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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-825

Medical Review(s)

#2

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-825
Sponsor: Pfizer
Drug: : (ziprasidone)
Material Submitted: Response to Nonapprovable Letter (3/10/00), Responses to Request for Information (4/6/00, 5/19/00, 5/22/00), Safety Update #3 (6/2/00)

I. Background

Summary

Ziprasidone is a new antipsychotic which has serotonin ($5\text{-}HT_{2A}$) and dopamine (D_2) antagonist properties and received a non-approvable on 6/17/98 for the original NDA submission. The nonapprovable letter delineated concerns regarding ziprasidone's safety data which demonstrated a dose dependent QTc prolongation observed in the short-term placebo controlled studies, and that this represented a risk of "potentially fatal ventricular arrhythmias that is not outweighed by a demonstrated and sufficient advantage of ziprasidone over already marketed drug products." In response to this nonapprovable letter, the sponsor designed and conducted Study 054 which would characterize the QTc effects of currently marketed neuroleptic agents (risperidone, olanzapine, haloperidol, thioridazine, and quetiapine) in an effort to compare ziprasidone's ability to prolong the QTc with these other neuroleptic agents.

The sponsor's response to the nonapprovable letter was submitted on March 10, 2000 and included the study report of Study 054; the submission included a small amount of summary safety information up to February 5, 1999. In subsequent submissions, at FDA's request, the sponsor submitted narratives of all serious adverse events, cases of overdose, updated mortality tables and selected discontinuations occurring from May 15, 1997 to February 5, 2000, and all deaths in the entire NDA data base. The cut-off date for the safety data base reviewed in this document is February 5, 2000.

Administrative History

The original consultations obtained by FDA Cardiorenal Division written by Charles Ganley, M.D. (1/13/98 &11/24/97) stated that "if ziprasidone does prolong the QT interval, as the short term, fixed-dose, placebo controlled trials suggest, then some patients will be at risk for the development of torsades de pointes based on the experiences with other QT prolonging drugs [1/13/98]." Dr. Ganley recommended that, "unless efficacy data suggests superior benefit over currently available drugs, ziprasidone should be considered for second line therapy with adequate warnings of risk associated with drugs that prolong the QT interval [11/24/97]."

In his memo of May 14, 1998, Thomas Laughren, M.D., Team Leader for Psychiatric Drug Products, Division of Neuropharmacological Drug Products expressed concern for the approval of ziprasidone at the recommended doses because of the issues of QTc prolongation, and recommended approval of ziprasidone at a lower dosing range (20-40 mg bid). He also recommended that ziprasidone "be made available only as a second line drug with very strong labeling." Dr. Laughren recommended that labeling include a contraindicated use with other drugs that prolong the QTc interval, and "a bolded and boxed warning regarding QTc prolongation...and... [recommendations] for screening and monitoring (ECGs; serum potassium; and Holter monitoring for symptomatic patients). "

In a memo of June 1, 1998, Paul Leber, M.D., then Director of the Division of Neuropharmacological Drug Products, stated that he may have considered recommending

approval if ziprasidone had demonstrated a "unique benefit or advantage not provided by already marketed antipsychotics....however, the only evidence...that we have makes a point to state that ziprasidone's comparative performance (Study 115) supports a conclusion that it is less efficacious than haloperidol, a long marketed antipsychotic drug." Dr. Leber recommended a nonapprovable action.

The nonapprovable letter of June 17, 1998 asserted that a sufficient advantage over currently marketed antipsychotics had not been demonstrated that could outweigh the risk of potentially fatal arrhythmias because of the demonstrated QTc prolongation. The letter went onto say that ".... we would find QTc prolongation at maximum blood levels in the 5-10 msec range, with adequate assurances that there are very few outliers and that there are no factors that lead to substantially greater values in individuals (such as drug-drug interactions), sufficiently reassuring...to support approval of a new antipsychotic such as ziprasidone."

Advisory Committee Meeting

A Psychopharmacological Drug Advisory Committee meeting was held on July 19, 2000 to discuss the NDA 20-825 for Zeldox (ziprasidone hydrochloride capsules) sponsored by Pfizer. The following summary is based on the Flash minutes distributed July 20, 2000 (full transcript to be available after August 20,2000 at < http://www.fda.gov/ohrms/dockets/ac/acmenu.htm >).The majority of the committee voted for the approval of ziprasidone based on the safety information presented. There were concerns expressed regarding the lack of dose escalation data; it is unknown what would occur when ziprasidone might be used as a concomitant medications in which the dose levels increased significantly, and whether or not there could be an additive effect of QTc when administered with another drug which prolonged the QTc. There was consensus that there needed to be strong warnings regarding the potential for fatal arrhythmias, but no clear consensus of how that should be communicated to practitioners.

II. Updated Clinical Data

The original NDA clinical review discussed the sponsor's primary integrated safety data base which included 2588 patients participating in Phase II/III studies as of a cut off of May 15, 1997. This original safety data base incorporated data from both the original NDA submission (cut-off 10/31/96) and a four month safety update (cut-off 5/15/97).

Updated Primary Integrated Database

This review will cover the sponsor's primary integrated safety data base with a new cut-off date of February 5, 2000. It is also noted that the sponsor has included trials conducted in Japan in this new integrated safety data base; whereas in the original NDA submission, Japanese studies were not included in the integrated safety data base.

The following table shows the number of patients and patient-years exposure of the primary integrated data base for Phase II/III oral ziprasidone trials as of the cut-off date of February 5, 2000:

TREATMENT GROUP	N	Patient-Years
Ziprasidone (cut-off: 2/2000)	4571	1732.6
Placebo	605	91.8
Haloperidol	1071	298.6
Risperidone	426	196.4

Since the original NDA review cut-off date of May 15, 1997 to the most recent cut-off of February 5, 2000, ziprasidone has had an additional 961 patient years exposure; the additional patient years exposure for the other treatment groups are as follows: 1) placebo: 39, 2) haloperidol:167, and 3) risperidone:91.

Of the 4571 patients exposed to oral ziprasidone, 603 patients participated in the oral portion/extension to an IM study, 991 patients received ziprasidone for longer than 6 months, and 605 patients were exposed to ziprasidone for at least one year.

Deaths

As of the sponsor's cut off date of February 5, 2000, there have been a total of 50 deaths. Please refer to Appendix I for a listing of all deaths known to occur in patients exposed to ziprasidone. Since the original NDA review of 4/30/98 (cut-off of 5/15/97), there have been an additional eleven deaths which occurred within 30 days or less of the patients' discontinuation of ziprasidone, making a total of twenty-eight deaths occurring within 30 days.

Of these twenty-eight deaths, eleven of them could be considered as sudden unexpected deaths in which the patients were either found dead or died within 24 hours of onset of their symptoms associated with death. There are four additional sudden and unexplained deaths since the last ziprasidone NDA review: 1) Subject 108E-7160157, a 49 y.o. male found unresponsive in the bathroom; the investigator is reported to think the cause of death was an acute myocardial infarction based in laboratory tests, yet, no autopsy or coroner's report were available, 2) Subject Yale-9990040, a 34 y.o. male with Tourette's Syndrome who was found dead in his truck; an autopsy report (submitted 6/15/00 under IND [redacted] stated that the cause of death was occlusive coronary atherosclerosis, 3) Subject NY-97031E0054, a 51 year old patient found dead, but no coroner or autopsy report was located in the sponsor's submission, and 4) JP-966024500811, a 50 y.o. Japanese male who experienced palpitations and nausea on the second day of ziprasidone treatment and was subsequently treated with an antibiotic, (flomoxef) was reported as dead by the police four days later. (Please refer to Appendix I for further detail).

The following table updates the mortality rates for patients in the Phase II/III trials of the integrated safety data base who have died during the study or within thirty days of discontinuing treatment with ziprasidone; as in the previous review, the placebo group appears to demonstrate the highest mortality.

Mortality rate for Phase II/III clinical programs in ziprasidone NDA 20-825

DRUGS	Number of Patients [1]	Patient-years exposure [1]	Total # deaths	# deaths ≤ 30 days	Crude mortality rate [2]	Mortality per 100 patient-years [2]
Ziprasidone (cut-off: 2/2000)	4571	1732.6	50	28	0.006	1.62
Placebo	605	91.8	10	5	0.008	5.45
Haloperidol	1071	298.6	3	3	0.003	1.00
Risperidone	426	196.4	2	1	0.002	0.51

[1] Includes integrated safety data base (which has been redefined to include Japanese studies), Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)
[2] Based on # of deaths ≤ 30 days

The tables below updates the sudden unexpected death rate. With the increased patient years exposure since the last NDA, it appears that there have been a decrease from 9.1 SUD per 1000 (n=772) to 5.8 SUD per 1000 for the ziprasidone treatment groups.

Rate of Sudden Unexpected Death* (SUD) in Ziprasidone NDA 20-825

DRUGS	Number of Subjects [1]	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone	4571	1732.6	11#	6.3
Placebo	605	91.8	0	0
Haloperidol	1071	298.6	0	0
Risperidone	426	196.4	1	5.1

*Sudden Unexpected Death (SUD) refers to subjects found dead or who died within 24 hours of symptoms Refer to Appendix I for listing of deaths considered to be SUD.
#Does not include subject 115-6940394; please refer to the text of Section 8.1.1 of NDA review of 4/98.
[1]Includes integrated safety data base, Study 105 (IM: ziprasidone n=11; placebo n=12) and Study 120 (dementia: ziprasidone n=12)

However, when updating the SUD comparison rate of ziprasidone and the most recently submitted antipsychotic NDAs (table below), it appears that both ziprasidone and sertindole continue to surpass the SUD rate of olanzapine, risperidone, and quetiapine:

Rate of SUD in most recently submitted antipsychotic NDA data bases *

DRUGS	Subject-years exposure	# Sudden Deaths	SUD per 1000 subject years
Ziprasidone (cut-off: 2/2000)	1733	11	6.3
Ziprasidone (orig. cut-off 6/98)	772	7	9.1
Sertindole	476	5	10.5
Olanzapine	1122.2	4	3.5
Risperidone	508	1•	1.9•
Quetiapine	865.3	1	1.1

*Sources are the current NDA 20-852 and Review of Clinical Data: *General Characteristics of the Deaths in the NDAs for Olanzapine, Risperidone, Quetiapine and Sertindole* by Greg Burkhart, M.D. (HFD-120: 3/3/98)
•Correction from NDA Review of 4/30/98 to exclude a SUD during drowning episode.

There may be limitations to interpreting a comparison of the sudden deaths across data bases. The system of assigning sudden deaths was not tested for consistency with blinded readers, and the definition of sudden death may not have been consistently applied for each NDA data base, not to mention the inherent difficulty in being able to accurately assign the true cause of death in many cases.

Overdose Experience

The sponsor did not define what they considered to be an overdose. The table below includes cases in which the overdose was thought to include ziprasidone. Please see Appendix II for cases in which the patient was currently being treated with ziprasidone, but the overdose was believed to be with a different medication.

Summary of overdoses with ziprasidone

Patient #	Age/ Sex	Overdose Mg	Concomitant medications	Comments
116B5290019	49/M	240 mg	Valproic acid	Intentional O/D. Hospitalized because of command hallucinations. Unclear what associated effects of O/D were. CT of head for chronic headaches and dizziness was WNL.
127E5810001	43/F	640 mg		Patient reported O/D. Hospitalized for moderate sedation.
301E1950995	21/F	24 day supply—dose unclear		Admitted to hospital after repeated vomiting. Received gastric lavage.
NY970020018	50/M	3240 mg		Initially reported as coma due to O/D; sponsor revised report to state that patient was drowsy and minimally sedated. QTc readings (central reading): Baseline QTc=454; Day of event: maxQTc=478
116B5950006	64/F	360 mg		Narrative not located. Table states that patient accidentally took ziprasidone. No QTc prolongation evident one day after incident.
116B5950014	26/M	Day 1: 400 mg Day 2: 480 mg		Narrative not located. Sponsor's table states that patient accidentally took ziprasidone with no QTc prolongation one day after incident.
NY970020105	29/F	Unknown		Patient reported to take O/D of ziprasidone (amt. unknown). Taken to hospital and released that day. No details submitted.

It appears that nausea, vomiting and sedation were the most prominent effects of overdose. There were no apparent sequela from overdoses with ziprasidone. There were also an additional 6 patients who were in blinded treatment listed as taking overdoses; the narratives did not report any remarkable events or treatments.

There were no deaths reported associated with an overdose of ziprasidone.

It is difficult to make definitive safety conclusions from the above overdose data. In most cases the serum level was not provided, and it was unclear if any of these overdoses were witnessed. At best, the above data speaks to concerns about an single elevated dose rather than allowing for conclusions to a longer exposure to high levels of ziprasidone.

Adverse Events

Since the original NDA review, additional data covered in this review has been collected from open label studies and three placebo controlled studies (Study 307:a 52 week flexible dose placebo controlled trial and Studies 601 & 602: placebo controlled studies being conducted in patients with mania). Data from these studies has been included in the serious adverse events and the discontinuation, but because these three placebo controlled studies are not yet completed and analyzed, there is currently no new information to contribute to the common adverse events profile. The remainder of this section will focus on significant adverse events, serious adverse events, and some adverse events which lead to premature discontinuations.

Upon request, the sponsor provided updates for the adverse events of syncope, rash and seizure as follows: 1) updated incidence rate for episodes of rash is 4.5% or 173 of 3834 patients, 2) for syncope, the rate is 0.57% (22/3824), and 3) for seizure, the rate is 0.39% or 15 of 3834 patients treated with ziprasidone.

Please refer to Appendix III which is a modification of the sponsor's table of all serious adverse events as submitted on May 22, 2000 covering the period of May 15, 1997 to February 5, 2000. All narratives submitted for each patient were read, and, for the most part, the sponsor's listing of the event accurately reflected the narrative.

Most of the serious adverse events observed in this report period were also observed in the original NDA submission, and not unexpected. Of note was a 25 y.o. patient (Subject #128-601E-189-0077 or 128-601E-0540-0077) who had an episode of neutropenia with a WBC =2.3 (NL range: 4.1-12.3) in the first month of treatment with ziprasidone; this neutropenia resolved after hospitalization (treatment unclear), and the patient was reported to have continued taking ziprasidone throughout and after this episode.

The following patient with a serious adverse event deserves mention:

Subject #302E-057-0456: 46 y.o. male with schizophrenia experienced weakness and **chest pain** after eight months of ziprasidone treatment. After being treated with isosorbide dinitrate in the hospital, he experienced a **syncopal event with bradycardia** (26 bpm). The centrally read ECGs three days prior to and one week after the event did not demonstrate any QTc prolongation; however, there were no ECGs submitted during the episodes of chest pain or bradycardia/syncope, and none located in the case report form requested from the sponsor (submitted 7/14/00) .

Discontinuations Due to Adverse Events

A review of the discontinuations revealed one notable case of an event not previously observed in the original NDA data:

Subject 601-0520-0027: 38 y.o. male experienced **priapism** after twelve days of ziprasidone treatment. The event resolved on the same day that the study drug was discontinued suggesting a temporal relationship of this event to treatment with ziprasidone.

Other reasons for discontinuations during this safety period were also observed in the original NDA submission and not unexpected (please see Appendix IV for a list reasons for discontinuations for this review period).

