CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-825/S034

Trade Name: Geodon

Generic Name: ziprasidone HCl

Sponsor: Pfizer, Inc.

Approval Date: November 20, 2009

Indications: for the maintenance treatment of bipolar disorder, as an adjunct to lithium or valproate.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20825/S-034 **SUPPLEMENT APPROVAL**

Pfizer Inc.
Attention: Mr. Robert B. Clark
Vice President, U.S. Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your supplemental new drug application dated December 19, 2008, received January 21, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Geodon, (ziprasidone HCl) capsules.

We acknowledge receipt of your submissions dated March 6, 2009, April 10, 2009, September 8, 2009 and November 3, 2009.

This "Prior Approval" supplemental new drug application provides for the use of Geodon (ziprasidone HCl) capsules for the maintenance treatment of bipolar disorder, as an adjunct to lithium or valproate.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm155657.htm that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **SPL for approved sNDA 20-825/S-034.**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Terry Harrison, Pharm.D., Regulatory Project Manager, at (301) 796-2770.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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

/s/

THOMAS P LAUGHREN
11/20/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GEODON safely and effectively. See full prescribing information for GEODON.

GEODON (ziprasidone HCl) capsules
GEODON (ziprasidone mesylate) injection for intramuscular use
Initial U.S. Approval: 2001

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo treatment (5.1)**
- **GEODON is not approved for elderly patients with dementia-related psychosis (5.1)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions:
Leukopenia, Neutropenia, and Agranulocytosis 8/2009
Indications and Usage: Bipolar Disorder Maintenance treatment (as an adjunct to lithium or valproate) [1.2]
Dosage and Administration: Bipolar Disorder Maintenance treatment (as an adjunct to lithium or valproate) [2.2]

----------INDICATIONS AND USAGE----------
GEODON is an atypical antipsychotic. In choosing among treatments, prescribers should be aware of the capacity of GEODON to prolong the QT interval and may consider the use of other drugs first (5.2)
GEODON is indicated as an oral formulation for the:
Treatment of schizophrenia. (1.1)
- Adults: Efficacy was established in four 4-6 week trials and one maintenance trial in adult patients with schizophrenia (14.1)

Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder (1.2)
- Adults: Efficacy was established in two 3-week trials in adult patients with manic or mixed episodes. (14.2)

Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate. (1.2)
- Adults: Efficacy was established in one maintenance trial in adult patients. (14.2)

GEODON as an intramuscular injection is indicated for the:
Acute treatment of agitation in schizophrenic patients. (1.3)
- Adults: Efficacy was established in two short-term trials in agitated patients with schizophrenia. (1.3)

----------DOSAGE AND ADMINISTRATION----------
Give oral doses with food.
• Schizophrenia: Initiate at 20 mg twice daily. Daily dosage may be adjusted up to 80 mg twice daily. Dose adjustments should occur at intervals of not less than 2 days. Safety and efficacy has been demonstrated in doses up to 100 mg twice daily. The lowest effective dose should be used. (2.1)
• Acute treatment of manic/mixed episodes of bipolar I disorder: Initiate at 40 mg twice daily. Increase to 60 mg or 80 mg twice daily on day 2 of treatment. Subsequent dose adjustments should be based on tolerability and efficacy within the range of 40-80 mg twice daily. (2.2)
• Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate: Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40-80 mg twice daily. (2.2)
• Acute treatment of agitation associated with schizophrenia (intramuscular administration): 10 mg-20 mg up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every 2 hours. Doses of 10 mg may be administered every 2 hours. Doses of 20 mg may be administered every 4 hours (2 3)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 20 mg, 40 mg, 60 mg, and 80 mg (3)
- Intramuscular injection: 20 mg/mL single-use vials (3)

----------CONTRAINDICATIONS----------
- Do not use in patients with a known history of QT prolongation (4 1)
- Do not use in patients with recent acute myocardial infarction (4.1)
- Do not use in patients with uncompensated heart failure (4.1)
- Do not use in combination with other drugs that have demonstrated QT prolongation (4.1)
- Do not use in patients with known hypersensitivity to ziprasidone (4.2)

----------WARNINGS AND PRECAUTIONS----------
- *QT Interval Prolongation*: GEODON use should be avoided in patients with bradycardia, hypokalemia or hypomagnesemia, congenital prolongation of the QT interval, or in combination with other drugs that have demonstrated QT prolongation (5.2)
- *Neuroleptic Malignant Syndrome* (NMS): Potentially fatal symptom complex has been reported with antipsychotic drugs. Manage with immediate discontinuation of drug and close monitoring. (5.3)
- *Tardive Dyskinesia*: May develop acutely or chronically (5.4)
- *Hyperglycemia and Diabetes Mellitus* (DM): Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. When starting treatment, patients with DM risk factors should undergo blood glucose testing before and during treatment (5.5)
- *Rash*: Discontinue in patients who develop a rash without an identified cause (5.6)
- *Orthostatic Hypotension*: Use with caution in patients with known cardiovascular or cerebrovascular disease (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis* has been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue Geodon at the first sign of a decline in WBC in the absence of other causative factors.
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold (5.8)
- *Potential for Cognitive and Motor impairment*: Patients should use caution when operating machinery (5.11)
- *Suicide*: Closely supervise high-risk patients (5.14)

