75% of baseline
14	ESR	MM/H	HEMATOLOGY	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
19	Prothrombin Time	SEC	HEMATOLOGY	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
608	Neutrophils (abs)	THOU/CMM	HEMATOLOGY	< 1.0 x ULN	< 1.0	< 75% of baseline
9	Eosinophils (%)	%	HEMATOLOGY	> 1.0 x ULN	>= 10%	> 150% of baseline
21	Total Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
22	Direct Bilirubin	MG/DL	LIVER FUNCTION	> 1.0 x ULN (x)	> 1.5 x ULN	> 150% of baseline
24	Total Protein	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 110% of baseline
				< 1.0 x LLN	0.9 < x LLN	< 90% of baseline
25	Serum Albumin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.1 x ULN	> 120% of baseline
				< 1.0 x LLN	< 0.9 x LLN	< 80% of baseline
26	Serum Globulin	G/DL	LIVER FUNCTION	> 1.0 x ULN	> 1.2 x ULN	> 150% of baseline
				< 1.0 x LLN	< 0.8 x LLN	< 50% of baseline

Appendix 8.1.6.3.2b (con't) Incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies (extracted from review of Pfizer's NDA 20-825 for ziprasidone po).

Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Column "A"	Column "B"
					Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
28	SGOT(AST)	IU/L	LIVER FUNCTION	>1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
30	SGPT(ALT)	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
32	LDH	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 200% of baseline
35	Alkaline Phosphatase	IU/L	LIVER FUNCTION	> 1.0 x ULN (x)	> 3 x ULN	> 150% of baseline
47	BUN	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
48	Creatinine	MG/DL	RENAL FUNCTION	> 1.0 x ULN (x)	> 1.3 x ULN	> 130% of baseline
54	Sodium	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.05 x ULN < 0.95 x LLN	> 105% of baseline < 95% of baseline
55	Potassium	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
56	Chloride	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
57	Bicarbonate	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
58	Calcium	MG/DL	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
59	Phosphorus	MG/DL	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.2 x ULN < 0.8 x LLN	> 120% of baseline < 80% of baseline
50	Uric Acid	MG/DL	ELECTROLYTES	> 1.0 x ULN	> 1.2 x ULN	> 120% of baseline
199	Magnesium	MEQ/L	ELECTROLYTES	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 110% of baseline < 90% of baseline
63	Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
173	HDL Cholesterol	MG/DL	LIPIDS	< 1.0 x LLN (?)	< 0.8 x LLN	< 80% of baseline
172	LDL Cholesterol	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 120% of baseline
64	Triglycerides	MG/DL	LIPIDS	> 1.0 x ULN (x)	> 1.2 x ULN	> 150% of baseline
67	Glucose, Fasting	MG/DL		> 1.0 x ULN < 1.0 x LLN	> 1.2 x ULN < 0.6 x LLN	> 150% of baseline < 50% of baseline
223	Prolactin	NG/ML		> 1.0 x ULN (x)	> 1.1 x ULN	> 150% of baseline

Appendix 8.1.6.3.2b (con't) Incidence of clinically significant laboratory abnormalities for all ziprasidone IM Phase II/III studies (extracted from review of Pfizer's NDA 20-825 for ziprasidone po).

Test Code	Lab Test	Standard Unit	Test Type	Baseline Abnormality Criterion	Column "A"	Column "B"
					Post-baseline Clin Sig Criterion for BL normal/abnormal (Tier 1)	Post-baseline Clin Sig Criterion for BL abnormal (Tier 2)
78	Protein (qual)		URINE	> 1.0 x ULN	≥ 2+	> baseline + 2
79	Urine Glucose		URINE	> 1.0 x ULN	≥ 2+	> baseline + 2
80	Urine WBC	/HPF	URINE	> 1.0 x ULN	≥ 6	> baseline + 6
81	Urine RBC	/HPF	URINE	> 1.0 x ULN	≥ 6	> baseline + 6
86	Ketones (qual)		URINE	> 1.0 x ULN	≥ 1+	> baseline + 1
88	Granular Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
90	Hyaline Casts	/LPF	URINE	> 1.0 x ULN	> 1	> baseline + 1
115	Bilirubin (qual)		URINE	> 1.0 x ULN	≥ 1+	> baseline + 1
600	Red Cell Cast	/LPF	URINE	> 1.0 x ULN	≥ 1	> baseline + 1
442	White Cell Cast	/LPF	URINE	> 1.0 x ULN	≥ 1	> baseline + 1
76	Specific Gravity		URINE	> 1.0 x ULN < 1.0 x LLN	> 1.035 < 1.000	> 1.035 < 1.000
77	Urine pH		URINE	> 1.0 x ULN < 1.0 x LLN	> 1.1 x ULN < 0.9 x LLN	> 1.1 x ULN < 0.9 x LLN
495	Creatinine	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
302	Calcium (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
308	Protein (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline
307	Glucose (quant)	MG/DAY	URINE	> 1.0 x ULN (x)	> 1.1 x ULN	> 110% of baseline

Appears This Way
On Original

Appendix 8.1.6.3.2c Incident of Clinically Significant Laboratory Test in all oral Phase II/III Studies
(adapted from sponsor's submission 12/18/98)

Incidence of Clinically Significant Laboratory Test Abnormalities
- All Phase II/III Studies - Intramuscular Dosing Tier 2 - Adjusted for Abnormal Baseline