QTc Outliers Reported by the Sponsor

In the reporting period covered by this review (5/15/97 to 2/5/00), the sponsor reported the following additional patients who had a prolonged QTc, but the readings of whether there was a QTc ≥ 500 msec depended on which central reader interpreted the ECG. The sponsor employed two central ECG readers:

Subject 121-590-0362: 48 y.o female with hypertension, had a QTc of 504 msec on Day 4, the first day of oral dosing after treatment with IM ziprasidone: QTc readings are in the following sponsor summary table:

Study Day	Date	Dose (Time)	ECG Time	QTc (GDXI)	QTc (PRW)
Baseline	20 January 1997			420 msec	424 msec
Day 3	23 January 1997	5 mg IM (15:30)	--	--	--
Day 4	24 January 1997	20 mg PO (9:00)	9:38	504 msec	442 msec
Day 7	27 January 1997	20 mg PO (9:00)	10:31	462 msec	438 msec

Subject 126-701-0079 /127E-701-0003

53 y.o. male with baseline ECG reading of left bundle branch block had the following ECG readings while being treated with ziprasidone:

Study Day	Date	Dose (Time)	ECG Time	QTc (GDXI)	QTc (PRW)
Baseline	25 June 1997			426 msec	520 msec
Day 2	26 June 1997	20 mg IM (3:00)	12:53	423 msec	522 msec
Day 2	26 June 1997	80 mg PO (?)	--	--	--
Day 6	30 June 1997	120 mg PO (?)	--	--	--
Day 7	1 July 1997	40 mg PO (?)	8:45	490 msec	468 msec

Subject 97-R-585-3027-3227: 37 y.o. female diagnosed with schizophrenia with an ECG showing a QTc=513 (later re-read by PRW as a QTc=434) after 3 months of treatment with ziprasidone. She continued treatment with ziprasidone 80 mg bid, started divalproex sodium as a mood stabilizer, and one month later reported experiencing two syncopal events while a new ECG showed nonspecific T wave changes and a QTc=387 msec.

As with the case above, there were numerous ECGs in the NDA data base, which, when locally read had a QTc ≥ 500 msec, but when re-read centrally (presumably blinded), the QTc intervals did not exceed 500. The sponsor listed the following as previously reported cases:

Subject 117-648-0167: 39 y.o. male discontinued treatment for a QTc of 503 msec on day 7 of ziprasidone treatment (80 mg/day). Baseline QTc=466 msec.

Subject 301-311-0977 28 y.o. female diagnosed with schizophrenia whose death occurred two days after discontinuing ziprasidone. Upon discharge from the study, ECG changes were consistent with subendocardial ischemia with substernal pinching sensation. ECG after last AM dose of 60 mg ziprasidone showed Qtc=391 msec. After receiving 200 mg thioridazine that afternoon two ECGs showed QTc= 518 &593 msec (timing unclear). Patient died the next day with cause of death reported to be myocarditis.

III. Pfizer's Response to the Nonapprovable Letter.

Study 054

As a response to the nonapprovable letter of June 17, 1998, the sponsor conducted Study 054, an open label, six arm study designed to assess the effects of ziprasidone on the QTc interval compared to currently marketed antipsychotics (risperidone, olanzapine, haloperidol, thioridazine, and quetiapine) at the maximum recommended dosage. This design allowed for assessment of ECGs at the time of maximum concentration (tmax) for each antipsychotic in the absence and presence of an appropriately chosen CYP450 inhibitor. The study was conducted in 185 patients (approximately 30 per treatment group) aged 18-59 y.o. diagnosed with a psychotic disorders (with no acute exacerbation within 3 months).

This study's results were reviewed in depth by Maryann Gordon, M.D. from the Division of CardioRenal Drug Products (Consult: 6/14/00). The following tables (based on tables from Dr. Gordon's review and the sponsor's table 5.2.2.1.1) summarize the results of Study 054:

Mean change from baseline in the **absence** of a Metabolic Inhibitor

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc*	20.6 msec	10.0	6.4	14.5	35.8	4.7
Heart Rate	4.6 bpm	6.4	6.5	11.2	5.7	-2.9
QT	7.0 msec	-11.8	-9.3	-12.2	19.7	12.5

*Using Bazett's formula

Mean change from baseline in the **presence** of a Metabolic Inhibitor

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Thioridazine	Haloperidol
QTc*	20.4	3.2	5.3	19.7	28.0	8.9
Heart Rate	3.6	0.5	3.0	15.1	-2.1	-5.7
QT	9.9	1.1	-1.8	-15.8	33.3	22.5

*Using Bazett's formula

From the above tables, it can be seen that ziprasidone demonstrates a QTc mean change from baseline that is higher than the recently marketed atypical antipsychotics and haloperidol, and that thioridazine demonstrates the greatest QTc mean change from baseline. Quetiapine may appear to have a relatively high QTc change from baseline; however, it has been proposed that Bazett's formula may not be accurately applied to drugs which have an appreciable increase in heart rate. In a preliminary review of Study 054, Greg Burkhart, M.D., M.S. (1/11/00), points out that the "for drugs that cause an increase in heart rate, one would expect the QT to decrease, as occurred with risperidone, olanzapine, and quetiapine. However, for thioridazine and ziprasidone, both of which increase in heart rate, the QT increased. (Haloperidol also had an increase in QT, but the heart rate decreased from baseline in this group so that the increase in QT would be expected.)" It can also be seen from the above tables that there is no appreciable change of QTc for ziprasidone in the presence of a metabolic inhibitor. (Please see Dr. Gordon's and Dr. Burkhart's reviews for more result details).

Considering the results of this study and the findings of a dose dependent increase in the QTc from the placebo controlled studies, Dr. Gordon stated that ziprasidone increased the QTc from baseline on an average of 10-20 msec, compared to thioridazine's change of approximately 36 msec, and the 21 msec QTc prolongation observed with sertidole (an antipsychotic withdrawn prior to marketing in the U.S. because of concerns regarding sudden deaths observed in the UK's post-marketing reports). The slight increase in blood level changes observed for ziprasidone in the presence of a metabolic inhibitor were negligible enough to not present an additional concern.

Dr. Gordon concluded that Study 054 demonstrated that ziprasidone and thioridazine adversely affect cardiac repolarization as seen by their ability to prolong the QTc and QT intervals in a concentration-related manner, and that some patients would be at an increased risk of potentially fatal arrhythmias when exposed to either of these drugs. Considering the characteristics of QTc prolongation as an added risk, Dr. Gordon recommended that a drug with this profile either not be marketed or be used only as second line therapy.

In an effort to establish some benefit for the use of ziprasidone as an antipsychotic, the sponsor also provided data showing that patients had a decrease in total cholesterol and triglycerides in the ziprasidone group compared to the other antipsychotic treatment groups in this open label

study 054. However, it is noted that in the short term placebo controlled trials, the ziprasidone groups were shown to have statistically significant increases in cholesterol and triglyceride levels when compared to placebo with respect to numbers of patients exceeding threshold values.

Also of interest in this study is that the mean serum concentration of a dose of ziprasidone 80 mg bid was 49 ng/ml on Day 2, and increased to 171 ng/ml at steady state (Day 8). In the presence of the 3A4 metabolic inhibitor ketoconazole, the mean ziprasidone concentration increased to 224 ng/ml.

Data Regarding Weight Changes

The sponsor claims that there is a beneficial weight gain profile to ziprasidone compared to other antipsychotics. However, in the placebo controlled studies, there was an increase of ≥ 7 % weight gain observed, which was statistically significant compared to placebo. The only head-to-head comparison study which the sponsor describes is Study 054 (an open label study) in which 2 patients (5.9%) in the ziprasidone group were observed to have a weight gain ≥ 7 % while 1 patient (3.1%) in the haloperidol group, 6 patients (23.1%) in the olanzapine group, 5 (18.5%) in the risperidone group, 3 patients (10.3%) in the quetiapine group, and 3 patients (9.7%) in the thioridazine group showed a weight gain ≥ 7 %; these results are difficult to interpret as there was no placebo control group, and it was a short term study (less than 28 days) in a relatively small sample (25-35 patients in each group). In the 52 week placebo-controlled study 303, two of the three ziprasidone treatment groups showed an higher percentage of patients with weight gain when compared to placebo (ziprasidone 20 mg bid: 11% gained ≥ 7 %, in 40 mg bid group: 4.3 %, in 80 mg bid group: 8.6 %, and placebo: 4.3 % patients gained ≥ 7 %); it is noted that 46% of the patients in the ziprasidone group and 20% of patients in the placebo group completed this study. Other studies sited by the sponsor were open label studies, and not located in the NDA submissions.

Labeling

If approved, the following are recommended revisions to the sponsor's proposed labeling (3/10/00):

1. The sponsor's proposed statements regarding a pharmacokinetic profile in the pediatric population based on a small study (n=25) of pediatric patients with Tourette's Syndrome (under Special Populations). These findings are preliminary and efficacy for schizophrenia (the labeled indication) has not been tested in children or adolescents, and it could be misleading to include this data. It is also recommended that the labeling not include outcomes of this pilot study of Tourette's Syndrome in children/adolescents until the sponsor has proven safety and efficacy in this population for the proposed indication of schizophrenia (under Clinical Trials: Pediatric Studies section of sponsor's proposed labeling).

2. Under Contraindications, it may be beneficial to add several other drugs by name which also prolong the QTc that should not be used concomitantly with ziprasidone such as quinidine, pimozide, thioridazine, sotalol, moxifloxicin, and sparfloxacin. It would be prudent to also contraindicate this medication in patients with congenital long QT syndrome, history of cardiac arrhythmias, uncompensated heart failure, and acute myocardial infarction, as the sponsor has proposed.

3. Under the Warnings Section, it is recommended that the labeling resemble the new proposed labeling for Mellaril, with a bolded, black box delineating concerns regarding ziprasidone's effect on the QTc interval, and making the language strong enough that this drug would be used as a second line with emphasis that efficacy has not been established in the treatment resistant schizophrenic population.

4. Under the Precautions Section, it is recommended that the following subsections be added to the sponsor's proposed labeling: rash, orthostatic hypotension, potential for cognitive and motor impairment (somnolence), and dysphagia to reflect both the integrated safety data base of ziprasidone and standard language in the labeling of antipsychotic medications.

   Because of one case of priapism observed in this data base, it is recommended that priapism be added to the precautions section of the labeling.

5. In the Information to Patients, it is important that patients be alerted to the risks involved with syncopal events and their need to seek medication attention if an episode occurs. Other information should include the current understanding of drugs which prolong the QTc interval, as ziprasidone does, to cause potential fatal arrhythmias, and sudden death, in addition to syncope. It may also be of some aid to have a patient insert with every prescription to maximize the efforts to educate patients and families. Ideally, there would be a mechanism to insure informed consent.

6. Under Laboratory Tests, it may be prudent to recommend patients obtain screening tests of an ECG and electrolytes to rule out circumstances which may leave patients more vulnerable to the cardiac adverse events associated with drugs which prolong the QTc interval. It might also be prudent to recommend routine ECGs to rule out any new onset ECG changes as a result of ziprasidone exposure.

7. Under Drug Interactions, it should be emphasized that there is no data regarding ziprasidone's effect when co-administered with another drug which prolongs the QTc, and that this combination should be avoided at the current time.

8. Because the NDA for { } has been withdrawn at this point, all references to the { } should be removed from the sponsor's proposed labeling.

IV. Financial Disclosure Information

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators in Section 19.3 entitled Financial Disclosure Information.

There were a total of 5 sites in the study including four U.S. sites (794, 602,782, 529) and one site in South Africa (529). Site 794 had 2 principle investigators and 13 subinvestigators; site 602 had 1 principle investigator and 9 subinvestigators; site 782 had one principle investigator and 13 subinvestigators; site 529 had one principle investigator and 6 subinvestigators, and site 5006 had 1 principle investigator and 6 subinvestigators.

Otherwise, there were no other specific financial disclosures made by other investigators. No disclosures were able to be collected from six individual subinvestigators who were no longer working at the study sites and either had no forwarding address or did not respond to forms sent to their forwarding address. The sponsor's Director of Medical Finance signed the Form 3454 certifying that there was no financial arrangement made with investigators that could affect the

outcome of the 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).

Because of the disclosed by , a cursory review of the ECG data of Site compared to other sites was performed. From this informal brief review, results from Site appeared to be consistent with results from the other sites. In a telecon of 7/12/00, Dr. Charles Ritrovato of Pfizer stated that he was unable to provide information at this time as to how many patients Dr. had enrolled in this study site, but it was noted that Dr. was one of 13 subinvestigators at this site. Based on the limited information available at this time, there does not appear to be a noticeable difference in the findings of Site compared to other sites. It cannot be definitively determined if Dr. potential financial conflict was problematic or not; however, the total results from the study site in which Dr. was a subinvestigator did not appear to distort the final outcome of Study 054 in any obvious manner.

Efforts on the sponsor's part to minimize bias of Study 054 included randomization of subjects through the use of a tele-randomization system operated in the UK. Also, the sponsor utilized a blinding process in which ECG tracings from each site were transmitted electronically to were they were blinded and then forwarded to the central reader at for interval determinations.

V. Foreign Marketing

Ziprasidone is not marketed anywhere in the world at this time.

The following countries have approved the marketing of ziprasidone: Brazil (February 5, 1998), Sweden (as of June 10, 1998), Venezuela (November, 25, 1998), Czech Republic (March 15, 2000), New Zealand (April 20, 2000).

The sponsor listed the following countries where the application for ziprasidone is currently under review: Canada, Turkey, Malaysia, Hungary, South Africa, Switzerland, Egypt, Colombia, Slovakia, Poland, Croatia, Indonesia, Morocco, Slovenia, Mexico, and Bulgaria.

VI. Conclusions/Recommendations

This safety update includes ECG data from Study 054, which indicate that ziprasidone produces a QTc prolongation that is substantially greater than the other tested atypical antipsychotics and haloperidol, but less than thioridazine. The magnitude of the mean change from baseline of 20 msec is well above that suggested as the threshold for concern (5-10 msec) stated in our non-approvable letter of June 17, 1998.

The cardiac risks associated with QTc prolongation in antipsychotic drugs have been discussed in two open public discussions (PDAC: for sertindole and ziprasidone). Aside from the formal votes, there was an acknowledgement of the association of QTc prolongation with the events of syncope, ventricular arrhythmia, and sudden unexplained death; however, there has been a lack of sufficient evidence to directly address the safety risk associated with this degree of QTc prolongation. Hence, there was no data presented to suggest that our previous level of concern regarding the cardiac safety of ziprasidone, the sole determinant of the non-approvable action in 1998, was unwarranted.

The sponsor states that ziprasidone has advantages over other marketed antipsychotics such as less weight gain and a less adverse effect on lipid profiles. However, it is questionable if these advantages outweigh the cardiac risks of this drug, such as potentially fatal arrhythmias. Weight gain and lipid abnormalities can be detected early, monitored, and managed, unlike ventricular arrhythmias, which cannot be predicted and may have irreversible consequences.

After consideration of this safety update and the discussion of the ziprasidone PDAC, I must conclude that the extent of QTc prolongation associated with ziprasidone represent a signal of cardiac risks which do not outweigh the benefits of treatment. If the sponsor were able to demonstrate ziprasidone's ability to effectively treat patients with treatment refractory schizophrenia, then, perhaps for some individuals, this would offer an overriding benefit. Until there is evidence to support that advantage, it is recommended that this application not be approved.