----------ADVERSE REACTIONS----------
Commonly observed adverse reactions (incidence ≥5% and at least twice the incidence for placebo) were**:**
- *Schizophrenia*: Somnolence, respiratory tract infection (6.1)
- *Manic and Mixed Episodes Associated with Bipolar Disorder*: Somnolence, extrapyramidal symptoms, dizziness, akathisia, abnormal vision, asthenia, vomiting (6.1)
- *Intramuscular administration* (≥5% and at least twice the lowest intramuscular ziprasidone group): Headache, nausea, somnolence (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Ziprasidone should not be used in combination with other drugs that have demonstrated QT prolongation (4.1, 7.3)
- The absorption of ziprasidone is increased up to two-fold in the presence of food (7.9)
- The full prescribing information contains additional drug interactions (7).

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy*: Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk (8.1).
- *Nursing Mothers*: Breast feeding is not recommended (8.3)
- *Pediatric Use*: Safety and effectiveness for pediatric patients has not been established (8.4)
- *Renal Impairment* Intramuscular ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration (8.10)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [X/XXXX]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis [*see Warnings and Precautions (5.1)]*).

1 INDICATIONS AND USAGE

GEODON is indicated for the treatment of schizophrenia, as monotherapy for the acute treatment of bipolar manic or mixed episodes, and as an adjunct to lithium or valproate for the maintenance treatment of bipolar disorder. GEODON intramuscular is indicated for acute agitation in schizophrenic patients.
When deciding among the alternative treatments available for the condition needing treatment, the prescriber should consider the finding of ziprasidone's greater capacity to prolong the QT/QTc interval compared to several other antipsychotic drugs [*see Warnings and Precautions (5.2*)]. Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia, and sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether ziprasidone will cause torsade de pointes or increase the rate of sudden death is not yet known *[see Warnings and Precautions (5.2)]*

Schizophrenia

Geodon is indicated for the treatment of schizophrenia. The efficacy of oral ziprasidone was established in four short-term (4- and 6-week) controlled trials of adult schizophrenic inpatients and in one maintenance trial of stable adult schizophrenic inpatients *[see Clinical Studies (14.1)]*.

1.2 Bipolar I Disorder

Geodon is indicated as monotherapy for the acute treatment of manic or mixed episodes associated with bipolar I disorder. Efficacy was established in two 3-week monotherapy studies in adult patients. *[see Clinical Studies (14.2)]*.
Geodon is indicated as an adjunct to lithium or valproate for the maintenance treatment of bipolar I disorder. Efficacy was established in a maintenance trial in adult patients. The efficacy of Geodon as monotherapy for the maintenance treatment of bipolar I disorder has not been systematically evaluated in controlled clinical trials. [see Clinical Studies (14.2)].

1.3 Acute Agitation in Schizophrenic Patients

GEODON intramuscular is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of agitation. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single day controlled trials of agitated schizophrenic inpatients. *[see Clinical Trials (14.1)]*

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Schizophrenic patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Dose Selection

GEODON Capsules should be administered at an initial daily dose of 20 mg twice daily with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg twice daily. Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state is achieved within 1 to 3 days. In order to ensure use of the lowest effective dose, patients should ordinarily be observed for improvement for several weeks before upward dosage adjustment.

Efficacy in schizophrenia was demonstrated in a dose range of 20 mg to 100 mg twice daily in short-term, placebo-controlled clinical trials. There were trends toward dose response within the range of 20 mg to 80 mg twice daily, but results were not consistent. An increase to a dose greater than 80 mg twice daily is not generally recommended. The safety of doses above 100 mg twice daily has not been systematically evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Maintenance Treatment

While there is no body of evidence available to answer the question of how long a patient treated with ziprasidone should remain on it, a maintenance study in patients who had been symptomatically stable and then randomized to continue ziprasidone or switch to placebo demonstrated a delay in time to relapse for patients receiving Geodon. *[see Clinical Studies (14.1)]*. No additional benefit was demonstrated for doses above 20 mg twice daily. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.2 Bipolar I Disorder

Acute Treatment of Manic or Mixed Episodes

Dose Selection--Oral ziprasidone should be administered at an initial daily dose of 40 mg twice daily with food. The dose may then be increased to 60 mg or 80 mg twice daily on the second day of treatment and subsequently adjusted on the basis of tolerance and efficacy within the range 40 mg-80 mg twice daily. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg *[see Clinical Studies (14.2)]*.