Number of Subjects: Evaluable for laboratory abnormalities With Clinically significant laboratory abnormalities				Ziprasidone 2mg** 90 14 (16%)			Other Ziprasidone 403 78 (19%)			Combined Ziprasidone 493 92 (19%)		
Group	Parameter	Units	Criteria*	Subjects with Abnormalities			Subjects with Abnormalities			Subjects with Abnormalities		
				N	n	%	N	n	%	N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL	> 20% decrease*	88	0	0	401	0	0	489	0	0
	Hematocrit (HCT)	%	> 20% decrease*	88	0	0	401	0	0	489	0	0
	RBC Count	Mill/CMM	> 25% decrease*	88	0	0	401	0	0	489	0	0
	Platelets	THOU/CMM	< 75	88	0	0	394	0	0	482	0	0
			< 700	88	0	0	394	0	0	482	0	0
	WBC Count	THOU/CMM	< 2.5	88	0	0	401	0	0	489	0	0
LIVER FUNCTION			> 17.5	88	0	0	401	1	0	489	1	0
			>= 10%	88	2	2	401	6	1	489	8	2
	Eosinophils (E)	%	< 1.0	88	0	0	401	0	0	489	1	0
	Neutrophils (abs)	THOU/CMM	< 1.5 x ULN	90	0	0	402	1	0	492	1	0
	Total Bilirubin	MG/DL	< 0.9 x LLN	90	0	0	391	0	0	481	0	0
	Total Protein	G/DL	> 1.1 x ULN	90	0	0	391	0	0	481	0	0
	Serum Albumin	G/DL	< 0.9 x LLN	90	0	0	390	0	0	480	0	0
	Serum Globulin	G/DL	> 1.1 x ULN	90	0	0	390	1	0	480	1	0
	SGOT(AST)	IU/L	< 0.8 x LLN	90	0	0	389	0	0	479	0	0
	SGPT(ALT)	IU/L	> 1.2 x ULN	90	0	0	389	0	0	479	0	0
RENAL FUNCTION	LDH	IU/L	> 3.0 x ULN	90	1	1	403	0	0	493	1	0
	Alk. Phosphatase	IU/L	> 3.0 x ULN	90	0	0	403	0	0	493	0	0
	Direct Bilirubin	MG/DL	> 1.5 x ULN	90	0	0	317	1	0	407	1	0
	Blood Urea Nitrogen	MG/DL	> 1.3 x ULN	90	0	0	351	0	0	441	0	0
	Serum Creatinine	MG/DL	> 1.3 x ULN	90	0	0	403	0	0	493	0	0
	Uric Acid	MG/DL	> 1.2 x ULN	90	0	0	319	0	0	409	0	0
	Sodium	MEQ/L	< 0.95 x LLN	90	0	0	402	0	0	492	0	0
	Potassium	MEQ/L	< 1.05 x ULN	90	0	0	402	0	0	492	0	0
			< 0.9 x LLN	90	0	0	402	0	0	492	0	0
			> 1.1 x ULN	90	1	1	402	5	1	492	6	1
ELECTROLYTES	Chloride	MEQ/L	< 0.9 x LLN	90	0	0	402	0	0	492	0	0
	Calcium	MG/DL	< 0.9 x LLN	90	0	0	402	0	0	492	0	0
			> 1.1 x ULN	90	0	0	402	0	0	492	0	0
	Phosphorus	MG/DL	< 0.8 x LLN	90	0	0	389	2	1	479	2	0
			> 1.2 x ULN	90	1	1	389	6	2	479	7	1
	Glucose, Random	MG/DL	> 1.2 x ULN	90	0	0	402	9	2	492	9	2
			< 0.6 x LLN	90	0	0	402	6	1	492	6	1
	Bicarbonate	MEQ/L	< 0.9 x LLN				2	0	0	2	0	0
			> 1.1 x ULN				2	0	0	2	0	0
	ELECTROLYTES	Glucose, Fasting	MG/DL	> 1.2 x ULN				1	0	0	1	0
			< 0.6 x LLN				1	0	0	1	0	0
LIPIDS	Cholesterol	MG/DL	> 1.2 x ULN	90	4	4	318	0	0	408	1	0
	Triglycerides	MG/DL	> 1.2 x ULN	90	4	4	318	24	8	408	28	7
URINE	Specific Gravity		< 1.000	90	0	0	315	0	0	405	0	0
			> 1.035	90	0	0	315	0	0	405	0	0
	Urine pH		< 0.9 x LLN	90	0	0	316	0	0	406	0	0
			> 1.1 x ULN	90	0	0	316	1	0	406	1	0
	Protein (qual)		>= 2+	90	0	0	334	0	0	424	0	0
	Urine Glucose		>= 2+	90	1	1	323	8	2	413	9	2
	Urine WBC	/HPF	>= 6	90	5	6	306	12	4	396	17	4
	Urine RBC	/HPF	>= 6	90	2	2	312	6	2	402	8	2
	Ketones (qual)		>= 1+	90	0	0	322	2	1	412	2	0
	Bilirubin (qual)		>= 1+	1	0	0	1	0	0	2	0	0
MORPHOSES	Protein (quant)	MG/DAY	> 1.1 x ULN				4	1	25	4	1	25
	White Cell Cast	/LPF	>= 1				1	0	1	0	0	
MORPHOSES	TSN	MCID/ML	< 0.8 x LLN	52	0	0	64	0	0	116	0	0
			> 1.2 x ULN	52	0	0	64	0	0	116	0	0

Includes protocols 046, 120, 121, 125, 126, 127E, 306, 306E
 ** Subjects randomized to "2mg maximum QID" in protocols 125, 126
 n = Total number of subjects with at least one observation of the given lab parameter while on study treatment or the one day after the last day of study treatment were included in this table.
 n = Number of subjects with a clinically significant abnormality
 * Change from baseline
 Date of Table Generation: 15OCT97

Appendix 8.1.6.3.2c (con't) Incident of Clinically Significant Laboratory Test in all oral Phase II/III Studies (adapted from sponsor's submission 12/18/98)

Incidence of Clinically Significant Laboratory Test Abnormalities
 - All Phase II/III Studies - Intramuscular Dosing Tier 2 - Adjusted for Abnormal Baseline