— 7/28/00

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

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

8-9-00

I disagree with the above conclusion & recommendation. I feel that ziprasidone can be approved. The basis for this view is provided in a memo to the file on this date.

/S/ , MD
Team Leader, DPDRP

APPENDIX I

Deaths occurring during or after trial treatment : Cut-off date: 2/5/00

Ziprasidone subjects who died ≤ 30 days after treatment

SUBJECT #	AGE / SEX	LAST DOSE (MG/D)	DAYS OF TREAT-MENT	CAUSE OF DEATH/COMMENTS
108E-7160157**	49/M	160	466	Found unresponsive on bathroom floor immediately after a thump was heard. Was reported to have been revived for several minutes after brother administered CPR, but ECG showed asystole in emergency room. Lab tests showed CPK=851 IU(24-195 IU) with MB fraction of 6.0 ng/ml (0-5.0 ng/ml), potassium=6mEq/L(3.3-5.1 mEq/L), bicarbonate=10 mEq/L(24-32 mEq/L). Ziprasidone level (at death)=14 ng/ml. Investigator thought cause of death was acute myocardial infarction. No autopsy performed. No coroner's report available. ECGs during the study: Screening: QTc=432 Baseline: QTc=396 Week 6: QTc=396 Week 40: QTc=415 Was on ziprasidone at time of death.
Yale-9990040**	34/M	100	319	Found dead. Had complained of chest pain on the day of his death.. Had complaint of brief episodes of "heart pounding" and "skipping heartbeats" during the study. An autopsy report stated that the cause of death was occlusive coronary atherosclerosis. ECGs during the study: Screening: QTc=377 msec Wk1: QTc=413 Wk8: QTc=378 Wk24: QTc=391 Wk40:QTc=429 Wk2: QTc=390 Wk12:QTc=425 Wk28:QTc=390 (died during Wk45) Wk3: QTc=409 Wk16:QTc=366 Wk32:QTc=405 Wk4: QTc=397 Wk20:QTc=407 Wk36:QTc=397 Was on ziprasidone at the time of death.

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
NY-97031E0054*•	51/M	40	151	Found dead. Two days prior to death, patient c/o not feeling well. Five days prior to death was seen by general practitioner with bp=140/100; no neurological findings noted. ECG at Day 7 showed flat T waves. ECGs during study: Screening: QT/QTc=358/428msec; HR=86bpm Wk1: " " =351/425 ; " =88 Wk6: " " =383/393 ; " =63 Wk13: " " =405/416 ; " =63 (patient died Wk21) According to sponsor, a discussion with medical examiner suggested left meningioma without evidence of brain injury was found on autopsy; however, no report available.
JP-96-602-450081*•	50/M	40	Unclear	Unknown cause of death. Baseline values: heart rate=46bpm; QT/QTc= 140/359 msec. One day after starting ziprasidone, patient presented at hospital with c/o palpitations and nausea; bp=150/100 mmHg, hr=119, QT/QTc=282/398. Two days after starting ziprasidone: ECG showed hr=47, QT/QTc=384/349; WBC=13130 cells/UL (NL: 3000-9000 cells/UL), neutrophils 81.4% (NL:40-74%), CPK=297 IU/I (NL:26-200 IU/I); diagnosed with URI and treated with antibiotic, flomoxef. Police contacted patient's physician to report his death; police ruled out suicide and homocide. **Death occurred within five days after starting ziprasidone (length of treatment unclear).**
105-5340021*	70/F	2	5	Patient had sudden onset of shallow respirations and diaphoresis. Death certificate stated acute cardiopulmonary arrest due to arteriosclerotic cardiovascular disease. Subject with history of right bundle branch block, otherwise ECG was normal. Was taking ziprasidone just prior to death.
108-6070305*	46/M	80	61	Found dead (in heat of 100°F). Autopsy report stated cause of death as acute and chromic asthmatic bronchitis and granulomatous myocarditis. ECG: Screening: QTc =366 msec Baseline: QTc =393 Week 6: QTc=395 Was on ziprasidone at time of death.
108-5920750*	39/F	120	8	Found dead one day after her estimated date of death of unknown cause. Patient's face was burned and it was thought that she had fallen against a hot water pipe. The investigator's postmortem diagnosis was alcohol abuse/diabetic ketoacidosis, but there is no evidence for this. No coroner's report located in the CRF. Was on ziprasidone at time of death.

*Included in Sudden Unexpected Death (SUD) rate calculation
•Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
116B-5080001*	54/M	120	71	Found dead in his hospital bed. Autopsy showed generalized atherosclerosis, coronary artery disease, cerebral artery disease, visceral congestion (liver, spleen, and lung), COPD, and cardiac hypertrophy. ECGs during the study: Screening: QTc=391 msec baseline: QTc=383 week 2: QTc=367 week 6:QTc=391 Patient had complaint of chest pain once during the study, but ECG was normal and diagnosed as anxiety. Was on ziprasidone at time of death.
302E-3190375*	48/M	120	162	Found dead. CRF showed hypertension and tachycardia on last day of study with hypertension as adverse event during study. Narrative states that subject had history of polydipsia and seizure disorder. Details regarding the death are unclear. Died one day after discontinuing ziprasidone.
304E-1930379*	52/M	80	221	Found dead while taking a nap. No autopsy performed and exact cause of death is unknown. ECG during the study as shown in the safety update: QTc at: Screening=374.7 msec Week 12=415.69 Week 28=413.12 with flat T wave in lead AVL; no evidence of ischemic changes. The CRF had minimal information and the patient profile in the safety update had different ECG QTc values than the original submission. Was on ziprasidone at time of death.
301-311-0977*	28/F	120	57	Patient reported be cachectic and had ECG changes consistent with subendocardial ischemia with substernal pinching sensation. Patient was d/ced from ziprasidone and treated with thioridazine, nitrazepam and patient died two days later. Cause of death reported to be myocarditis. Death occurred 2 days after d/c from ziprasidone.
308-0350003	63/M	80	485	Sudden collapse and died. Coroner's report stated that cause was a ruptured abdominal aortic aneurysm and atherosclerosis. Was on ziprasidone at the time of death.
115-6940394	43/M	40	16	Found dead. Coroner's cause of death listed as asphyxiation due to aspiration of vomit . Was on risperidone, clonazepam and lorazepam at time of death. Patient had difficulty breathing three days before death, and complained of dyspnea on morning of death. Died 29 days after discontinuing ziprasidone.

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
116B-6590001	44/F	120	47	Patient had a UTI upon d/c and was diagnosed with gastritis with Helicobacter pylori 13 days later. She was seen in ER with diagnosis of panic attack 21 days after d/c (three days prior to death). Sponsor reports that the autopsy was not available due to legal issues in medical examiners, but Subject's attending physician reportedly got information from the medical examiners that subject had a benign cardiac neoplasm (myxoma).ECG: screening: QTc=444 msec baseline: QTc=443 week 1: QTc=433 week 2: QTc=440 week 6: QTc=407 Patient reported chest pain one day after starting ziprasidone: cardiology w/u was normal, but had elevated transaminases. Episodes of tachycardia and hypertension during the study: day 6:102 bpm day 20:120/100; 104 bpm day 27:140/100; 102 bpm day 42:164/98 It is unclear what medications she was on as the patient summary and the CRF do not list the same medications. **Death occurred 24 days after d/c from ziprasidone.**
303-1970299	79/F	80	30	Cardiac arrest. No autopsy was performed. Patient had new diagnosis of atrial fibrillation and ischemic heart disease 27 days after d/c. At time of death was taking perphenazine, deparkin, digoxin, verapamil, and enalapril. **Death occurred 30 days after d/c from ziprasidone.**
Suicides and accidents				
108-6090381	21/F	160	54	Suicide by gunshot while on ziprasidone.
116B-6940004	24/M	160	146	Suicide by hanging while on ziprasidone. Subject had been complaining of increasing depressed mood; treatment included an increase in ziprasidone.
117-6870317	51/M	120	205	Death by defenestration. According to study profile, patient did not appear suicidal prior to death.
117-7060529	40/M	160	54	Patient stopped ziprasidone on his own and four days later he drove his car off a cliff. Subject was driving his car after a sleep deprived EEG against medical advice. Autopsy listed asphyxiation due to drowning and was classified as a probable traffic accident.
302-2600156	46/M	120	7	Patient's body found drowned in local river after being missing from the hospital for five days.
302E-1590029	22/M	120	179	Suicide by falling under a train. Was being treated with ziprasidone at time of suicide with plans to be admitted to the hospital that same day.
JP-95-6011622	53/M	53	20	Suicide seventeen days after discontinuing ziprasidone (Japanese studies: not part of the integrated safety data base.)
NY-97-002-0022*	34	160	9	Probable suicide by drowning. Was on ziprasidone at time of death. Postmortem finding reported pulmonary congestion and pulmonary edema consistent with drowning episode as cause of death.
NY-97-002-0077*	37	60	13	Died of carbon monoxide poisoning and cardio-respiratory arrest secondary to accidental fire, according to coroner's report. Patient found unconscious. Was on ziprasidone at time of death.
NY-97-033-053 *	23	160	53	Suicide by gunshot while on ziprasidone

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)				
NY-97-033-266*	20	160	8	Drowned while swimming in the sea. Patient had c/o palpitations for 4 months prior to death; also c/o dystonia 4 days prior to death, treated with trihexyphenidyl and benztropine, and was on propranolol. On ziprasidone at time of death.
601E-0187-0118*	41	80	46	Probable suicide; autopsy report states cause of death: exsanguination from multiple deep incised wounds. On ziprasidone at time of death.
R0553012097-R0267*	47	80	19	Suicide by hanging. Was on ziprasidone at time of death.

Ziprasidone subjects who died ≥ 30 days after treatment

SUBJECT #	AGE/ SEX	DOSE (MG/D)	DURATION (DAYS)	CAUSE OF DEATH
104-5130213	40/M	40	28	Sudden death; cause unknown. Occurred 7½ months after discontinuation from ziprasidone .
106-05550117	35/M	40	27	Unknown cause of death but possible seizure and aspiration of vomit. Was taking risperidone at time of death. Death occurred 4½ months after stopping ziprasidone .
108-5780020	37/M	80	8	Accidental drowning. Died 1½ months after stopping ziprasidone .
117-6940542	38/M	160	15	Suicide by gun shot one year after d/c from ziprasidone .
127E-06810002*	25/M	160	185	Died of lobar pneumonia 2 months after stopping ziprasidone. IM:po extension study.
127E-07190004*	48/F	120	164	Died of unknown causes over 2 months after stopping ziprasidone.
301-1140331	30/M	200	26	Died of complication due to pancreatitis 9 months after stopping ziprasidone
301-1320771	34/M	120	53	Suicide by hanging approximately 3 months after stopping ziprasidone .
303-0640276	61/M	40	69	Died of bronchopneumonia with bronchial adenocarcinoma and metastasis. Death occurred 4 months after stopping ziprasidone.
303-1950250	68/M	40	350	Died of cranial trauma 2° to fall. Ziprasidone was stopped 45 days prior to death.
303-1950256*	68/F	80	63	Died of heart failure more than 2 years after stopping ziprasidone.
303-1950281	71/F	40	61	Sudden death due to acute purulent leptomeningitis. Death occurred 4 ½ months after stopping ziprasidone.
303-1970269	67/F	80	37	Bronchopneumonia. Stopped ziprasidone112 days before diagnosis.
303-1990089 no CRF available	55/M	80	27	Sudden death due to acute cerebral edema. death occurred 60 days after stopping ziprasidone.
303-2120222	58/M	160	349	Died of post operative cerebral edema after tumor removal. Occurred two months after stopping ziprasidone

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

Appendix I: Table of Deaths (con't)

304-2040222	55/F	160	29	Sudden death with proposed cause of acute heart failure due to pulmonary disease. Death occurred approximately 2 months after stopping ziprasidone.
307-2650034*	47/M	80	365	Death from trauma of fall from window over one year after discontinuing ziprasidone.
307-2690047	49/F	100	196	Died of hepatic coma, cholestatic jaundice and malignant neoplasm 95 days after stopping ziprasidone. Discontinued ziprasidone because of jaundice and elevated AST (244 U/L) and ALT (375 U/L).
NY-97-001-355*	25/M	160	41	Suicide by hanging 2 months after stopping ziprasidone. IM/po extension study.
NY-98-035-0572*	23	160	71	Suicide by hanging 6 weeks after stopping ziprasidone. IM/po extension study.
NY-98-035-586*	30/M	160	60	Died of pneumonia 33 days after stopping ziprasidone.
JP-94-601 0014*	51/F	20	37	Died of myocardial infarction. Symptoms began 6 days after d/c from ziprasidone when patient fell, diagnosed with cyanosis requiring oxygen therapy. Fifty-five days, later patient died. During study ECGs were read as abnormal as follows: Baseline: ST-T Abnormal Wk8: ST-T Abnormal Follow Up: ST-T Abnormal Wk4:ST-T Abnormal Right Atrial Hypertrophy Right Atrial Hypertrophy Right Atrial Hypertrophy Sinus Tachycardia

*Included in Sudden Unexpected Death (SUD) rate calculation
*Reported after 8/29/97

APPENDIX II

Other Overdose Cases During Treatment with Ziprasidone

3083200008	36/F	Unknown		Randomized to ziprasidone group. Patient reported to have ingested alcohol and taken O/D of risperidone. Had postural hypotension and lengthening of QTc (centrally read): Baseline QTc=413; On day of event: QTc=458.
1085230870	41/M	Unknown		Patient reporting taking O/D of diazepam and lorazepam to self treat insomnia.
1085820420	35/M	Unknown		Patient found comatose and thought to have overdosed. Responded to naloxone with improved respiration. Drug screen positive for propylene glycol, cocaine & opiate. Lithium level=0.5 mEq/L; ziprasidone serum concentration < 1ng/ml (below limit of quantization). Treated with gastric lavage and charcoal. Many complications during course of treatment (see 4/6/00 submission for details).
116B5510005	38/M	Unknown	Aspirin	Patient reported O/D of aspirin. ECG was WNL; blood gas showed respiratory alkalosis and metabolic acidosis. Recovered in 24 hours.
116B5553002	62/F	Unknown	Thioridizine	Patient admitted to hospital for sedation and discharged 12 days later. Narrative suggests possible O/D of thioridizine, but this is unclear.
116B5810014	35/F	Unknown	Lorazepam	Patient reported O/D of lorazepam. Gastric lavage performed.
116B5950018	33/F	Unknown	Lorazepam flurazepam	Staff reported O/D of lorazepam and flurazepam
116B6690025	41/F	Unknown	Acetominophen	Patient reported O/D of acetominophen and drinking alcohol. No symptoms reported.
1175080352	54/M	Unknown	Chloral hydrate Lorazepam	Found on floor. Thought to be intentional overdose of chloral hydrate and lorazepam. L Treated with activated charcoal; rhabdomyolysis in leg.
3011110384	28/F	Unknown		Patient reported O/D on cyamemazine with recovery after gastric lavage.
3011320771	34/M	Unknown		Reported as suicide attempt by poisoning. No details located.
3011380814	27/M	Unknown	Temazepam	Report to have ingested zopiclone; hospitalized and recovered after gastric lavage.
3021500046	18/M	Unknown		Reported to have ingested haloperidol. Hospitalized and received gastric lavage.
3040390343	27/F	Unknown		Reported to have ingested O/D of aspirin.
3041720304	24/M	Unknown	Parcetamol lorazepam	O/D of lorazepam.
601E1920034	40/F	Unknown	Lorazepam	O/D of lorazepam to treat insomnia. Patient hospitalized for confusion, disorganized thoughts and bizarre behavior.
R5550007	19/M	Unknown		Excessive alcohol intake reported. Event resolved 4 days later.
NY980350474	?/F	Unknown		Reported to have taken O/D of zopiclone.
980350338	33/M	Unknown		Reported to have taken O/D of zolpidem & chlordiazepoxide.

APPENDIX III
SERIOUS ADVERSE EVENTS FOR ZIPRASIDONE GROUPS
Period of May 15, 1997 to February 5, 2000
(table revised from sponsor's submission of 5/22/00)

PID	Event
Cardiovascular	
302E-057-0456	Syncope and bradycardia
127E-595-0013	Bradycardia (2 episodes)
127E-701-0003	Cardiomegaly; Possible Congestive Heart Failure; Pneumonia
R-0554-0070	Congestive Heart Failure; Chronic Obstructive Pulmonary Disease
303-269-0207	Hypertension
308-320-0008	Prolonged QT Interval; Worsening Schizophrenia
NY-97-014 252	Convulsion; Prolonged QT Interval
R-0554-0129	Arterial Occlusion; Leg Amputation
JP-96-602 460001-1	Cerebral Infarction
Seizure	
123-1001-0061	Recurrence of Tonic-Clonic Seizure
127E-795-0002	Seizure
NY-97-O31E 0033	Generalized Tonic-Clonic Seizure
601E-0624-0123	Seizure
602-0651-0105 (also listed as 602-216-0105)	Tonic-Clonic Seizure
R-0554-0126	Grand Mal Seizure
NY-97-014 252	Convulsion; Prolonged QT Interval
Movement Disorders	
116B-0581-0017	Exacerbation of Tardive Dyskinesia
108E-0523-0148	Left Leg Dystonia; Gait Disturbance
R-0554-012	Restlessness; Abnormal Movements of Lower Extremities; Tightness in Chest; Anxiety
R-0553-0045	Acute Dystonia
Possible NMS	
601E-0756-0085 (aka 69202190080)	Medication of induced movement disorder (NMS Like); Bipolar disorder, recurrent depression; respiratory distress; aspiration pneumonia
JP-95-601 57-2	Decreased Level of Consciousness; Hyponatremia; Increased Blood Pressure; Increased Heart Rate; Increased Creatine Phosphokinase
Metabolic/Hematologic	
JP-96-602 20601-1	Elevated Blood Sugar
R-0553-0201	Hyperglycemia
601E-0540-0077	Neutropenia
NY-97-014 052	Dizziness; Unstable Balance; Falls; Shallow Respirations; Decreased Hemoglobin; Increased Platelets; Unsteadiness in Feet; Oculogyric Crisis; Extrasystoles; Postural Hypotension
Skin	
108-0681-0618	Cellulitis, Facial
116B-0590-0003	Cellulitis
108E-0509-0168	Ulcerated Basal Cell Carcinoma
NY-97-031 0041	Cellutitis
307-0265-0035	Sunburn

Pulmonary	
108E-0594-0094	Aspiration of Food
R-0553-0083	Pulmonary Emboli
R-0553-0160	Pneumonia; Worsening of Schizoaffective Disorder
127E-595-0016 127E-669-0008	Exacerbation of Asthma; Exacerbation of Schizophrenia Traumatic Pneumonthorax,
NY-98-035 0585	Left Lower Lobe Pneumonia; Pneumothorax
601E-0627-0070	Right Lower Lobe Pneumonia
Gastrointestinal	
NY-98-035 0246	Nausea; Serious Diarrhea
116B-0596-0006	Worsening of Gastroesphogeal Reflux Disorder; Barrett's Esophagitis; Laparoscopy with partial Fundoplication
116B-0556-0001	Worsening Diverculosis
601-0540-0217	Worsening Gastric Erosion; Worsening Duodenitis; Exacerbation of Bipolar Disorder, Mania
Miscellaneous	
602E-0651-0084 (Previously listed as 602E-0246-0084)	Excessive Sedation
108E-0620-0041	Papilloma, left Ureter; Transitional Cell Carcinoma in Situ, Left Ureter
R-0553-0191	Breast Cancer - Female
601E-0756-0086	Carcinoma of the Bladder, Deep Vein Thrombosis
NY-98-035 0576	Tonsillitis
Fractures	
1160-603-0002	Open Reduction Internal Fixation of Right Humerus
116B-0523-0002	Fractured Femur, Accidental
116S-0653-0003	Ankle Fracture; Accidental
168E-0881-0079	Surgical Site Infection, Right Foot
127E-719-0005	Ankle Fracture, Accidental; Staphylococcus Infection; Increased Depression
JP-96-602 270050-4	Accidental Bone Fracture
R-0554-0024	Fractured Ankle
Exacerbation of Psychiatric Illness and Suicidal Gestures	
116B-0551-0002	Exacerbation of Schizophrenia; Recurrent Depression; Suicidal Gesture
116S-0650-0001	Exacerbation of Chronic Paranoid Schizophrenia
108E-0523-0203	Exacerbation of Psychotic Symptoms; Suicidal Ideation; Increased Insomnia
116B-0581-0014	Suicide Attempt; Intentional Drug Overdose; Persistent Depression
116B-717-0003	Exacerbation of Schizophrenia
R-0554-0050	Exacerbation of Psychosis; Attempted Suicide (Laceration of Wrist)
JP-95-601 131-2	Exacerbation of Schizophrenia; Suicide Attempt
301E-0102-0231	Alcohol Intoxication; Alprazolam Intoxication
NY-97-031E 0016	Suicidal Ideation
NY-97-032 020	Relapse of Schizophrenia; Manic Seizure
NY-97-033 288	Exacerbation of Psychosis
NY-98-035 0025	Suicide Attempt
NY-98-035 0043	Exacerbation of Schizophrenic Symptoms; Manic Episodes; Zona (Herpes Zester)
NY-98-035 0058	Psychotic Relapse
NY-98-035 0079	Increased Irritability; Anxiety, Lesions on Hands; Possible Hallucinations; Exacerbation of Psychosis

NY-98-035 0093	Exacerbation of Schizophrenia
NY-98-035 0518	Worsening Psychosis
NY-98-035 218	Suicide Attempt (Laceration of Wrists)
NY-98-035 0255	Suicide Attempt; Worsening Hallucinations
NY-98-035-0923	Suicide Attempt By Jumping from window; fractured Clavicle; Brain Contusion
601-0615-0120	Exacerbation of Bipolar Disorder, Mania; Exacerbation of Bipolar Disorder, Depression; Suicidal Gesture
601E-0669-0021	Suicidal gesture; Exacerbation of bipolar disorder, depression
601E-0529-0176	Exacerbation of Bipolar Disorder, Depression; Suicidal Ideation
601E-0646-0059 (Previously listed as 601 E-0201-0059)	Anxiety
601E-0279-0319	Recurrent Suicide Attempt
602E-0719-0123	Exacerbation of Mania
602E*0662-0051 (Previously listed as 602E-0244-0051)	Exacerbation of Mania
602E-0662-0125	Exacerbation of Bipolar Disorder, Mania
602E-0764-0062 (Previously listed as 602E-0255-0062)	Bipolar Disorder, Recurrent Depression; Suicidal Ideation
R-0554-0061	Worsening Psychosis; Suicide Attempt
R-0555-6039	Suicide Attempt
R-0585-6061	Exacerbation of Psychosis

APPENDIX IV

Reasons for Discontinuations For Period of May 15, 1997 to February 5, 2000

Nausea, vomiting, chest pain, headache, dizziness, hypertension, tardive dyskinesia, cerebrovascular accident, dystonias, tic disorder, EPS, akathisia, tardive dyskinesia, excessive weight loss, increased liver function test (alkaline phosphatase, SGPT, SGOT), somnolence, bradycardia, impotence, convulsion, ataxia, multiple sclerosis, insomnia, leg cramps, pancreatic cancer, tuberculosis, hepatic metastases, orthostasis, bronchospasm, meningitis, billiary tract disorder, catatonia, mania, sweating, anxiety, gynocomastia, and anemia.

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REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA 20-825
Sponsor: Pfizer Inc.
Original User Fee Due Date: March 17, 1998
Extended User Fee Due Date: June 17, 1998

Drug Name

Generic Name: Ziprasidone hydrochloride
Trade Name:

Drug Characterization

Pharmacologic Category: Serotonin and Dopamine Antagonist
Proposed Indication: Management of the Manifestations of Psychotic Disorders
NDA Classification: 1S
Dosage Forms: Oral tablets; 20, 40, 60, 80 mg capsules

Reviewer Information

Clinical Reviewer: Roberta L. Glass, M.D.
Review Completion Date: April 30, 1998

Table of Contents for Clinical Review of NDA 20-825

7.0 Review of Efficacy

8.0 Integrated Review of Safety

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. Addendum submissions clarifying issues of the original submission (3/18/97) were in hard copy only except for the safety update (8/29/97) which was submitted in both hard copy electronic format . There were no electronic datasets 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 104, 106, 114, 115, and 303
Safety update report of 8/29/97
Literature summary

Also considered were Pfizer's commercial IND(for agitated psychotic subjects) and IND( )(ziprasidone po for mania).

Case report forms were examined for the following subjects: all reported deaths, 116B-5510007,303-1970265, 303-0070098, 109-5720027, 117-6200029, 108-5740080, 114-6560036, 116B-551-0008, 303-2120105, 303-1970265, 102-5130005, 108-5740080, 109-5650041, 303-2710228, 116B-05230001, 304-1890367, 108-6170817, 117-7060373, 117-7060380, 115-06560036.

1.2 Related Reviews and Consults for the NDA

The Division of Cardio-Renal Drug Products was consulted for issues concerning ziprasidone's prolongation of the QTc interval on ECG recordings by Charles J. Ganley(HFD-110: 11/18/98 and 1/6/98). Also referred to were the following reports: 1) *A Review of UK Post-Marketing Surveillance Experience with Sertindole, Olanzapine and Risperidone* by Greg Burkhart, M.D., M.S. (HFD-120: 12/12/97), 2) Clinical Pharmacology and Biopharmaceutics Review by Sayed Al-Habet, Ph.D. (HFD-860: 3/3/98), 3) Review of Clinical Data: *General Characteristics of the Deaths in the NDAs for Olanzapine, Risperidone, Quetiapine and Sertindole* by Greg Burkhart, M.D. (HFD-120: 3/3/98), 4) Review of Data Quality, Coding, All Cause Mortality and Sudden Deaths by Gerard Boehm, M.D., M.P.H. & James F. Knudsen, M.D., Ph.D. (HFD-120: 2/3/98), 5) Review of Ziprasidone ECG Data by Gerard Boehm, M.D., M.P.H. (HFD-120: 1/23/98), and 6) Statistical Review and Evaluation by Sue-Jane Wang, Ph.D. (HFD-710: 11/24/98).

1.3 Other Resources

Dr. Andrew Mosholder provided excellent mentoring in the preparation of this document and throughout the review process.

2.0 Background

2.1 Indication

The majority of the fifteen medications currently labeled for the indication of psychosis are considered to be traditional dopamine antagonist agents. These traditional agents have been associated with a high incidence of extrapyramidal symptoms (EPS) and long term risks of tardive dyskinesia. The more recently marketed 'atypical' antipsychotic agents (clozapine, risperidone, olanzapine, and quetiapine) possess serotonin type 2 ($5\text{-}HT_2$) receptor blocking activity in addition to their dopamine 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 be more effective in treating the negative symptoms of schizophrenia. In light of the risks of agranulocytosis associated with clozapine, it is indicated only for refractory patients. Of these 'atypical' antipsychotic drugs, only clozapine has shown superior efficacy in refractory patients thus far.

The sponsor of ziprasidone has characterized this drug as an 'atypical' antipsychotic demonstrating dopamine and serotonin receptor antagonist activity. The sponsor proposes that this medication minimizes EPS and also treats both positive and negative symptoms of schizophrenia.

The NDA for another 'atypical' neuroleptic, sertindole, was recently withdrawn because of concerns about QT interval prolongation and sudden deaths.

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

Pfizer has submitted IND( ).

This sponsor also submitted IND( )to study( )The review for these other submissions are still in progress and will not be discussed in this review except for relevant safety data.

According to a teleconference of September 4, 1997 with Dr. Ritrovato from Pfizer, all clinical studies of ziprasidone have been done under Pfizer's sponsorship.

In a recently reviewed NDA for the 'atypical' antipsychotic sertindole, concerns arose regarding the high incidence of sudden death and prolongation of the QTc interval within this NDA safety data base. In the literature there have been observations that QTc prolongation may be correlated with the development of ventricular arrhythmia, syncope, and sudden death (Morganroth, 1993). This safety concern was intensified when post marketing data from the U.K. were reviewed by Greg Burkhart, M.D., MPH (12/12/97), and it was found that sertindole demonstrated a higher sudden unexplained death reporting rate than olanzapine and risperidone. The sponsor of sertindole withdrew this NDA.

2.3 Administrative History

The original commercial IND for oral ziprasidone was filed on April 3, 1990. FDA allowed women of child bearing potential to be included in clinical trials in October, 1991; the sponsor began to include women of child bearing potential in August, 1993.

An End of Phase II meeting between FDA and the sponsor was held in March 1994. At that time, the FDA requested that the sponsor repeat the Segment II study in rabbits because of the low survival rate of fetuses and the lack of skeletal and visceral examination in all fetuses. FDA also requested that if the sponsor was interested in correlating neoplastic changes in pre-clinical carcinogenicity studies to an increase in serum prolactin, they would need to document that serum prolactin levels were simultaneously elevated in these animal studies. Characterizing the pharmacokinetic characteristics of ziprasidone and its metabolites was also emphasized.

According to FDA records, a pre-NDA meeting was held in May, 1996. During this meeting, the pharmacology group requested that the sponsor submit separate tables describing neoplastic and non-neoplastic findings from rat carcinogenicity studies; it was again requested that the sponsor submit pre-clinical data characterizing ziprasidone's effect on serum prolactin concentration and its relationship to neoplastic changes. The sponsor was also encouraged to identify the metabolic pathway of ziprasidone and cytochrome characterization to develop information regarding drug interactions. The format for the NDA submission was discussed during the pre-NDA meeting.

In July 1996, the sponsor met with the FDA to discuss and demonstrate the electronic submission of the NDA. In September, 1996, Pfizer was granted a waiver for submitting the case report forms in hard copy.

In November 1996, the sponsor met with the FDA chemistry group to discuss issues regarding chemistry, manufacturing and controls.

The original NDA was submitted to FDA on March 18, 1997 with a cut-off date listed as October 31, 1996. A safety update was submitted by the sponsor on August 29. 1997 with a cut-off date recorded at May 15, 1997.

In October 1997, the Division notified the sponsor by letter that there were concerns regarding the finding of QT interval prolongation with the use of ziprasidone.

On December 16, 1997, the sponsor notified DNDP that they intended to submit a major amendment to the NDA which would subsequently entitle the sponsor to have a 3 month user fee extension; this amendment (submitted 1/23/98) included one pre-clinical study and data from two pediatric studies (one completed study with n=18 and one interim report) in children with Tourette's Syndrome.