Number of Subjects:				Haloperidol			Placebo		
Evaluable for laboratory abnormalities				125			6		
With Clinically significant laboratory abnormalities				19 (15%)			1 (17%)		
Group	Parameter	Units	Criteria*	Subjects with Abnormalities			Subjects with Abnormalities		
				N	n	%	N	n	%
HEMATOLOGY	Hemoglobin (HGB)	G/DL	> 20% decrease*	125	0	0	6	0	0
	Hematocrit (HCT)	%	> 20% decrease*	125	0	0	6	0	0
	RBC Count	MILL/CMM	> 25% decrease*	124	0	0	6	0	0
	Platelets	THOU/CMM	< 75	121	0	0	6	0	0
			> 700	121	0	0	6	0	0
	WBC Count	THOU/CMM	< 2.5	125	0	0	6	0	0
		> 17.5	125	0	0	6	0	0	
LIVER FUNCTION	Eosinophils (%)	%	>= 10%	125	0	0	6	0	0
	Neutrophils (abs)	THOU/CMM	< 1.0	125	0	0	6	0	0
	Total Bilirubin	MG/DL	> 1.5 x ULN	125	0	0	6	0	0
	Total Protein	G/DL	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Serum Albumin	G/DL	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Serum Globulin	G/DL	< 0.8 x LLN	125	0	0	6	0	0
			> 1.2 x ULN	125	0	0	6	0	0
	SGOT(AST)	IU/L	> 3.0 x ULN	125	3	2	6	0	0
SGPT(ALT)	IU/L	> 3.0 x ULN	125	0	0	6	0	0	
LDH	IU/L	> 3.0 x ULN	95	0	0	6	0	0	
Alk. Phosphatase	IU/L	> 3.0 x ULN	125	0	0	6	0	0	
RENAL FUNCTION	Direct Bilirubin	MG/DL	> 1.5 x ULN				1	0	0
	Blood Urea Nitrogen	MG/DL	> 1.3 x ULN						
ELECTROLYTES	Serum Creatinine	MG/DL	> 1.3 x ULN	101	0	0	6	0	0
	Uric Acid	MG/DL	> 1.2 x ULN	125	0	0	6	0	0
	Sodium	MEQ/L	< 0.95 x LLN	95	0	0	6	0	0
			> 1.05 x ULN	125	0	0	6	0	0
	Potassium	MEQ/L	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	1	1	6	0	0
	Chloride	MEQ/L	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Calcium	MG/DL	< 0.9 x LLN	125	0	0	6	0	0
			> 1.1 x ULN	125	0	0	6	0	0
	Phosphorus	MG/DL	< 0.8 x LLN	125	0	0	6	0	0
			> 1.2 x ULN	125	3	2	6	0	0
	Glucose, Random	MG/DL	> 1.2 x ULN	125	0	0	6	0	0
		< 0.6 x LLN	125	1	1	6	0	0	
Bicarbonate	MEQ/L	< 0.9 x LLN	1	0	0				
		> 1.1 x ULN	1	0	0				
ELECTROLYTES	Glucose, Fasting	MG/DL	> 1.2 x ULN						
			< 0.6 x LLN						
LIPIDS	Cholesterol	MG/DL	> 1.2 x ULN	95	0	0	6	0	0
URINE	Triglycerides	MG/DL	> 1.2 x ULN	95	3	3	6	1	17
	Specific Gravity		< 1.000	95	0	0	6	0	0
			> 1.035	95	0	0	6	0	0
	Urine pH		< 0.9 x LLN	95	0	0	6	0	0
			> 1.1 x ULN	95	0	0	6	0	0
	Protein (qual)		>= 2+	99	0	0	6	0	0
	Urine Glucose		>= 2+	99	3	3	6	0	0
	Urine WBC	/HPF	>= 6	94	7	7	3	0	0
	Urine RBC	/HPF	>= 6	97	0	0			
	Ketones (qual)		>= 1+	99	0	0	6	0	0
	Bilirubin (qual)		>= 1+						
HORMONES	Protein (quant)	MG/DAY	> 1.1 x ULN						
	White Cell Cast	/LPF	>= 1						
	TSH	MCIU/ML	< 0.8 x LLN						
			> 1.2 x ULN						

Includes protocols 046, 120, 121, 125, 126, 127E, 306, 306E

** Subjects randomized to "2mg maximum QID" in protocols 125, 126

N = Total number of subjects with at least one observation of the given lab parameter while on study treatment or the one day after the last day of study treatment were included in this table.

n = Number of subjects with a clinically significant abnormality

* Change from baseline

Appendix 8.1.6.4 Incidence of Clinically Significant Renal Laboratory Results taken during days 1-4 of Study 121 (adapted from sponsor's submission)

Incidence of Clinically Significant Renal Laboratory Results
Protocol 121

Day Category—Patients Abnormal Anytime During Day 1-4

Test	Criteria	Ziprasidone 5mg			Ziprasidone 10mg			Ziprasidone 20mg			All Ziprasidone		Haloperidol			
		N	Total Abn.	%	N	Total Abn.	%	N	Total Abn.	%	N	Total Abn.	%	N	Total Abn.	%
U. Microalbumin	>=20 mg/L	65	6	9.2	67	2	3.0	64	4	6.3	196	12	6.1	95	9	9.5
U. NAG:creat ratio	>1.0 U/mmol	65	5	7.7	67	2	3.0	64	4	6.3	196	11	5.6	95	3	3.2
U. Total Protein	>=0.1 g/L	65	1	1.5	67	4	6.0	64	3	4.7	196	8	4.1	95	5	5.3
U. B2-Microglobulin	>=0.3 mg/L	65	0	0	67	0	0	64	0	0	196	0	0	95	0	0
At Least One Test		65	10	15.4	67	5	7.5	64	6	9.4	196	21	10.7	95	12	12.6
Two or More Tests		65	1	1.5	67	2	3.0	64	4	6.3	196	7	3.6	95	4	4.2

Total Changed = number of subjects with an renal reading meeting criteria while on study treatment or within six days after the last day of study treatment (IM or oral).

Source Data: Appendix V - Table 8 Date of table generation: 14OCT97.

Appendix 8.1.7.3.1 Study 046 Mean changes in standing and supine systolic blood pressure, heart rate, and QTc, comparing changes from baseline (sponsor's submission 10/19/98)

Mean QTc, Standing and Supine Systolic Blood Pressure and Heart Rate, at Baseline and Changes at Day 2 and Day 4
Ziprasidone Protocol 128-046 13:08 Monday, October 19, 1999

Treatment	Baseline (Raw Values)										Day 2 - 1 Hour Post Dose (Changes from Baseline)									
	QTc (msec)		Standing Heart Rate (bpm)		Standing Systolic (mmHg)		Supine Heart Rate (bpm)		Supine Systolic (mmHg)		QTc (msec)		Standing Heart Rate (bpm)		Standing Systolic (mmHg)		Supine Heart Rate (bpm)		Supine Systolic (mmHg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
20 mg	404	11.3	77	11.1	111	10.6	75	10.0	116	10.3	4	20.4	13	8.2	3	11.2	7	7.6	-3	12.2
40 mg	395	16.4	90	14.4	127	15.3	79	14.1	127	13.4	11	13.2	11	6.9	5	15.7	8	7.8	2	18.9
80 mg	400	16.6	94	7.4	127	23.4	86	7.0	128	18.4	13	9.8	8	15.2	5	13.5	0	14.7	-3	12.7
Placebo	399	11.4	85	10.7	126	5.1	79	9.4	126	8.7	5	18.4	13	17.4	1	7.1	6	8.3	-5	11.8

(CONTINUED)

Treatment	Day 4 - 17 Hours Post Dose (Changes from Baseline)									
	QTc (msec)		Standing Heart Rate (bpm)		Standing Systolic (mmHg)		Supine Heart Rate (bpm)		Supine Systolic (mmHg)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
20 mg	-4	20.3	19	9.0	10	10.5	5	11.7	8	13.6
40 mg	22	15.3	14	13.8	4	9.8	6	11.9	-1	14.2
80 mg	19	7.3	9	13.5	3	19.4	1	10.7	2	15.8
Placebo	1	11.8	1	13.4	-10	7.7	-5	4.3	-6	7.0

Clinically significant vitals from study 046 (from sponsor's submission 12/18/97)

Vital Signs: Incidence of Clinically Significant Changes from Baseline
Ziprasidone Protocol 046

	Ziprasidone 20mg/day		Ziprasidone 40mg/day		Ziprasidone 80mg/day		Placebo	
	N	Total Percent Changed	N	Total Percent Changed	N	Total Percent Changed	N	Total Percent Changed
Standing Systolic BP (mmHg)								
Increase (BP>180, CHG>=20)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0
Decrease (BP<90, CHG<=-20)	6	0 0.0	7	0 0.0	6	0 0.0	6	1 16.7
Standing Diastolic BP (mmHg)								
Increase (BP>105, CHG>=15)	6	0 0.0	7	0 0.0	6	0 0.0	6	1 16.7
Decrease (BP<50, CHG<=-15)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0
Standing Heart Rate (bpm)								
Increase (HR>120, CHG>=15)	6	2 33.3	7	4 57.1	6	1 16.7	6	1 16.7
Decrease (HR<50, CHG<=-15)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0
Supine Systolic BP (mmHg)								
Increase (BP>180, CHG>=20)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0
Decrease (BP<90, CHG<=-20)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0
Supine Diastolic BP (mmHg)								
Increase (BP>105, CHG>=15)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0
Decrease (BP<50, CHG<=-15)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0
Supine Heart Rate (bpm)								
Increase (HR>120, CHG>=15)	6	0 0.0	7	1 14.3	6	0 0.0	6	0 0.0
Decrease (HR<50, CHG<=-15)	6	0 0.0	7	0 0.0	6	0 0.0	6	0 0.0

N is the total number of subjects with a baseline observation and at least one observation while on study drug or within 1 day of the day of dosing for the given vital sign parameter.

Source Data: Appendix Y Table 9

Date of Data Extraction: 07AUG97

Date of Table Generation: 13AUG97

Appendix 8.1.7.3.2 Incidence of clinically significant changes in vital signs in the integrated safety data base. (from sponsor's submission: 12/18/97)

	Ziprasidone Zmg*			Other Ziprasidone			Combined Ziprasidone			Haloperidol			Placebo		
	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed	N	Total Changed	Percent Changed
Standing Systolic BP (mmHg)															
Increase (BP>180, CHG<-20)	90	0	0.0	412	5	1.2	502	5	1.0	131	3	2.3	6	0	0.0
Decrease (BP<90, CHG<-20)	90	2	2.2	412	28	6.8	502	30	6.0	131	8	6.1	6	1	16.7
Standing Diastolic BP (mmHg)															
Increase (BP>105, CHG<-15)	90	2	2.2	412	30	7.3	502	32	6.4	131	4	3.1	6	1	16.7
Decrease (BP<50, CHG<-15)	90	0	0.0	412	9	2.2	502	9	1.8	131	3	2.3	6	0	0.0
Standing Heart Rate (bpm)															
Increase (HR>120, CHG<-15)	89	2	2.2	412	76	18.4	501	78	15.6	131	17	13.0	6	1	16.7
Decrease (HR<50, CHG<-15)	89	0	0.0	412	1	0.2	501	1	0.2	131	0	0.0	6	0	0.0
Sitting Systolic BP (mmHg)															
Increase (BP>180, CHG<-20)	92	1	1.1	400	3	0.8	492	4	0.8	133	1	0.8	0	0	0.0
Decrease (BP<90, CHG<-20)	92	1	1.1	400	15	3.8	492	16	3.3	133	4	3.0	0	0	0.0
Sitting Diastolic BP (mmHg)															
Increase (BP>105, CHG<-15)	92	0	0.0	400	23	5.8	492	23	4.7	133	7	5.3	0	0	0.0
Decrease (BP<50, CHG<-15)	92	0	0.0	400	8	2.0	492	8	1.6	133	3	2.3	0	0	0.0
Sitting Heart Rate (bpm)															
Increase (HR>120, CHG<-15)	92	0	0.0	400	24	6.0	492	24	4.9	133	10	7.5	0	0	0.0
Decrease (HR<50, CHG<-15)	92	0	0.0	400	2	0.5	492	2	0.4	133	0	0.0	0	0	0.0
Supine Systolic BP (mmHg)															
Increase (BP>180, CHG<-20)	0	0	0.0	19	0	0.0	19	0	0.0	0	0	0.0	6	0	0.0
Decrease (BP<90, CHG<-20)	0	0	0.0	19	0	0.0	19	0	0.0	0	0	0.0	6	0	0.0
Supine Diastolic BP (mmHg)															
Increase (BP>105, CHG<-15)	0	0	0.0	19	0	0.0	19	0	0.0	0	0	0.0	6	0	0.0
Decrease (BP<50, CHG<-15)	0	0	0.0	19	0	0.0	19	0	0.0	0	0	0.0	6	0	0.0
Supine Heart Rate (bpm)															
Increase (HR>120, CHG<-15)	0	0	0.0	19	1	5.3	19	1	5.3	0	0	0.0	6	0	0.0
Decrease (HR<50, CHG<-15)	0	0	0.0	19	0	0.0	19	0	0.0	0	0	0.0	6	0	0.0
Weight (kg)															
Increase (CHG>7%)	27	0	0.0	55	0	0.0	82	0	0.0	7	0	0.0	0	0	0.0
Decrease (CHG<-7%)	27	0	0.0	55	0	0.0	82	0	0.0	7	0	0.0	0	0	0.0

* Subjects randomized to 'Zmg maximum QED' group in protocols 125,126
N is the total number of subjects with a baseline observation and at least one observation while on study treatment or within one day after the last day of study treatment for the given vital sign parameter.
To be a clinically significant change, a value has to both meet the criterion value and represent a change from baseline of at least the magnitude noted at any time during the study treatment or within the one day after the study treatment.
Protocols: 046,120,121,125,126,127E,306,306E
Date of Table Generation: 880C197

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Appendix 8.1.8.3a Study 046: Mean change from baseline to ECG Reading one hour (approximately tmax) after the fourth dose on day 2

Change from baseline to ECG Reading following Fourth IM dose on Day 2
Protocol 046 - Central Reader Data