2.4 Proposed Labeling

The dosing instructions in the draft labeling recommended an initial dose of 40 mg bid with food, and, if needed, followed by dose titration up to 80 mg bid at intervals of 2 days or more. The labeling states that doses above 80 mg bid were not shown to be more efficacious than 80 mg bid, and that clinical assessment is recommended if a dose greater than 80 mg bid is to be undertaken. It is also mentioned that the safety profile of doses above 100 mg bid have not been assessed.

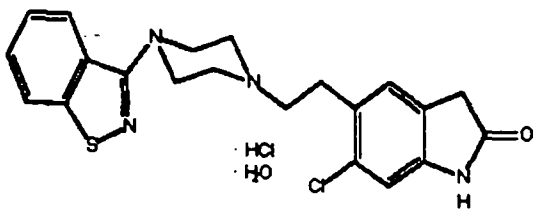
For maintenance therapy, the draft labeling recommends that the dose be 40 mg bid with allowance for individual patient differences. There is no maximum time period stated for use. It also states that no dose adjustments are necessary for age, gender, race, renal or hepatic impairment.

2.5 Foreign Marketing

Ziprasidone is not marketed anywhere in the world.

3.0 Chemistry, Manufacturing and Controls

The chemical structure for ziprasidone is:



4.0 Animal Pharmacology and Toxicology

In vitro studies have shown that ziprasidone is a serotonin (5-HT_{2A})and dopamine type 2 (D_2) antagonist. Other receptor effects of ziprasidone include histamine (H_1), α_1 adrenergic, 5-HT_{1A} (agonist), $5HT_{1D}$ (antagonist), and $5HT_{2C}$ (antagonist) receptor affinity. There is evidence that ziprasidone blocks neuronal reuptake of serotonin and norepinephrine, and inhibits the contractile effect of norepinephrine on guinea pig aortic strips.

In animal models, ziprasidone demonstrated potential for antipsychotic properties. The suggestion that it would have less severe motor side effects than traditional antipsychotics was supported by its weak ability to induce catalepsy in animals; its potential to treat negative symptoms was theoretically demonstrated in its ability to increase the release of dopamine in rat prefrontal cortex.

Reproductive studies in rabbits resulted in decreased birth weight, decreased birth survival, decreased maternal weight gain, decrease in the number of viable litters, and abnormal fetal heart development. Ziprasidone has been shown to exhibit placental transfer in rats and rabbits. In chronic toxicology studies, sedation and reduced body weight gain were observed in rats and dogs. Also observed in dogs were motor side effects, and intrahepatic cholestasis (correlated with increases in ALT and alkaline phosphatase).

The mouse carcinogenicity studies showed dose related increases in the incidence of pituitary adenomas and mammary gland adenocarcinomas.

In the opinion of FDA consultants, the safety preclinical pharmacology evaluation of the original NDA submission did not include an adequate work up of ziprasidone's effect on the QT interval.

In a meeting package (2/13/98), the sponsor concluded that ziprasidone and the metabolite ziprasidone-sulfoxide did not demonstrate significant effects on the action potentials of Purkinje fibers in dogs; FDA cardiology consultants (HFD-110) expressed concern that the sponsor did not test a high enough concentration of ziprasidone in this study to fully characterize the effects of ziprasidone in the therapeutic dosage range (note: the sponsor has not submitted a study report for review). In a meeting with FDA and the sponsor (3/27/98), the sponsor presented a brief summary of data which suggested that ziprasidone may inhibit the IKr channel, an ion channel implicated in the process of QTc prolongation (no data was submitted for review).

5.0 Description of Clinical Data Sources

5.1 Primary Source Data (Development Program)

5.1.1 Study Type and Design/Patient Enumeration

The sponsor submitted three different calculations to characterize the subject exposure history of ziprasidone, and there was some discrepancy amongst the tables presented by the sponsor; this review will attempt to clarify these submissions. The following table (adapted from the sponsor's submission of 3/20/98) gives a summary of person time in the ziprasidone safety data base:

Subject-years exposure in ziprasidone safety data base*

ORIGINAL NDA	ZIPRASIDONE	PLACEBO	HALOPERIDOL	RISPERIDONE
N=	2163*	366	407	206
Subject-years exposure*	626*	51	86	84
SAFETY UPDATE				
N=	2588	382	585	295
Subject-years exposure*	772	52	131	105
REPORT of 12/31/98				
N=	2993	424	653	298
Subject-years exposure*	1189	82	228	155

*** Includes Studies 105 and 120 which were not in the integrated safety data base.(see below for details)**

Discrepancies in the total number of subjects exposed is explained by the fact that the sponsor did not consistently exclude or include studies 105 (11 elderly demented subjects) and study 120 (12 psychotic subject taking the IM formulation). Studies 105 and 120 were not included in the integrated safety data base. Therefore, in the original submission (submitted: 3/18/97;cut off date: 10/31/96), there were actually a total of **2140** subjects enrolled in phase II/III oral ziprasidone studies in the integrated safety data base. This is the number of subjects upon which the demographic characteristics presented below (section 5.1.2) is based.

Appendix Table 5.1.1.1 lists the cumulative number of subjects in the original integrated safety data base and the safety update with a cut-off date of May 15, 1997. The safety data base (submission of 8/29/97) for Phase I, II, and III of ziprasidone trials included a total of 3318 subjects exposed to ziprasidone. There were 742 subjects in Phase I studies and 2565 subjects in the Phases II/III studies; this doesn't include study 105 in which 11 elderly subjects with dementia were exposed to oral ziprasidone. One other trial (study 120) for the IM formulation with 12 subjects was included in the enumeration of subjects in the original submission, but the sponsor did not include this data in the integrated safety data base for the oral ziprasidone NDA.

Please refer to Appendix 5.1.1.2 for a listing of all studies. The integrated safety data base encompasses 29 Phase II/III studies. The majority of subjects were enrolled in controlled studies.

5.1.2 Demographics

Please refer to Appendix 5.1.2.1 for a demographic profile of all Phase I studies. The sponsor did not recalculate demographics based on the additional information in the safety update for phase I trials.

All demographic information for the cumulative Phase II/III safety data base as of 8/29/97 can be found in Appendix 5.1.2.2.

These tables show that the majority of subjects in Phases I and II/III were Caucasian males between the ages of 18-64 years old.

5.1.3 Extent of Exposure (dose/duration)

The modal daily dose and duration for Phase I studies are shown in Appendix 5.1.3.1 (note: these figures are based on the original submission; the sponsor did not provide additional information in the safety update for phase I trials). This table reflects that the majority of subjects were exposed to low doses (< 100 mg daily) for less than 30 days which is not unusual for Phase I studies.

Appendix 5.1.3.2 is a table of the mean daily dose and duration during all oral dosing in Phase II/III studies (including data from the safety update of 9/29/97). There have been 1686 subjects (65.7%) within this pool who have been exposed to ziprasidone in the dosage range of 80 to 160 mg daily which is the recommended dose in the proposed labeling. There were 533 subjects (20.8%) exposed to ziprasidone for six months or longer. The following table (adapted from the sponsor's safety update, and presented above) gives a summary of person time in the ziprasidone safety data base:

Subject-years exposure in ziprasidone safety data base

ORIGINAL NDA	ZIPRASIDONE	PLACEBO	HALOPERIDOL	RISPERIDONE
N=	2163	366	407	206
Subject-years exposure*	626	51	86	84
SAFETY UPDATE				
N=	2588	382	585	295
Subject-years exposure*	772	52	131	105

REPORT of 12/31/98				
N=	2993	424	653	298
Subject-years exposure*	1189	82	228	155

* Includes Studies 105 and 120 which were not in the integrated safety data base.(see Section 5.1.1 for details)

The sponsor recorded the cut off date as 10/31/98 for the original submission . The cut-off date for the safety update calculations (submitted 8/29/97) was not made clear by the sponsor despite requests to do so. The sponsor reported that the subject-years exposure calculations for the REPORT of 12/31/98 was 12/31/98.

Please note that the sponsor included subjects from blinded groups to calculate the subject-years exposure; they did not explain their procedure despite requests to do so.

5.2 Secondary Source Data

5.2.1 Other Studies

The studies conducted in Japan were not included in the integrated summary data base, but safety data including discontinuations, adverse events, and laboratory test abnormalities was included in this submission. The cut-off date, including the safety update, is May 15, 1997. The Japanese studies include the following:

Phase I Studies (n= ziprasidone exposure)
93-501 (n=13)
93-502 (n=8)
93-503 (n=6)
93-504 (n=10)
94-501 (n=6)
96-501 (n=25)

Phase II Studies
94-601 (n=49)
95-601 (n=84)

The eight Phase I and three Phase II Japanese trials included 201 subjects as of the safety update of May 15, 1997 who were exposed to ziprasidone; the sponsor calculated that this represents 14.8 subject-years exposure.

5.2.2 Postmarketing Experience

As of September 4, 1997, Ziprasidone is not marketed in any country as per a teleconference with Dr. Ritrovato at Pfizer.

5.2.3 Literature

According to a teleconference of September 4, 1997 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 has submitted nineteen published papers and abstracts (NDA Vol. 153 and 154) that either focused on or contained new information about ziprasidone. Publications which make only a reference to ziprasidone were not submitted; the cut-off for the bibliography was listed as October 31, 1996. The literature search was conducted by David L. Larson, Ph.D. who has been employed at Pfizer since 1971.

Of note in this literature review, there were two studies (Bench, 1996; Bench, 1993) which reported large elevations of prolactin levels when comparing baseline and peak plasma levels of ziprasidone in twelve normal volunteers taking between 5 and 60 mg of a single dose of ziprasidone.

Otherwise, my 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.

Oral ziprasidone is absorbed up to 100 % when administered in the fed state. In the fed state, the mean half-life is 6.6 hours (variability ranging from 3 to 18 hours) and a steady state is achieved within 1 to 3 days. In addition to increasing the AUC and Cmax, food was found to delay the Cmax and decrease the half-life by approximately 4 hours. Ziprasidone is highly protein bound with an absolute bioavailability of 60 % in the fed state. The mean volume of distribution is approximately 1.5 L/kg with a mean systemic clearance of approximately 7.5 ml/min/kg. Ziprasidone demonstrates linear kinetics in the fasting state. In an interim report of study 044, a single dose pharmacokinetic study in 15 pediatric subjects with Tourette's Syndrome (ages 7-16; n=15), preliminary finding showed that the half-life range was 3.3-4.7 hours (note: an oral suspension of 40 mg/ml was used in study 044).

The major metabolites identified are ziprasidone-sulfoxide and ziprasidone-sulfone; both demonstrate a low affinity to D_2 and $5HT_{2A}$ receptors. 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. Excretion was determined to be 20% in the urine and 66% the in feces.

Study 028 showed that there was a longer half-life in the elderly ($t_{½}$=5.5) than in the younger adults ($t_{½}$=3.5). The differences in Cmax and AUC were less than 15 % between the elderly and younger adults; elderly men had similar values to the young adult males and females, but elderly women displayed a higher AUC (23%) and Cmax(44%). In the proposed labeling , the sponsor concluded that a dose adjustment was not necessary for age or gender.

Study 026 examined the pharmacokinetic differences in subjects with renal impairment compared to subjects with normal renal functioning. The sponsor found that ziprasidone levels were not affected by hemodialysis and that there was no statistical significance seen in the AUC and Cmax when comparing normal subjects with renally impaired subjects. The sponsor concluded that renal impairment does not alter the pharmacokinetic properties of ziprasidone; however, the biopharmaceutics review (HFD-860: 3/3/98) makes note that the sponsor used only a dosage of 20 mg bid of ziprasidone in this studies when the proposed labeling recommends 40 mg bid as the minimum dosage.

Study 030 compared pharmacokinetic properties in subjects with hepatic cirrhosis and subjects with normal hepatic functioning. There was a higher mean half-life in the subjects with cirrhosis ($t_{½}$=7.1) compared to the normal controls ($t_{½}$=4.8). Otherwise, the sponsor did not find statistical significance in the Cmax and Tmax between the groups by day 5. The sponsor's proposed labeling states that impaired liver functioning does not appreciably affect ziprasidone's pharmacokinetic properties; however, as with the renal impairment study above, the sponsor used the dose of 20 mg bid ziprasidone in this study and did not test the recommended minimum dose of 40 mg bid.

Theoretically, inducers of CYP3A4 (e.g. carbamazepine) may decrease ziprasidone exposure while inhibitors (e.g. cimetidine, ketoconazole) may increase ziprasidone levels. The sponsor's studies showed that concomitant use of carbamazepine resulted in a < 40 % decrease of ziprasidone AUC and Cmax; however, it was noted in the Biopharmaceuticals Review (3/3/98) that the sponsor used the dose of 200 mg bid (for 21 days) instead of a dose in the recommended dosage range (800 to 1200 mg qd carbamazepine); this suggests that ziprasidone levels may be even further reduced when administered concomitantly with a

therapeutic maintenance dose of 800 to 1200 mg qd carbamazepine. In vivo study 050 demonstrated that the concomitant use of ketoconazole, a potent CYP3A4 inhibitor, resulted in approximately a 30 percent increase of both AUC and Cmax of ziprasidone over placebo, suggesting that ziprasidone may have some potential to inhibit the CYP3A4 isozyme.

Concomitant use of the cimetidine and aluminum/magnesium antacids did not show clinically significant interactions with ziprasidone. Ziprasidone was shown to have no statistically significant change in the pharmacokinetics of dextromethorphan (a CYP2D6 substrate), ethinyl estradiol (a CYP3A4 substrate), and did not affect the steady state or renal clearance of lithium.

7.0 Review of Efficacy

7.1 Background

Pfizer reports they have six well controlled studies testing the effectiveness of ziprasidone in treating the psychotic symptoms of schizophrenia and schizoaffective disorders. They consider that four of these studies (106, 114, 115, and 303) are adequate to support the efficacy of ziprasidone, and that the other two studies (104 and 106) provide relevant data to their claims of effectiveness. This review will discuss the following studies which are all randomized, double blind, placebo controlled multicentered trials in subjects diagnosed with schizophrenia or schizoaffective disorder:

Study 106, n=139 total, comparing ziprasidone 20 mg bid, 60 mg bid, and placebo,
4 weeks

Study 114, n=302 total, comparing ziprasidone 40 mg bid, 80 mg bid, and placebo,
6 weeks

Study 115, n=419 total, comparing ziprasidone 20 mg bid, 60 mg bid, 100 mg bid, and placebo,
6 weeks

Study 303, n=294 total, comparing ziprasidone 20 mg bid, 40 mg bid, 80 mg bid, and placebo,
52 weeks

Study 104, n=200 total, comparing ziprasidone 5 mg bid, 20 mg bid, 40 mg bid, and placebo,
4 weeks.

Study 101 utilized the comparator control of haloperidol and will be briefly summarized, because the sponsor considered this study to be relevant to their labeling claims. There were three other controlled studies in this submission: two haloperidol controlled (studies 109 and 111) and one placebo controlled utilizing subjects with dementia (study 105); these studies were of a small size with thirty-five or less subjects.

A brief summary will be presented of the pilot study 122, an eight week, double-blind, placebo-controlled trial in the pediatric population with Tourette's Syndrome.