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc Int (msec)	20mg/day	6	404.3	404.5	389-418	407.8	411.0	369-437	3.5
	40mg/day	6	395.3	386.5	380-422	406.3	404.0	388-436	11.0
	80mg/day	6	399.5	401.0	375-422	412.0	410.5	380-440	12.5
	Placebo	6	398.7	396.0	385-413	404.0	402.5	382-424	5.3
QT Int (msec)	20mg/day	6	352.8	352.0	311-395	344.8	346.0	291-388	-8.0
	40mg/day	6	339.3	336.5	295-390	333.5	336.5	286-373	-5.8
	80mg/day	6	337.0	336.5	328-347	345.3	345.5	322-379	8.3
	Placebo	6	341.3	339.0	321-370	343.0	339.5	324-381	1.7
Heart Rate (bpm)	20mg/day	6	79.8	77.5	66-94	84.7	82.5	76-97	4.8
	40mg/day	6	84.0	82.5	58-123	91.7	85.0	68-140	7.7
	80mg/day	6	84.5	84.0	77-94	86.0	82.5	78-106	1.5
	Placebo	6	82.0	81.5	74-89	84.0	87.5	67-92	2.0
PR Int (msec)	20mg/day	6	139.0	136.5	123-165	137.3	136.0	124-157	-1.7
	40mg/day	6	153.5	154.5	126-176	138.2	139.0	124-150	-15.3
	80mg/day	6	152.5	154.5	136-168	147.0	148.0	123-165	-5.5
	Placebo	6	165.0	165.5	142-190	160.7	160.5	136-180	-4.3
QRS Int (msec)	20mg/day	6	89.0	87.0	80-100	88.0	86.0	80-102	-1.0
	40mg/day	6	86.2	85.0	79-98	86.7	86.0	81-94	0.5
	80mg/day	6	89.0	88.5	85-94	91.3	93.0	82-96	2.3
	Placebo	6	88.5	88.0	81-97	90.0	89.5	82-101	1.5

*QTc Int = QT Int/SQRT(60/(Heart Rate))
 Baseline - last ECG taken before the first day of study treatment.
 Final - last ECG taken while on study treatment or within one day after the last day of study treatment.
 Subj. 05570021 (40mg/day) withdrew following the 2nd injection on Day 1 and is not included in this summary.
 Source Data: Appendix V, Table 10 Date of Data Extraction: 24OCT97 Date of table generation: 05NOV97

Study 046: Change from baseline to last observation (approx. 18 hours after last dose of IM ziprasidone)

Change from Baseline to Last Observation in ECG Readings
Protocol 046 - Central Read Data

Variable	Treatment Group	N	Base Mean	Base Median	Base Range	Final Mean	Final Median	Final Range	Mean Change
*QTc Int (msec)	20mg/day	6	404.3	404.5	389-418	400.8	406.0	371-429	-3.5
	40mg/day	7	395.1	389.0	380-422	419.0	427.0	394-431	23.9
	80mg/day	6	399.5	401.0	375-422	418.0	418.5	405-430	18.5
	Placebo	6	398.7	396.0	385-413	399.5	401.5	389-406	0.8
QT Int (msec)	20mg/day	6	352.8	352.0	311-395	347.2	354.5	305-370	-5.7
	40mg/day	7	336.6	327.0	295-390	335.1	337.0	292-380	-1.4
	80mg/day	6	337.0	336.5	328-347	341.5	335.0	321-380	4.5
	Placebo	6	341.3	339.0	321-370	354.0	359.5	322-369	12.7
Heart Rate (bpm)	20mg/day	6	79.8	77.5	66-94	80.3	79.5	74-89	0.5
	40mg/day	7	85.0	83.0	58-123	95.3	88.0	71-131	11.3
	80mg/day	6	84.5	84.0	77-94	90.5	93.0	77-98	6.0
	Placebo	6	82.0	81.5	74-89	76.8	75.5	72-88	-5.2
PR Int (msec)	20mg/day	6	139.0	136.5	123-165	137.0	132.5	124-160	-2.0
	40mg/day	7	152.3	153.0	126-176	146.3	146.0	131-167	-6.0
	80mg/day	6	152.5	154.5	136-168	151.8	151.5	137-168	-0.7
	Placebo	6	165.0	165.5	142-190	159.3	161.0	134-187	-5.7
QRS Int (msec)	20mg/day	6	89.0	87.0	80-100	90.7	88.5	79-103	1.7
	40mg/day	7	86.7	86.0	79-98	87.1	85.0	80-96	0.4
	80mg/day	6	89.0	88.5	85-94	88.0	90.5	79-96	-1.0
	Placebo	6	88.5	88.0	81-97	86.7	84.0	81-97	-1.8

*QTc Int = QT Int/SQRT(60/(Heart Rate))
 Baseline - last ECG taken before the first day of study treatment.
 Final - last ECG taken while on study treatment or within one day after the last day of study treatment.
 Source Data: Appendix V, Table 10 Date of Data Extraction: 24OCT97 Date of table generation: 24OCT97

Appendix 8.1.8.3b ECG parameters for study 121

Study 121: ECG Parameters from Baseline to Final Reading after IM ziprasidone (from sponsor's submission (12/18/98))

Electrocardiogram Data - IM Formulation
Ziprasidone Protocol 121

Variable	Treatment Group	N	Baseline Mean	Baseline Median	Baseline Range	Final Mean	Final Median	Final Range	Mean Change
QTc Int* (msec)	Ziprasidone 5 mg QID	68	421.17	423.32	358-464	422.83	421.13	354-504	1.66
	Ziprasidone 10 mg QID	68	422.68	423.87	372-474	420.95	421.13	376-469	-1.72
	Ziprasidone 20 mg QID	63	420.66	424.56	367-464	422.70	421.75	360-484	2.04
	Haloperidol	95	419.29	420.12	367-474	421.65	420.86	358-464	2.36
QT Int (msec)	Ziprasidone 5 mg QID	68	377.94	380.00	300-490	374.85	370.00	310-470	-3.09
	Ziprasidone 10 mg QID	68	384.12	380.00	310-460	376.91	375.00	320-440	-7.21
	Ziprasidone 20 mg QID	63	375.71	370.00	280-450	370.79	370.00	310-450	-4.92
	Haloperidol	95	381.26	380.00	290-450	372.32	370.00	300-450	-8.95
Heart Rate (bpm)	Ziprasidone 5 mg QID	68	76.19	75.50	50-115	77.63	77.00	47-111	1.44
	Ziprasidone 10 mg QID	68	74.22	72.00	48-107	76.35	77.50	53-102	2.13
	Ziprasidone 20 mg QID	63	76.94	74.00	53-119	79.25	81.00	54-102	2.32
	Haloperidol	95	74.12	72.00	49-110	78.42	77.00	52-113	4.31
PR Int (msec)	Ziprasidone 5 mg QID	68	148.68	150.00	90-200	150.29	150.00	100-200	1.62
	Ziprasidone 10 mg QID	68	155.59	150.00	110-380	152.06	150.00	100-240	-3.53
	Ziprasidone 20 mg QID	63	145.24	140.00	100-210	145.40	140.00	110-200	0.16
	Haloperidol	95	148.32	150.00	100-190	148.00	150.00	80-200	-0.32
QRS Int (msec)	Ziprasidone 5 mg QID	68	87.50	90.00	60-120	88.82	90.00	60-130	1.32
	Ziprasidone 10 mg QID	68	86.76	90.00	60-120	84.12	90.00	50-110	-2.65
	Ziprasidone 20 mg QID	63	87.62	90.00	60-130	89.37	90.00	50-140	1.75
	Haloperidol	95	88.11	90.00	50-150	86.63	90.00	50-140	-1.47

*QTc Int = QT Int/SQRT(60000/(Heart Rate*1000))
Baseline = last ECG taken before the first IM injection.
Final = last ECG done within 1 day after the last day of IM treatment.
Source data: Appendix V Table 14. Date of data extraction: 15SEP97. Date of table generation: 15SEP97.

Study 121: mean QTc changes (submitted 10/19/98)

Ziprasidone Protocol 121
Mean Change from Baseline of QTc, Heart Rate, and Systolic Blood Pressure

		Baseline						Day 1*				Day 3/4**			
		Sitting		Standing		QTc	Sitting		Standing		Sitting		Standing		
		HR	Sys.	HR	Sys.		HR	Sys.	HR	Sys.	HR	Sys.	HR	Sys.	
Zip 5 mg QID	Mean	421.2	82.8	124.0	89.1	120.8	5.9	-3.4	2.8	-0.9	1.7	7.2	-1.9	4.5	1.5
	Std. Dev.	21.1	11.0	15.1	14.0	14.8	13.7	14.2	15.4	14.5	24.2	15.4	14.9	17.8	13.7
	N	68	68	68	68	68	0	64	64	63	63	68	65	65	64
Zip 10 mg QID	Mean	422.7	86.8	124.7	92.0	122.2	5.3	-4.7	2.1	-2.9	-1.7	8.1	-3.2	5.8	-1.8
	Std. Dev.	22.4	13.6	15.2	14.9	15.7	16.1	15.2	15.2	15.5	21.3	17.6	15.4	19.9	14.5
	N	68	68	68	68	68	0	68	68	67	67	68	61	61	60
Zip 20 mg QID	Mean	420.7	86.5	126.3	92.4	124.4	6.0	-4.1	3.6	-4.0	2.0	7.7	-1.1	2.7	3.1
	Std. Dev.	20.0	13.3	15.0	14.0	15.8	17.4	15.2	16.4	16.1	23.3	13.6	14.1	15.4	17.3
	N	63	63	63	61	61	0	60	60	58	58	63	57	57	55
Hal	Mean	419.3	82.1	123.3	89.5	120.4	1.0	-2.4	-2.0	-1.9	2.4	2.4	2.9	-0.1	3.2
	Std. Dev.	21.5	12.0	15.8	12.9	15.1	14.2	16.9	16.4	16.3	22.3	15.0	14.7	13.7	15.9
	N	95	95	96	94	94	0	91	91	90	90	95	92	92	90

* Heart rate and blood pressures taken on day 1, 1 hour post dose after the 1st IM dose
** ECG taken 18-19 hours post last IM dose on day 4, heart rate and blood pressures taken 1 hour post last IM dose on day 3
Date of Data Extraction: 15SEP97. Date of Table Generation: 15OCT98.

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: December 8, 1998

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

12-8-98

SUBJECT: Recommendation for Not-Approvable Action for Zeldox IM (ziprasidone IM) for the "acute control and short-term management of the agitated psychotic patient"

TO: File NDA 20-919
[Note: This overview should be filed with the 12-18-97 original submission.]

1.0 BACKGROUND

Ziprasidone IM is an intramuscular formulation of the antipsychotic drug ziprasidone that is being proposed for use in the "acute control and short-term management of the agitated psychotic patient." It is noteworthy that NDA 20-825 for the PO formulation of ziprasidone was the subject of a 6-17-98 nonapproval action based primarily on a finding of insufficient evidence for the safety of this product.

IND 49,045 for the intramuscular formulation of ziprasidone was filed 10-30-95. Since it was determined early in the development program that IM and PO formulations of ziprasidone were not bioequivalent, we alerted the sponsor in a 3-21-96 letter of the need for clinical studies to demonstrate effectiveness for the IM product. One approach we suggested was to focus on the same clinical target as for the PO formulation, i.e., a demonstration of an antipsychotic effect. Since the objective for this new formulation was to provide an alternative strategy for initiating treatment in acutely agitated psychotic patients, we suggested approaches that involved either (1) demonstrating the effectiveness of short-term treatment with IM ziprasidone (e.g., 2-3 days) followed by PO dosing for the remainder of a short-term treatment phase (e.g., total of 6 weeks), or (2) a somewhat more complicated approach for demonstrating that ziprasidone IM hastens the antipsychotic response. Alternatively, we suggested focusing on another target of therapy, e.g., the agitation and restlessness that often characterize acute psychotic episodes. Pfizer chose this alternative approach, and designed a program focusing on a calming effect for ziprasidone IM.

8-13-97: This was a pre-NDA meeting. It was largely a technical meeting focusing on formatting of the NDA and potential problems with the filing.

The original NDA 20-919 for ziprasidone IM was submitted 12-18-97.

The NDA was reviewed by Roberta Glass, M.D. from the clinical group (safety and efficacy; 11-13-98 review) and by Sue-Jane Wang, Ph.D. from the biometrics group (efficacy; 10-26-98 review).

We decided not to take ziprasidone to the PDAC.

2.0 CHEMISTRY

The chemistry review identified numerous deficiencies regarding both the drug substance and the drug product, two of which were considered sufficient to recommend a not approvable action on the basis of CMC deficiencies. One of the key deficiencies pertains to manufacture of the drug substance, and the other to the manufacture of an excipient, beta-cyclodextrin (SBECD). These deficiencies have been noted in the not-approvable letter, along with a separate listing of the numerous other deficiencies.

3.0 PHARMACOLOGY

The pharmacology/toxicology group concluded that the 2-week IV studies of ziprasidone in SBECD are not sufficient to support the intended IM use. Rather, they have asked for 1 month studies in both a rodent and nonrodent species of ziprasidone in the SBECD, given by the IM route. They have recommended, in addition, that the 1-month rodent study include an assessment of the effects of ziprasidone on micronucleus formation. While not a basis for non-approval, they have also asked for a phase 4 commitment, should this drug be approved, for a reproductive and developmental toxicity study. These requests have been incorporated into the not-approvable letter.