7.2 Review of individual studies

7.2.1 Study 106

Investigators/Location

This study was conducted in twelve centers in the United States. Please refer to Appendix 7.2.1.1 for a list of investigators and sites. The sponsor did not provide reasons why [redacted] were terminated prior to randomization of any subjects.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder.

Population

Subjects chosen for this study were physically healthy males and females aged 18-64 y.o. with a DSM IIIR diagnosis of chronic or subchronic (less than one year) schizophrenia with acute exacerbation, or schizoaffective disorder (for at least a year). Females of childbearing potential were required to use effective contraception during the study. Baseline scores needed to be at least 37 on the total Brief Psychiatric Rating Scale (BPRS) and at least 4 (moderate) on 2 or more of the BPRS core items (Core items include scorings for conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.). Also required was a score of > 2 on the Clinical Global Impressions Improvement scale (CGI-I) assessed at baseline in comparison to the Clinical Global Impressions-Severity (CGI-S) score previously obtained during the screening period. 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 residual schizophrenia, mental retardation, organic mental syndromes, organic mental disorder, brief reactive psychosis, resistance to neuroleptic treatment (i.e. adequate trial of two or more marketed antipsychotics within two years prior to study), comorbid substance abuse/dependence within 6 months, use of depot neuroleptic within 8 weeks of beginning the study, and a high risk for suicide. Concurrent medications allowed during the double-blind trial period included lorazepam, benztropine, and beta-blockers; prohibited medications included other psychotropic drugs, antianginal agents, antiarrhythmics, antinauseants, anticoagulants (except aspirin), steroids, tryptophan, and insulin. If used chronically, antihypertensives, diuretics, hormones (except insulin), oral contraceptives, hypoglycemic agents and Zantac were allowed.

? => WD

Design

This was a randomized, double blind, placebo controlled 28 day study. After spending four to seven inpatient days in a single-blind placebo washout period, subjects were required to be inpatients for the following 21 days of the double blind placebo controlled study, and were permitted to be inpatient or outpatient for the final 7 days of the study. Psychotropic drugs other than lorazepam and a low dose beta-blocker were to be discontinued during the washout phase. A history and physical was to be performed during screening; thyroid function tests were performed at screening only. Baseline data, taken at the end of the washout period, would include vital signs (including supine and standing blood pressures), routine laboratory tests, ECG, assessment of abnormal movements (Simpson-Angus Rating Scale, Barnes Scale and AIMS), efficacy instruments (BPRS, CGI, Nurse Global Impression Scale [NGI]), and the Scale for the Assessment of Negative Symptoms (SANS).

? washout

Subjects were to be randomly assigned to one of three treatment groups: ziprasidone 20 mg bid, ziprasidone 60 mg bid, or placebo; the group taking ziprasidone 60 mg would be titrated to the target dose within five days (20 mg bid x 2 days, then 40 mg bid x 2 days followed by 60 mg bid x 24 days). Dosing was to occur with mealtime. Serum samples for pharmacokinetic analysis were to be drawn in the mornings of day 1, 7, 14, 21, and 2 hours after the morning dose on days 14 and 21. Repeat laboratory tests were to be drawn prior to dosing on the morning of days 1, 7, 14, 21,and 28. Vital signs were assessed prior to the morning dose on days 1, 2, 7, 14, 21, and 28. ECG and body weight were again recorded prior to the morning dose on days 1, 14, 28. Repeat physical exams were conducted at completion of the study.

The BPRS, CGI, and NGI were scheduled 3 to 7 hours after the morning dose on days 7, 14, 21, and 28; subjects who discontinued prior to completing were to be interviewed within 24 hours of the last dose. The SANS was also repeated on days 14 and 28 or at discontinuation.

Analysis Plan

The primary efficacy variables were defined in the protocol as the mean change in score from baseline to last visit in the following instruments: 1) the BPRS total score, 2) the BPRS core items (suspiciousness, conceptual disorganization, hallucinatory behavior, unusual thought content), and 3) the CGI- S and CGI- I scores.

The protocol states that the BPRS total score was to be analyzed with an analysis of variance with treatment, center, and their interaction. CGI was to be analyzed nonparametrically as a discrete variable.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 203 subjects screened to enter the study, 139 subjects were randomized to one of the three treatment groups and had at least one dosage of double blind treatment. 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 discontinuations in the three treatment groups:

Discontinuations from Study
Ziprasidone Protocol 106

	Ziprasidone 20 mg BID	Ziprasidone 60 mg BID	Placebo
Number of Subjects Randomized	44	47	48
Number of Subjects Discontinued			
Related to Study Drug	11	10	12
Insufficient clinical response	11	8	12
Adverse event	0	1	0
Laboratory test abnormality	0	1	0
Not related to Study Drug	6	13	12
Adverse event	1	3	0
Protocol violation	2	2	2
Lost to follow-up	0	1	0
Withdrawn consent	1	6	9
Other	1	2	1
TOTAL	16	23	24

Appendix 7.2.1.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varied depending on the data available for each efficacy endpoint.

The rate of dropout for the treatment group taking ziprasidone 60 mg bid is almost identical to the profile of dropouts for placebo showing approximately a fifty percent withdraw by the end of the study. However, the group taking ziprasidone 20 mg bid appeared to have slightly fewer dropouts, with a sixty-four percent completer rate.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with mean ages of approximately 40 years old. The mean ages of the female subjects were higher than the male subjects for all treatment groups. 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 BPRS Total Score, BPRS Core Items, CGI -S, and CGI-I were very close, if not identical when comparing placebo with the two treatment groups (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE		PLACEBO
	20 MG BID	60 MG BID	
BPRS Total	36.5	36.6	37
BPRS Core	13.4	13.6	13.9
CGI-S	4.7	4.7	4.7

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 106

	Ziprasidone		
	20 mg bid (n=44)	60 mg bid (n=47)	Placebo (n=48)
Lorazepam	36	40	43
Benztropine	3	9	4
Beta-Blocker	3	3	2
Antidepressant	0	1	0
Antipsychotic	2	1	2
Antihistamine	1	6	3

During the double-blind trial, lorazepam was used with a mean total cumulative dosage of 53 mg for the 36 subjects in the 20 mg bid group; 43 mg of lorazepam was the mean usage in the 60 mg bid group, while the placebo group had a mean usage of 30 mg. Benztropine was taken by 3 subjects in the 20 mg bid group with a mean dose of 15 mg during the trial; 14 mg was the mean dose for the 60 mg bid group, and the placebo group used a mean dosage of 5.5 mg.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRS Total, BPRS Core, CGI-S, and SANS). The ziprasidone 60 mg bid group was the only group that showed statistical significance in week 4 for the primary efficacy variables of the BPRS Total and the CGI-S for both OC and LOCF when compared with placebo. However, neither of the treatment groups provided statistical

significance with the BPRS Core or the SANS with a 95% confidence interval when compared with placebo.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. On day 21, the mean trough level for the ziprasidone 20 mg bid group was 18.6 ng/ml, and for the ziprasidone 60 mg bid group, the mean level was 56.4 ng/ml.

The sponsor performed an interim analysis which they state did not modify the design of the study.

Conclusions

Because this study showed statistical significance in only two of the three primary efficacy variable in week four only, it merely provides fair evidence for the antipsychotic properties of ziprasidone at a dose of 60 mg bid.

7.2.2 Study 114

Investigators/Location

This study was conducted in thirty-four centers in the United States and Canada. Please refer to **Appendix Table 7.2.2.1** for a list of investigators and sites.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to evaluate the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder.

Population

Entrance criteria were similar to Study 106 with the exception that this study required a baseline score of > 59 for the total score of the Positive and Negative Syndrome Scale (PANSS). Please refer to Study 106 for a list of concurrent medications permitted during the double-blind trial period.

Design

This was a randomized six week, double blind, placebo controlled study. Subjects who met entry criteria were required to undergo an inpatient single-blind placebo washout period for 3-7 days followed by 14 days of inpatient double-blind treatment. During the remaining 28 days of the study, subjects could be inpatient or outpatient during which time they would be evaluated at weekly visits. A history and physical was to be performed during screening; thyroid function tests were performed at screening only. Baseline data, taken at the end of the washout period, would include vital signs (including sitting and standing), routine laboratory tests, ECG, assessment of abnormal movements (Simpson-Angus Rating Scale, Barnes Scale and AIMS), and efficacy instruments (PANSS, CGI, and the Montgomery-Asberg Depression Rating Scale [MADRS]).

Once chosen for the study, subjects were to be randomized to one of three treatment groups: 1) ziprasidone 40 mg bid, 2) ziprasidone 80 mg bid 3) placebo. The double-blind medication was to be administered orally two times a day (dosing spaced about 12 hours apart) with food. Titration occurred over a period of

3 days for the 80 mg bid group (40 mg x 2 days, then 80 mg x 40 days). Serum samples for pharmacokinetic analysis were to be drawn pre-dosing of days 7,14, 42, or at early termination. Repeat laboratory tests were to be drawn on days 7, 21, 42, or at early termination. Vital signs were assessed on days 7, 14, 21, 28, 35 and 42. ECG were again recorded on days 14 and 42 or at early termination. Repeat physical exams were conducted at completion of the study.

The PANSS and the CGI-S were to be given weekly, and the MADRS would be repeated on days 7, 14, 21, and 42. Subjects who discontinued prior to completing were to be interviewed within 24 hours of the last dose.

Analysis Plan

The primary efficacy variables specified in the protocol were the total score of the BPRS derived from the PANSS (BPRSd), BPRSd core items (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content) and the CGI-S. Secondary efficacy variables included the PANSS-total, PANSS negative sub-scale, the CGI-I, and the MADRS.

The protocol stated that linear models will be fitted to the primary efficacy variables analyzing baseline values and treatment centers. The protocol also states that an analysis of discrete or categorical data may be used as an alternative method.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 440 subjects screened to enter the study, 302 subjects were randomized to one of the three treatment groups and had at least one dosage of double blind treatment. 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 discontinuations in the three treatment groups:

Discontinuations from Study
Ziprasidone Protocol 114

	Ziprasidone 40 mg BID	Ziprasidone 80 mg BID	Placebo
Number of Subjects Randomized	106	104	92
Number of Subjects (%) Discontinued			
Related to Study Drug	27 (25.5)	23 (22.1)	32 (34.8)
Insufficient clinical response	26 (24.5)	16 (15.4)	32 (34.8)
Adverse event	1 (0.9)	7 (6.7)	0 (0.0)
Not Related to Study Drug	25 (23.6)	14 (13.5)	15 (16.3)
Adverse event	1 (0.9)	1 (1.0)	1 (1.1)
Protocol violation	3 (2.8)	1 (1.0)	1 (1.1)
Lost to follow-up	6 (5.7)	2 (1.9)	3 (3.3)
Does not meet randomization criteria	0 (0.0)	3 (2.9)	1 (1.1)
Withdrawn consent	15 (14.2)	6 (5.8)	8 (8.7)
Other	0 (0.0)	1 (1.0)	1 (1.1)
TOTAL	52 (49.1)	37 (35.6)	47 (51.1)

Appendix 7.2.2.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varied depending on the data available for each efficacy endpoint.

The dropout rate was lowest for the treatment group taking ziprasidone 80 mg bid with a sixty-four percent completer rate. The withdrawal rate for both the placebo and ziprasidone 40 mg bid treatment group was approximately fifty percent by the end of the study.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with mean ages of approximately 36 years old in all groups. The mean ages of the female subjects were higher than the male subjects for all treatment groups. 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 mean baseline values for the BPRSd Total Score, BPRSd Core Items, CGI -S, and PANSS were comparable (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE		PLACEBO
	40 MG BID	80 MG BID	
BPRSd Total	56.5	55.0	55.1
BPRSd Core	16.9	16.6	16.4
CGI-S	4.8	4.8	4.8
PANSS total	98.2	95.8	97.3
PANSS neg.	25.4	24.3	24.9

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 114

	Ziprasidone		
	40 mg bid (n=106)	80 mg bid (n=104)	Placebo (n=92)
Lorazepam	90	96	85
Benztropine	21	26	12
Beta-Blocker	5	10	3
Antihistamine	3	3	1
Rx for alcoholism and drug addiction	2	8	1

The sponsor did not provide dosages of lorazepam and benztropine use for this study.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRSd Total, BPRSd core items, CGI-Severity, and PANSS). When compared with placebo at a 95% confidence interval, both ziprasidone treatment groups showed statistical significance by week six for efficacy variables of the BPRSd Total, BPRSd core items, CGI-S, and PANSS total for LOCF. For OC, the only statistically significant result at week six was the CGI-S for the ziprasidone 80 mg bid group.

Miscellaneous Issues

This study included data that was generated from a study site ( ) with the investigators Drs. . . The sponsor recalculated the efficacy data of Study 114 excluding data submitted from study site they concluded that the efficacy data was not significantly affected by the exclusion of Dr. . data.

This efficacy review of study 114 includes data from site . The only noteworthy observation from the analysis of the data without study site is that there was no statistically significant findings at week 6 for the ziprasidone 40 mg bid treatment group.

Serum plasma levels of ziprasidone were obtained during this study. On day 42, the mean trough level for the ziprasidone 40 mg bid group was 47 ng/ml, and for the ziprasidone 80 mg bid group, the mean level was 109 ng/ml.

Conclusions

This study demonstrated statistical significance when comparing both the treatment groups and placebo in the three primary efficacy variables by week six. These results provide evidence that ziprasidone is effective in treating the acute symptoms of psychosis associated with schizophrenia or schizoaffective disorder. Results for the 80 mg bid group were generally superior to the 40 mg bid group results.

7.2.3 Study 115

Investigator(s)/Location

This study was conducted in 54 sites in the United States. Please refer to the sponsor's list of investigators and sites in Appendix 7.2.3.1. The sponsor did not provide reasons for terminating prior to randomization of any subjects.

Study Plan

Objective(s)/Rationale

The primary objective of this study was to assess the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder as compared to placebo and haloperidol.

Population

Please refer to Study 114 which had the same entrance criteria. Concurrent medications were similar to those used in previous studies.

Design

This was a randomized, double-blind, placebo controlled, six week study. The details of this study's design were similar to Study 114 (please refer to Study 114 for more information).

Once chosen for the study, subjects were to be randomized to one of five treatment groups: 1) ziprasidone 20 mg bid, 2) ziprasidone 60 mg bid 3) ziprasidone 100 mg bid, 4) haloperidol 15 mg qd, and 5) placebo. The double-blind medication was to be administered orally two times a day (dosing spaced about 12 hours apart) with food. Titration occurred over a period of 3 days for the 60 mg bid group (40 mg x 2 days, then 60 mg x 40 days) and over a period of 5 days for the 100 mg bid group (40 mg bid x 2 days, then 80 mg

bid x 2 days, followed by 100 mg bid x 38 days). Serum samples for pharmacokinetic analysis were to be drawn pre-dosing on days 7,14, 42, or at early termination, and, also, at specified time intervals after dosing (i.e. 1-4 , 4-7, or 7-10 hours) on days 14 and 21. Repeat laboratory tests were to be drawn on days 7,14, 42, or at early termination. Vital signs were assessed on days 7, 14, 21, 28, 35 and 42. ECGs were repeated on days 14 and 42 or at early termination. Another physical exam was to be conducted at completion of the study.

The PANSS, CGI-S, and CGI-I were to be given weekly; the MADRS would be repeated on days 7, 14, 21, and 42. Subjects who discontinued prior to completing were to be interviewed within 24 hours of the last dose.