4.0 BIOPHARMACEUTICS

The pharmacokinetic evaluation of the IM ziprasidone formulation was found to be adequate by OCPB staff, and from their standpoint, the application was considered approvable. However, they noted the absence of studies in patients with renal failure, a consideration arising from the fact that the vehicle, cyclodextrin, is excreted by filtration. They also noted that the fate of cyclodextrin at the intramuscular site after multiple injections was not explored. We will note both issues for the not-approvable letter, but not as bases for the nonapproval action.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The sponsor presented the results of 2 controlled trials involving the use of ziprasidone IM in the control of agitation in psychotic patients (125 & 126). Both utilized a low (2 mg) ziprasidone IM dose as the control against which a higher ziprasidone IM dose was compared. In each case, the focus was on the control of agitation following the initial ziprasidone IM dose. Although the protocols identified 3 primary outcomes for each study, i.e., (1) AUC for the Behavioral Assessment Scale (BAS) after the first dose, (2) change from baseline to 4 hours for the CGI-S, and (3) change from baseline to study endpoint for the CGI-S, we decided, prior to looking at the data, that the most critical endpoint would be the AUC for the BAS. The BAS was developed by Pfizer specifically for these 2 trials, and consists of a 7-point scale targeting both agitation and level of consciousness. The 7 items are defined as follows:

- 1 = difficult or unable to rouse;
- 2 = asleep, but responds normally to verbal or physical contact;
- 3 = drowsy, appears sedated;
- 4 = quiet and awake (normal level of activity);
- 5 = signs of overt activity (physical or verbal), calms down with instructions;
- 6 = extremely or continuously active, not requiring restraint;
- 7 = violent, requires restraint.

The CGI outcome is less pertinent, given the target indication of control of agitation, since the CGI is a measure that includes, not only agitation, but also psychosis, and it would not be expected that psychosis would be substantially impacted by even several acute doses of intramuscular ziprasidone. In addition, it is difficult to obtain a valid CGI assessment in patients sedated by ziprasidone IM, since psychotic symptoms may be obscured (i.e., patients may still be psychotic but it may be more difficult to detect, given a high level of sedation). Thus, I will not even consider the CGI-S outcomes, since it is my view that these outcomes are not particularly relevant for these trials.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 125

This was a randomized, double-blind, 17-center, US inpatient study comparing 2 fixed doses of ziprasidone IM (2 mg vs 10 mg) in agitated patients who met DSM-IV criteria for one of several psychotic disorders, including both schizophrenia and bipolar disorder with psychotic features. As noted, assessments included the BAS and the CGI, however, this discussion will focus exclusively on the results for the BAS, in particular, the AUC for BAS from 0 to 2 hours (as specified by protocol). After randomization, subjects received an initial IM dose, and then could receive up to

3 additional doses, with a minimum of 2 hours between any 2 doses, during the 24 hours of the study. The total maximum doses for each group, therefore, would be 8 mg or 40 mg. The BAS was administered at baseline and at the following times after the initial dose: 15, 30, 45, 60, 90, and 120 minutes.

117 patients were randomized, with only about 4% overall not being considered completers. The mean AUC from 0 to 2 hours for the BAS was less for the 10 mg group compared to the 2 mg group to a highly statistically significant extent ($p < 0.001$), and thus, in my view, this study was successful in demonstrating a calming effect for ziprasidone in agitated psychotic patients.

5.1.2.2 Study 126

This was a randomized, double-blind, 18-center, US inpatient study comparing 2 fixed doses of ziprasidone IM (2 mg vs 20 mg) in agitated patients who met DSM-IV criteria for one of several psychotic disorders, including both schizophrenia and bipolar disorder with psychotic features. As noted, assessments included the BAS and the CGI, however, this discussion will focus exclusively on the results for the BAS, in particular, the AUC for BAS from 0 to 4 hours (as specified by protocol). After randomization, subjects received an initial IM dose, and then could receive up to 3 additional doses, with a minimum of 4 hours between any 2 doses, during the 24 hours of the study. The total maximum doses for each group, therefore, would be 8 mg or 80 mg. The BAS was administered at baseline and at the following times after the initial dose: 15, 30, 45, 60, 90, 120, 180, and 240 minutes.

79 patients were randomized, with only about 6% overall not being considered completers. The mean AUC from 0 to 4 hours for the BAS was less for the 20 mg group compared to the 2 mg group to a highly statistically significant extent ($p < 0.001$), and thus, in my view, this study was also successful in demonstrating a calming effect for ziprasidone in agitated psychotic patients.

5.1.3 Comment on Other Important Clinical Issues Regarding Ziprasidone IM for the Control of Agitation in Psychotic Patients

Evidence Bearing on the Question of Dose/Response for Efficacy

Both the 10 and 20 mg ziprasidone IM doses were superior to the 2 mg dose in controlling agitation, as measured by the BAS. Since there was no direct comparison of the 10 and 20 mg doses, it is not possible to comment on their comparative efficacy regarding control of agitation. In labeling, the sponsor has recommended an initial IM dose of either 10 or 20 mg, with additional doses of either 10 mg, not oftener than q2hrs, or 20 mg, not oftener than q4hrs, and a maximum total dose of no more than 80 mg in any 24 hour period. Since the sponsor has provided no data to distinguish between the effectiveness of the 10 and 20 mg doses, I would prefer a recommendation for 10 mg doses, with consideration of the higher 20 mg dose only if the 10 mg dose is not having a satisfactory effect on control of agitation.

Clinical Predictors of Response

The sponsor's subgroup analyses revealed no differences in effectiveness based on factors of age, gender, or race. Dr. Glass commented on the rather mild baseline scores for agitation on the BAS and the tension, hostility, and excitement items for the PANSS for the patients studied in these trials. While I agree, these scores are likely a reflection of the reality of getting subjects who are able and willing to give informed consent. In my view, it is not unreasonable to extrapolate the findings in these studies to populations with greater levels of excitement and agitation, since there would be even greater potential for improvement in the more agitated/excited patients and therefore a better opportunity for demonstrating an effect.

Size of Treatment Effect

The AUC for the BAS does not lend itself to any obvious clinical interpretation. However, I think the highly statistically significant result for both studies, given rather modest sample sizes, is persuasive that this is a clinically meaningful outcome. What also helps is the fact that this is not a surprising outcome, given prior knowledge of the sedative effects of ziprasidone, and in fact for this class of drugs generally.

Duration of Treatment

While both trials focused only on the first dose, the recommended use of ziprasidone IM is for no more than 3 days, with a maximum total dose recommendation for each day of 80 mg. I do not think it is unreasonable to extrapolate these positive findings to the 3 days of recommended treatment.