Analysis Plan

The primary efficacy variables were the BPRSd total score (derived from the PANSS), BPRSd core items and the CGI-S. Secondary efficacy variables included the PANSS-total, PANSS negative sub-scale, the CGI-I, and discontinuation status due to lack of efficacy.

The protocol stated that a linear model investigating the dose-response relationship across the ziprasidone and placebo treatment groups would be used. This analysis would use the baseline values of the primary efficacy variables as a covariate and also look at interaction effects between centers and treatment. It is also noted that there were several amendments made to the analysis section of the protocol.

Study Conduct/Outcome

Patient Disposition

Of the 567 subjects screened to enter the study, 419 were randomized to one of the three treatment groups and had at least one dosage of double blind treatment. 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 discontinuations in the five treatment groups:

Discontinuations from Study
Ziprasidone Protocol 115

	Ziprasidone 20 mg BID		Ziprasidone 60 mg BID		Ziprasidone 100 mg BID	
Number of Subjects Randomized	87		78		86	
Number of Subjects (%) Discontinued						
Related to Study Drug	22	(25.3)	26	(33.3)	22	(25.6)
Insufficient clinical response	22	(25.3)	22	(28.2)	18	(20.9)
Adverse event	0	(0.0)	2	(2.6)	4	(4.7)
Laboratory test abnormality	0	(0.0)	2	(2.6)	0	(0.0)
Not Related to Study Drug	15	(17.2)	13	(16.7)	16	(18.6)
Adverse event	1	(1.1)	1	(1.3)	2	(2.3)
Protocol violation	0	(0.0)	2	(2.6)	0	(0.0)
Lost to follow-up	3	(3.4)	0	(0.0)	1	(1.2)
Does not meet randomization criteria	1	(1.1)	1	(1.3)	2	(2.3)
Withdrawn consent	10	(11.5)	8	(10.3)	10	(11.6)
Other	0	(0.0)	1	(1.3)	1	(1.2)
TOTAL	37	(42.5)	39	(50.0)	38	(44.2)

Discontinuations from Study
Ziprasidone Protocol 115

	Haloperidol		Placebo	
Number of Subjects Randomized	85		83	
Number of Subjects (%) Discontinued				
Related to Study Drug	19	(22.4)	35	(42.2)
Insufficient clinical response	13	(15.3)	35	(42.2)
Adverse event	6	(7.1)	0	(0.0)
Laboratory test abnormality	0	(0.0)	0	(0.0)
Not Related to Study Drug	18	(21.2)	21	(25.3)
Adverse event	1	(1.2)	3	(3.6)
Protocol violation	0	(0.0)	2	(2.4)
Lost to follow-up	2	(2.4)	1	(1.2)
Does not meet randomization criteria	1	(1.2)	1	(1.2)
Withdrawn consent	13	(15.3)	14	(16.9)
Other	1	(1.2)	0	(0.0)
TOTAL	37	(43.5)	56	(67.5)

Appendix 7.2.3.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varies depending on the data available for each efficacy endpoint.

The completer rate was highest for the ziprasidone 60 mg bid group (64%), and, as expected, lowest in the placebo group (32%). The other three groups had approximately a 45% withdraw by the end of the study.

Demographics/Group Comparability

The majority of patients in this study were Caucasian males with mean age of approximately 40 years old. There did not appear to be any imbalances in the treatment groups. Appendix 7.2.3.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRSd total score, BPRSd core items, CGI -S, and PANSS were comparable (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE			PBO	HALDOPERIDAL
	20 MG BID	60 MG BID	100 MG BID		15 MG
BPRSd Total	53.8	51.8	51.8	54.3	53.9
BPRSd Core	16.1	16.0	15.9	16.6	16.2
CGI-S	4.9	4.9	4.7	4.9	5.0
PANSS total	93.2	90.4	89.5	93.3	94.1
PANSS neg.	22.9	23.4	22.5	22.4	24.1

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 115

	Ziprasidone			Haloperidol	
	20 mg bid (n=87)	60 mg bid (n=78)	100 mg bid (n=86)	15 mg (n=85)	Placebo (n=83)
Lorazepam	76	69	75	76	75
Benztropine	24	15	36	43	26
Beta-Blocker	7	7	7	16	6
Antidepressant	0	0	0	0	0
Antipsychotic	2	4	1	5	9
Antihistamine	0	2	0	1	0

The sponsor did not provide dosages of lorazepam and benztropine use for this study.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRSd Total, BPRSd Core, CGI-S, and PANSS). All treatment groups showed statistical significance by week 6 for efficacy variables of the BPRSd Total, BPRSd core items, CGI-S, and PANSS Negative total for LOCF, but not for OC when compared to placebo at a 5% significance level. In week six, the PANSS negative showed statistical significance for LOCF in the ziprasidone 100 mg bid and haloperidol groups only.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. For the ziprasidone 20 mg bid treatment group, the mean trough serum concentrations were 28 ng/ml; the mean trough levels for the ziprasidone 60 mg bid group was 62 ng/ml, and the ziprasidone 100 mg bid treatment group had a mean trough level of 111 ng/ml.

The following table from the sponsor's submission lists the pharmacokinetic parameters established as a result of 825 samples from 237 subjects:

Pharmacokinetic Parameter		Estimated Value	Standard error	% CV
Systemic clearance	CL/F (L/hr)	53.5	1.25	2.34
Volume of central compartment	V_c/F (L)	381	65.2	17.1
Absorption coefficient	K_a (1/hr)	0.661	0.147	22.2
Volume of peripheral compartment	V_p/F (L)	1430	951	66.5
Intercompartmental clearance	Q (1/hr)	76.5	10.8	14.1
Absorption lag time	LAG (hr)	1.41	0.012	0.850

The sponsor claims that a dose response relationship among the three ziprasidone treatment groups and placebo were found to be statistically significant for all primary efficacy variables. This dose response was found when the ziprasidone treatment groups were compared to placebo. However, when comparing the ziprasidone treatment groups with each other, it does not appear that increasing doses yielded higher scores on efficacy variables.

Also of note is that the number of centers was increased to 54 where as the protocol estimated 30-40 centers.

Conclusions

This study demonstrated statistical significance when comparing all the treatment groups with placebo in the three primary efficacy variables at week six. These results provide evidence that ziprasidone is effective in treating the acute symptoms of psychosis associated with schizophrenia or schizoaffective

disorder. Results were generally similar between ziprasidone dose groups. The haloperidol arm results (including negative symptoms) were numerically superior to the ziprasidone groups.

This pharmacokinetic data supports the sponsor's claim that ziprasidone follows linear kinetics.

7.2.4 Study 303

Investigator(s)/Location

Appendix 7.2.4.1 gives the sponsor's list of 33 sites designated for this study; however, the study was conducted in 29 of these centers in Europe (Czech Republic, Estonia, Hungary and Poland). The sponsor did not provide reasons for closing the) prior to subject randomization.

Study Plan

Objective(s)/Rationale

The objectives of this fifty-two week study were to assess relapse prevention of psychotic episodes in hospitalized subjects with schizophrenia and to assess the safety and efficacy of ziprasidone compared to placebo.

Population

Subjects chosen for this study included physically healthy males and females aged 18 years or older who had been hospitalized at least two months prior to entry into the study with a primary diagnosis of chronic or subchronic schizophrenia. Females of childbearing potential were required to use methods of birth control that include an IUD, implanted or oral contraceptive methods. A baseline score of five or less on the CGI-S was required for inclusion in this trial. The protocol allowed investigator discretion for positive benzodiazepine or cannabinoids result in the urine drug screen; otherwise, it was required to be negative. Excluded from this study were patients scoring ≥ five (moderate severe) on the hostility or uncooperativeness items of the PANSS, with a history of psychosurgery, mental retardation, organic mental syndromes, organic mental disorder, brief reactive psychosis, epilepsy, resistance to neuroleptic treatment (i.e. adequate trial of two or more marketed antipsychotics within two years prior to study), comorbid substance abuse/dependence within 3 months, and a high risk for suicide or homicide. Concurrent medications allowed during the double-blind trial period included lorazepam, temazepam, anticholinergic medication, and beta-blockers. Other psychotropic drugs were prohibited.

Design

This study was a randomized, double blind, placebo controlled, fifty-two week inpatient study. Subjects who met entry criteria were required to undergo an inpatient single-blind placebo lead-in for 3 days followed by 52 weeks of inpatient double-blind treatment. Screening included a history and physical (including sitting and standing vital signs), routine laboratory tests, ECG, and an ophthalmology assessment (including a funduscopy and a slit-lamp examination). Baseline data, taken at the end of the lead-in period included assessment of abnormal movements (Simpson-Angus Rating Scale, Barnes Scale and AIMS) and efficacy instruments (PANSS, CGI, and Global Assessment of Functioning [GAF])

Once chosen for the study, subjects were to be randomized to one of four treatment groups: 1) ziprasidone 20 mg bid, 2) ziprasidone 40 mg bid 3) ziprasidone 80 mg bid, and 4) placebo. The double-blind medication was to be administered orally twice daily postprandially. Titration occurred over a period of 3 days for the 80 mg bid group (40 mg x 2 days, then 80 mg for the remainder of the study). Serum samples for pharmacokinetic analysis and repeat laboratory tests were to be drawn at weeks 4, 12, 28, and 52 or at early termination; thyroid function tests were done at screening and at week 52 only. Vital signs were

assessed at weeks 2, 4,12, 28, 40, and 52. ECGs were again recorded at weeks 12, 28, 52 or at early termination. Repeat physical exams and ophthalmology assessments were repeated at completion of the study.

The PANSS, CGI, and assessments for abnormal movements were administered at weeks 3, 6, 16, 28, 40, and 52; the GAF was evaluated at weeks 28 and 52.

Analysis Plan

The protocol states that the primary efficacy variable is the measurement of time to impending psychotic relapse. The sponsor defines "impending relapse" as CGI-I score of 6 (much worse) or greater and/or a score of 6 (severe) or greater on either of the PANSS items P7 (hostility) or G8 (uncooperativeness) on two successive days. A score of 5 (minimally worse) on the CGI-I would require ratings to be done on the following three days. If the CGI score remained at 5, then CGI ratings would be performed at weekly intervals until the score improved to 4 or less and then ratings could be performed according to the study schedule.

Other efficacy variables included the PANSS, CGI, and GAF.

The Kaplan-Meier analysis and the Cox proportional hazards model were to be used to analyze the time to discontinuation. ANCOVA models were to be used for continuous and most of the categorical efficacy variables. The analysis plans would look at the interaction effects of treatment groups.
Study Conduct/Outcome

Patient Disposition

Of the 351 subjects screened to enter the study, 294 were randomized to one of the four treatment groups and had at least one dosage of double blind treatment. Reasons for not being chosen to participate in this trial were not provided in this submission.

The following tables from the sponsor's study report itemizes reasons for discontinuations in the four treatment groups:

Discontinuations from Study
Ziprasidone Protocol 303

	Ziprasidone 20 mg BID		Ziprasidone 40 mg BID		Ziprasidone 80 mg BID		Placebo	
Number of Subjects Randomized	76		72		71		75	
Number of Subjects (%) Discontinued								
Related to Study Drug	33	(43.4)	28	(38.9)	27	(38.0)	50	(66.7)
Insufficient clinical response	27	(35.5)	22	(30.6)	24	(33.8)	43	(57.3)
Adverse event	6	(7.9)	6	(8.3)	1	(1.4)	6	(8.0)
Laboratory test abnormality	0	(0.0)	0	(0.0)	2	(2.8)	1	(1.3)
Not Related to Study Drug	9	(11.8)	13	(18.1)	11	(15.5)	11	(14.7)
Adverse event	1	(1.3)	1	(1.4)	4	(5.6)	5	(6.7)
Laboratory test abnormality	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Lost to follow-up	0	(0.0)	1	(1.4)	0	(0.0)	0	(0.0)
Withdrawn consent	4	(5.3)	5	(6.9)	5	(7.0)	1	(1.3)
Special safety test	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.3)
Other	4	(5.3)	5	(6.9)	2	(2.8)	4	(5.3)
TOTAL	42	(55.3)	41	(56.9)	38	(53.5)	61	(81.3)

Appendix 7.2.4.2 shows the number of subjects who completed each treatment group at specified intervals; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varies depending on the data available for each efficacy endpoint.

The three ziprasidone groups had similar discontinuation rates with 46% of subjects completing both the 20 mg bid and 40 mg bid group, and 48% of subjects completing the 60 mg bid group. As expected, the completer rate was lowest for the placebo group (19%).

Demographics/Group Comparability

All patients were Caucasian; the mean ages was approximately 37 years old. The mean ages of the female subjects were higher than the male subjects for all treatment groups. There did not appear to be imbalances in the treatment groups. Appendix 7.2.4.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRSd total score, BPRSd core items, CGI -S, and PANSS were comparable (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE			PLACEBO
	20 MG BID	40 MG BID	80 MG BID	
BPRSd Total	46.1	47.1	45.9	48.0
BPRSd Core	11.2	11.7	11.2	11.7
CGI-S	4.0	4.0	4.0	4.1
PANSS total	85.1	86.6	85.2	88.9
PANSS neg.	24.9	24.7	25.0	25.7

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 303

	Ziprasidone			
	20 mg bid (n=76)	40 mg bid (n=72)	80 mg bid (n=71)	Placebo (n=75)
Lorazepam	46	39	41	50
Antimuscarinic Drug for Parkinsonism	12	9	14	10
Beta-Blocker	4	1	2	1
Antidepressant	0	1	0	0
Antipsychotic	0	1	0	1
Antihistamine	0	0	0	1

The sponsor did not provide dosages of lorazepam and benztropine use for this study.

Efficacy Results

The rate of relapse (as defined in the analysis section above) was lower in the ziprasidone groups (mean of 33%) than in the placebo group (57%). Compared to placebo, the three group showed a statistically significant less risk of relapse in the ziprasidone groups; however, there was no significant difference in the risk when comparing the three different ziprasidone dosage groups. (please refer to Appendix Table for details).

Please refer to Appendix Tables for results of the other important outcome measures (BPRSd total, BPRSd core, CGI-S, PANSS total and PANSS neg.). By week 52, all ziprasidone treatment groups showed

statistically significant improvement in these score for LOCF, but not for OC when compared to placebo at a 5% significance level.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. For the ziprasidone 20 mg bid treatment group, the mean trough serum concentrations were 26 ng/ml; the mean trough levels for the ziprasidone 40 mg bid group was 49 ng/ml, and the ziprasidone 80 mg bid treatment group had a mean trough level of 82 ng/ml.

Conclusions

It is debatable if the sponsor has proven that ziprasidone is superior to placebo in the prevention of relapse. Their definition of "relapse" and this study design do not follow traditional methods of proving relapse prevention. There is no presumption that subjects were stable at the beginning of the study nor were subjects selected as responders in an open label study. However, the fact that subjects were hospitalized for two months prior to the start of the study may suggest that subjects had been somewhat stable prior to initiation of the study, and Dr. Wang (HFD 710:11/24/97) concluded that, using the definitions of the sponsor, the ziprasidone treatment group showed a longer time to relapse than placebo that was statistically significant.

Trade & descr

The results from the other efficacy variables in this study provide support to the efficacy of ziprasidone in the treatment of psychosis in schizophrenia.