5.1.3 Conclusions Regarding Efficacy Data

In my view, the sponsor has demonstrated that ziprasidone IM, at a dose of either 10 or 20 mg, has a beneficial effect on the control of agitation in psychotic patients during the initial few days of treatment.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for ziprasidone IM were reviewed by Roberta Glass, M.D. (review dated 11-13-98). A consultative review on cardiovascular findings was provided by Sughok Chun, M.D. from HFD-110. This original review was based on a database consisting of 4 phase 1 studies (033, 037, 038, 046), 5 phase 2/3 studies (120, 121, 125, 126, 306), and 2 extension studies (127E & 306E). The cutoff date for the integrated database was 7-31-97. 523 patients were exposed to ziprasidone IM in the sponsor's phase 2/3 development program. Patients in this integrated database were predominantly male and white, with a mean age of roughly 40. About 70% of subjects received doses

of ≤ 60 mg/day, with about half of the total subjects getting dosed for 3 days. There was no dosing for > 3 days.

This safety review was conducted given our prior knowledge of the risks associated with the oral formulation of ziprasidone, which was the subject of a not-approvable action for safety reasons (see 6-17-98 letter). The focus was on confirming the expected events associated with this drug and identifying any additional risks that might be specifically associated with the intramuscular formulation.

5.2.2 Overview of Adverse Event Profile for Ziprasidone IM

Overall, there were no surprises regarding the safety of ziprasidone IM, given what we already know about orally administered ziprasidone. While there was a significant tolerance problem in normal volunteers, in particular, orthostatic hypotension, this was less of a problem in agitated schizophrenic patients. I will comment here on several findings of importance for the use, labeling, and further study of ziprasidone IM.

5.2.2.1 Vital Signs Changes

Two phase 1 studies (033 and 038) in normal males involved single doses of 5, 10, or 20 mg. At the 5 mg dose, there were substantial decreases in systolic blood pressure (SBP) and increases in heart rate (HR). At the higher doses, it was not possible to record orthostatic changes in most subjects, since most were unable to stand. Thus, orthostatic hypotension and associated tachycardia was clearly a problem in nonschizophrenic subjects administered ziprasidone IM. In agitated schizophrenic patients, while most patients were able to stand after IM ziprasidone administration, there were clearly measurable orthostatic changes, e.g., in study 121, patients at the higher ziprasidone doses had a higher proportion of clinically significant SBP decreases and HR increases compared to those getting the lower ziprasidone dose.

5.2.2.2 ECG Changes

While ECGs were obtained in most of the ziprasidone IM studies, apparently only in 1 study (046) were ECGs obtained near what would be expected to be peak concentrations for ziprasidone. This study included 3 fixed dose groups (5 mgx4/day; 10 mgx4/day; 20 mgx4/day) and placebo, each for 3 days. ECGs were obtained at baseline, 1 hour after the 4th dose on day 2, and on day 4, about 18 hours after the last dose on day 3. For both the day 2 and day 4 assessments, there was a strong suggestion of a dose dependent increase in QTc, of roughly similar magnitude to that seen with the oral formulation. Since the samples were small in this study (n=6 per group), this effect was not statistically significant. Nevertheless, this finding was consistent with what has been observed with the oral formulation. In the entire ziprasidone IM database, only 1 subject had what might be considered a clinically significant prolongation in QTc, i.e., that subject went from QTc of 420 msec at baseline to 504 msec at 1 hour post dose (5 mg).

5.2.2.3 Extrapyramidal Symptoms (EPS)

As was the case for orally administered ziprasidone, EPS was observed in association with IM ziprasidone. In fact, 4 patients discontinued from these studies (3 from study 121 and 1 from study 125) for EPS.

5.2.2.4 Priapism

1 subject experienced an episode of priapism in temporal association with ziprasidone IM dosing. This should be noted in labeling if this drug is ultimately approved.

5.2.3 Conclusions Regarding Safety of Ziprasidone IM

There were no new safety findings to suggest a substantially different safety profile for ziprasidone IM compared to that observed for oral ziprasidone. Orthostatic hypotension may be a significant problem, particularly in nonschizophrenic patients not accustomed to taking antipsychotic agents. A dose dependent increase in QTc was apparent for ziprasidone IM, as it was for oral ziprasidone, and it remains to be determined whether or not a change of the magnitude observed is of any clinical significance.

5.3 Clinical Sections of Labeling

Since we are not recommending an approvable action for this NDA, we have not prepared draft labeling. However, it should be noted that the sponsor's proposed labeling represents an integrated label for both the oral and intramuscular formulations.

6.0 WORLD LITERATURE

Dr. Glass reviewed the literature search for ziprasidone included in the NDA and did not discover any previously unrecognized important safety concerns for this drug.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, ziprasidone IM is not marketed anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take ziprasidone IM to the PDAC.

9.0 DSI INSPECTIONS

I am not aware of any results from DSI inspections for this NDA at the time of preparation of this memo. However, since I am recommending a not-approvable action, this omission is not critical.

10.0 NOT-APPROVABLE LETTER

A draft not-approvable action letter is included in the package.

11.0 CONCLUSIONS AND RECOMMENDATIONS

In my view, Pfizer has not submitted sufficient clinical data to support the conclusion that ziprasidone IM is approvable for the "acute control and short-term management of the agitated psychotic patient." The deficiencies are for safety, not efficacy. I believe Pfizer has demonstrated with 2 adequate and well-controlled trials that ziprasidone IM is effective for this indication. However, the approval of the IM ziprasidone formulation is inextricably linked with the approval of the oral formulation. Indeed, the sponsor's proposed labeling represents a blending of information for both formulations, and therefore, would not be approvable unless both formulations were approvable. The major issues continue to be (1) the finding that ziprasidone prolongs the QTc interval, and (2) the judgement that this represents a risk of potentially fatal ventricular arrhythmias that is not outweighed by a demonstrated and sufficient advantage of ziprasidone over already marketed drug products. While the finding of QTc prolongation is clearest for the oral ziprasidone formulation, there are data, especially from study 046, that are suggestive of a similar effect for the intramuscular formulation. Until this issue can be resolved, as detailed in the 6-17-98 nonapproval letter for oral ziprasidone, I do not believe we can reasonably take an approvable action for the IM product. This is especially true since the indication sought for ziprasidone IM is hardly one for which other treatments are not available. Several other antipsychotic drugs are available in intramuscular formulations, as are benzodiazepines and other sedative hypnotic drugs. While none of these drugs is specifically approved for agitation associated with psychosis, they are, nevertheless, widely used for this indication and represent a reasonable alternative. As noted, there are also CMC and pharm/tox deficiencies that would preclude an approvable action for ziprasidone IM. Consequently, I recommend that we issue the attached not-approvable letter.

cc:

Orig NDA 20-919 (Zeldox IM)

HFD-120

HFD-120/TLaughren/RKatz/RGlass/SHardeman

HFD-100/RTemple

DOC: MEMZIPIM.NA1