7.2.5 Study 104

Investigators/Location

This study was conducted in seventeen centers in the United States. Please refer to Appendix 7.2.5.1 for a list of investigators and sites. closed prior to randomization of subjects.

Study Plan

Objective(s)/Rationale

The primary objective of this twenty-eight day, double blind, placebo controlled study was to evaluate the safety and efficacy of ziprasidone in treating subjects with an acute exacerbation of schizophrenia or schizoaffective disorder.

Population

Subjects chosen for this study were physically healthy males and females aged 18-64 y.o. Please refer to Study 106 for details of the entrance criteria and a list of concurrent medications allowed during the double-blind trial period.

Design

This is a randomized double-blind placebo controlled 28 day study. For details of the general study design and concomitant medications, please refer to Study 106.

After the lead-in phase, subjects were to be randomly assigned to one of four treatment groups: ziprasidone (CP-88,059-1) ziprasidone 5 mg bid, 2) ziprasidone 20 mg bid, 3) ziprasidone 40 mg bid, or 4) placebo;

the group taking ziprasidone 40 mg would be titrated to the target dose within four days (20 mg bid x 3 days, then 40 mg bid for the remainder of the study).

Analysis Plan

The primary efficacy variables were defined as the mean change in score from baseline to last visit in the following instruments: 1) the BPRS total score, 2) psychotic core items, and 3) the CGI- S.

The protocol states that the BPRS total score was to be analyzed with an analysis of variance with treatment, center, and their interaction. CGI was to be analyzed nonparametrically, as a discrete variable.

Other efficacy variables included the Nurses Global Impression (NGI).

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 303 subjects screened to enter the study, 200 subjects were randomized to one of the four treatment groups and had at least one dosage of double blind treatment. 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 discontinuations in the three treatment groups:

Discontinuations from Study
Ziprasidone Protocol 104

	Ziprasidone 5mg BID		Ziprasidone 20mg BID		Ziprasidone 40mg BID		Placebo	
Number of Subjects Randomized	47		55		48		50	
Number of Subjects (%) Discontinued								
Related to Study Drug	11	(23.4)	16	(29.1)	17	(35.4)	17	(34.0)
Insufficient clinical response	11	(23.4)	16	(29.1)	15	(31.3)	16	(32.0)
Adverse event	0	(0.0)	0	(0.0)	2	(4.2)	1	(2.0)
Not related to Study Drug	6	(12.8)	13	(23.6)	11	(22.9)	6	(12.0)
Adverse event	2	(4.3)	0	(0.0)	0	(0.0)	1	(2.0)
Laboratory test abnormality	0	(0.0)	1	(1.8)	0	(0.0)	0	(0.0)
Protocol violation	3	(6.4)	5	(9.1)	5	(10.4)	0	(0.0)
Withdrawn consent	0	(0.0)	7	(12.7)	5	(10.4)	4	(8.0)
Other	1	(2.1)	0	(0.0)	1	(2.1)	1	(2.0)
TOTAL	17	(36.2)	29	(52.7)	28	(58.3)	23	(46.0)

Appendix 7.2.5.2 shows the number of subjects per week who completed each treatment group; the reviewing statistician, Dr. Sue-Jane Wang, explained that the sample size under the "Treated" column and the "Week 1" column differ because there were subjects who did not complete the first seven days of the study. The sponsor defines their intent-to-treat as any subject who had baseline measurements and at least one post-baseline measurement; according to Dr. Wang, the sample size used in the efficacy analysis varies depending on the data available for each efficacy endpoint.

The dropout rate was lowest for the treatment group taking ziprasidone 5 mg bid (36%). The remaining treatment groups demonstrated a dropout rate of approximately fifty percent by the end of the study.

Demographics /Group Comparability

The majority of patients in this study were Caucasian males with mean ages of approximately 40 years old. The mean ages of the female subjects were higher than the male subjects for all treatment groups. There did not appear to be imbalances in the treatment groups. Appendix 7.2.5.3 shows the breakdown of demographics by treatment group.

The mean baseline values for the BPRS total score, BPRS core items, CGI -S, and CGI-I had similar scores across all treatment groups (please refer to table below). The sponsor did not provide any statistical comparisons of baseline values.

Mean Baseline Values of Primary Efficacy Variables

MEAN SCORE	ZIPRASIDONE			PLACEBO
	5 MG BID	20 MG BID	40 MG BID	
BPRS Total	34.1	34.5	36.2	33.4
BPRS Core	12.8	13.0	12.8	13.7
CGI-S	4.9	4.8	4.9	5.0

Concomitant Medications

Lorazepam was taken by the majority of subjects in all treatment groups. Please refer to the table below for select concomitant medication use.

Selected concomitant medication used in Study 104

	Ziprasidone			
	5 mg bid (n=47)	20 mg bid (n=55)	40 mg bid (n=48)	Placebo (n=50)
Lorazepam	34	42	39	41
Benztropine	6	11	6	8
Beta-Blocker	4	2	1	3
Antidepressant	0	1	0	0
Antipsychotic	5	3	3	4
Antihistamine	1	1	0	3

During the double-blind trial, lorazepam was used with an mean cumulative dosage of 60 mg for the 34 subjects in the 5 mg bid group; 40.5 mg of lorazepam was the mean usage in the 20 mg bid group, while the 40 mg bid group had a mean dosage of 46 mg of lorazepam. The placebo group had a mean dose of 43 mg of lorazepam. Benztropine was taken by the 6 subjects in the 5 mg bid group with a mean dose of 20.5 mg during the trial; 15 mg was the mean dose for the 20 mg bid group, and the 40 mg bid group took a mean dose of 41.5 mg. The placebo group used a mean dosage of 24 mg of benztropine.

Efficacy Results

Please refer to Appendix Tables for results of the important outcome measures (BPRS total, BPRS core, CGI-S). Statistical significance when compared with placebo was seen only in the ziprasidone 20 mg bid treatment group in the BPRS total and core for OC. Otherwise, no other parameters proved to be statistically significant in this trial.

Miscellaneous Issues

Serum plasma levels of ziprasidone were obtained during this study. At week four, the mean concentration of ziprasidone found in the 5 mg bid group was 3.7 ng/ml; the 20 mg bid group had a mean ziprasidone concentration of 29.7 ng/ml , while the ziprasidone 40 mg bid group had a mean plasma concentration of 34.8 ng/ml.

Conclusions

This study did not provide evidence for the efficacy of ziprasidone in the treatment of an acute exacerbation of schizophrenia or schizoaffective disorder. One possible reason for these negative results is that the baseline scores in this study were lower (i.e. subjects may have been less ill) than baseline scores in studies with more positive results.

7.2.6 Other Studies

Study 101 was a four week, double-blind, haloperidol controlled trial conducted in six US centers. Ninety subjects diagnosed with schizophrenia and schizoaffective disorder were randomized to one of 5 groups: 1) ziprasidone 2 mg bid, 2) 5 mg bid, 3) 20 mg bid, 4) 80 mg bid, or 5) haloperidol 15 mg. Efficacy variables included were the BPRS, CGI, NGI, and Nurses Observation Scale for Inpatient Evaluation (NOSIE). In the protocol, a primary efficacy variable was only identified as the changes from baseline to last observation. Results from this study do not support the efficacy of ziprasidone, because no differences were found when comparing each treatment with the lowest dosage group.

7.2.7 Pediatric Studies

Study 122 was a double blind, placebo controlled, 8 week flexible dose (maximum: 20 mg bid ziprasidone) pilot study in 16 pediatric subject (ages 7-16) with Tourette's Syndrome to test the effectiveness of ziprasidone in treating their symptoms of Tourette's Syndrome. Results showed that there was statistical significance seen in one primary efficacy variable (Yale Global Tic Severity Scale), but statistical significance was not demonstrated in the other primary efficacy variable (Clinical Global Impression Severity Scale for TS) when comparing improvement of subjects in the ziprasidone treatment group with placebo .

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 (PANSS total, PANSS negative, BPRS [BPRSd] total, BPRS [BPRSd] core items, CGI-S, CGI-I).

7.3.2 Choice of Dose

In the fifty-two week study 303, all doses (ziprasidone 20 mg bid, 40 mg bid, and 80 mg bid) tested were shown to be efficacious when compared to placebo. However, in study 106, statistical significance was seen in this four week study in the ziprasidone 60 mg bid group, and not in the ziprasidone 20 mg bid group. Study 114 was able to show statistically significant improvement at doses of ziprasidone 40 mg bid and 80 mg bid. The results of study 115 were supportive of efficacy in all doses tested (ziprasidone 20 mg bid, 60 mg bid, and 100 mg bid) at week six. Utilizing results from study 115, the sponsor was able to statistically show a dose response relationship when comparing all doses with placebo; however, the actual numerical differences seen between doses in the efficacy variable scores resembled more of a plateau phenomenon. Therefore, it can not be definitively concluded that increasing the dose clinically would increase the efficacy of this drug.

The drug was administered post-prandial in all studies.

The sponsor has recommended a daily dose of ziprasidone 40 mg bid administered with food. The proposed labeling includes suggestions to increase the dosage to 80 mg bid for some patients and that doses

above 80 mg bid were not shown to be more efficacious than 100 mg bid. This information accurately reflects the findings from these efficacy studies, but the sponsor does not mention that for some patients ziprasidone 20 mg bid proved to be efficacious.

7.3.3. Duration of Treatment

Both six week studies reviewed (114 and 115) demonstrated better efficacy results than the four week studies (106 and 104). It appears that the longer trials of six weeks had a better treatment outcome for psychotic symptoms. The proposed labeling does not address the issue of what time period constitutes a sufficient trial.

Study 303 shows that, after 52 weeks, this drug continues to be effective in the treatment of psychosis. As discussed previously, this trial is not useful with respect to evaluating relapse prevention.

7.4 Conclusions Regarding Efficacy Data

Ziprasidone has been proven to be efficacious in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder in more than one well controlled study. Results of the a year long study have shown that responders of ziprasidone in this trial had fewer psychotic symptoms compared to placebo, but it is unclear if the sponsor's definition of prevention is accurate enough to make a claim of relapse prevention.

8.0 Integrated Review of Safety

8.1 Methods and Findings for Safety Review

The sponsor submitted the integrated safety data base of Phase II/III studies and a safety update for review. The electronic submission did not include the ability to manipulate safety data and the review was dependent on the sponsor's compilation of data into tables. The safety update and Integrated Safety Summary (ISS) did not always include needed summary information and a careful review of the text was required. There was some additional information from Japanese studies which was not a part of the integrated safety data base, but is referred to when a serious event emerged. The main focus of the review was on the Phase II/III integrated safety data base to identify significant adverse events. To examine for common adverse events, more emphasis was placed on safety data pooled from the placebo controlled studies which were of similar duration (Studies 104, 106, 114, 115) to allow for comparator control. The only other placebo controlled study was the 52 week study 303 which was examined within the integrated safety data base and provided data on events occurring over a longer period of time.

Amongst the data submitted, there were several subjects listed as being in blinded groups in the safety update; the sponsor was able to reveal the specific treatment group when it was requested. Subjects in blinded groups were included in the calculations of subject years exposure.

There were 2140 subjects exposed to ziprasidone that were included in the original submission (cut-off date 10/31/96); data on an additional 425 subjects taking ziprasidone was in the safety update (cut off date 5/15/97). Therefore, the total integrated safety data base recounted the experience of 2565 psychotic patients who were medicated with ziprasidone. When calculating subject-years exposure, the sponsor chose to include the additional studies Study 120 (for dementia: n=12) and Study 105 (IM ziprasidone: n=11) despite their not being part of the integrated safety data base. Including these additional studies, the exposure time calculated by the sponsor is 772 subject-years based on a total of 2588 subjects. In the 3/20/98 submission, the sponsor submitted a recalculated patient exposure time with a cut-off date of December 31, 1997 based on 2993 subjects which totaled 1189 subject years of exposure to ziprasidone. **For the purposes of this review, the calculation of subjects years exposure will be based on the figure of 772 subject-years (from the safety update of 8/29/97), because the report of December 31, 1997**

did not include safety data for review. Please refer to Section 5.0 for further details of subject exposure information.

Individual subjects will be referred to by their study subject number. This review will omit the first three numbers (128) which denote that the study was conducted in the Pfizer Central Research. Also omitted will be the first zero in each subject number. In the subject number presented, the first three digits indicate the number of the study in which the subject participated. Subjects were reassigned numbers when they entered an extension study; whenever relevant, both numbers will be listed.

8.1.1 Deaths

Please refer to Appendix 8.1.1.1 for a full list of all deaths known to have occurred in subjects ever exposed to ziprasidone. As of the sponsor's cut off date of May 15, 1997 in the safety update, there have been a total of 32 subjects taking ziprasidone who have died; this includes one death (Subject JP-95-601162-02) which occurred in a Japanese study which is not considered part of the integrated safety data base. As of the sponsor's submission of 3/20/98, the sponsor reports that there was a total of 35 deaths as of 12/31/97); however, this submission was not accompanied by any supporting data. Therefore, this review can only discuss **deaths as of 5/15/97.**

Eighteen deaths occurred within 30 days or less of the subjects' discontinuation of ziprasidone, **eight** of them could be considered as sudden unexpected deaths in which the subjects were either found dead or died within 24 hours of onset of their symptoms associated with death. Of these eight deaths, it seems that only **one** case (115-6940394) may be determined to be temporally unrelated to the use of ziprasidone; this subject died 29 days after discontinuing ziprasidone and was being treated with risperidone at the time of death. [Note: the sponsor included an additional sudden unexpected death after the May 15, 1997 cut-off (in 12/31/97 report: submitted 3/20/98), but did not submit any data regarding this death; therefore, this additional sudden death will not be discussed in this review]. **There were no sudden unexpected deaths in the placebo group** in which the subjects were either found dead or died within 24 hours of onset of their symptoms associated with death (the sponsor refers to one sudden unexpected death in the placebo group in the submission of 2/13/98; however, this was unable to be confirmed by review of the safety data base.).

Of the other seven subjects who died suddenly, **two** subjects died of undetermined causes: 1) Subject 304E-1930379, a 52 year old male with schizophrenia died while taking a nap; 2) Subject 108-5920750, a 39 year old female with schizophrenia was found dead with a cause not clearly determined; the sponsor offered speculation regarding her diabetic and alcohol use history to explain this death. The sponsor's CRFs did not include autopsy reports for these subjects.

Three of the subjects who experienced a sudden death were reported on autopsy to have symptoms related to cardiopulmonary systems: 1) Subject 108-6070305 was a 46 year old male with schizophrenia whose death was attributed to acute and chronic asthmatic bronchitis and granulomatous myocarditis, 2) Subject 105-5340021 was a 70 year old female with dementia who died by cardiopulmonary arrest attributed to arteriosclerotic cardiovascular disease, and 3) Subject 116B-5080001 was a 54 year old male with schizophrenia who was found dead in his hospital bed with an autopsy showing COPD, cardiac hypertrophy, and diffuse atherosclerosis.

One subject (302E-3190375), a 48 year old male with schizophrenia was found dead; he had a history of seizures and polydipsia, and exhibited hypertension and tachycardia during his treatment with ziprasidone. An autopsy was not included in the NDA submission.

Subject 308-0350003, a 63 year old male with schizophrenia collapsed in a "lunch club." The cause of death was determined to be a rupture of an abdominal aortic aneurysm and gross diffuse atherosclerosis.