Maintenance Treatment (as an adjunct to lithium or valproate)

Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40 mg-80 mg twice daily with food. Patients should be periodically reassessed to determine the need for maintenance treatment. *[see Clinical Studies (14.2)]*

2.3 Acute Treatment of Agitation in Schizophrenia

Intramuscular Dosing

The recommended dose is 10 mg to 20 mg administered as required up to a maximum dose of 40 mg per day. Doses of 10 mg may be administered every two hours; doses of 20 mg may be administered every four hours up to a maximum of 40 mg/day. Intramuscular administration of ziprasidone for more than three consecutive days has not been studied.

If long-term therapy is indicated, oral ziprasidone hydrochloride capsules should replace the intramuscular administration as soon as possible.

Since there is no experience regarding the safety of administering ziprasidone intramuscular to schizophrenic patients already taking oral ziprasidone, the practice of co-administration is not recommended.

Ziprasidone intramuscular is intended for intramuscular use only and should not be administered intravenously.

Intramuscular Preparation for Administration

GEODON for Injection (ziprasidone mesylate) should only be administered by intramuscular injection and should not be administered intravenously. Single-dose vials require reconstitution prior to administration.

Add 1.2 mL of Sterile Water for Injection to the vial and shake vigorously until all the drug is dissolved. Each mL of reconstituted solution contains 20 mg ziprasidone. To administer a 10 mg dose, draw up 0.5 mL of the reconstituted solution. To administer a 20 mg dose, draw up 1.0 mL of the reconstituted solution. Any unused portion should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final solution. This medicinal product must not be mixed with other medicinal products or solvents other than Sterile Water for Injection. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.4 Dosing in Special Populations

Oral Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment. Geodon is not approved for use in children or adolescents.

Intramuscular Ziprasidone intramuscular has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function. Dosing adjustments are not required on the basis of gender or race *[see Use in Specific Populations (8)]*.

3 DOSAGE FORMS AND STRENGTHS

GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with "Pfizer" and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON Capsules	
Capsule Strength (mg)	Imprint
20	396
40	397
60	398
80	399

GEODON for Injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[see Dosage and Administration (2.3)]*. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

4 CONTRAINDICATIONS

4.1 QT Prolongation

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

- in patients with a known history of QT prolongation (including congenital long QT syndrome)
- in patients with recent acute myocardial infarction
- in patients with uncompensated heart failure

Pharmacokinetic/pharmacodynamic studies between ziprasidone and other drugs that prolong the QT interval have not been performed. An additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with:

- dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.
- other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning *[see Warnings and Precautions (5.2)]*.

4.2 Hypersensitivity

Ziprasidone is contraindicated in individuals with a known hypersensitivity to the product.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON is not approved for the treatment of dementia-related psychosis. *[see Boxed Warning]*

5.2 QT Prolongation and Risk of Sudden Death

Ziprasidone use should be avoided in combination with other drugs that are known to prolong the QTc interval [*see Contraindications (4.1), Drug Interactions (7.4)]*. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias *[see Contraindications (4)]*.

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

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

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

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received GEODON and 1/440 (0.23%) patients who received placebo revealed QTc intervals exceeding the potentially clinically relevant threshold of 500 msec. In the ziprasidone-treated patients, neither case suggested a role of ziprasidone. One patient had a history of prolonged QTc and a screening measurement of 489 msec; QTc was 503 msec during ziprasidone treatment. The other patient had a QTc of 391 msec at the end of treatment with ziprasidone and upon switching to thioridazine experienced QTc measurements of 518 and 593 msec.

Some drugs that prolong the QT/QTc interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QTc prolongations may also

increase risk, or increase it in susceptible individuals**.** Although torsade de pointes has not been observed in association with the use of ziprasidone in premarketing studies and experience is too limited to rule out an increased risk, there have been rare post-marketing reports (in the presence of multiple confounding factors) *[see Adverse Reactions (6.2)]*.

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

As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking ziprasidone at recommended doses. The premarketing experience for ziprasidone did not reveal an excess risk of mortality for ziprasidone compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, ziprasidone's larger prolongation of QTc length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for ziprasidone than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products *[see Indications and Usage (1)]*.

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

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

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

5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

5.4 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ziprasidone should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ziprasidone, drug discontinuation should be considered. However, some patients may require treatment with ziprasidone despite the presence of the syndrome.

5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON. Although fewer patients have been treated with GEODON, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies, which did not include GEODON, suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics included in these studies. Because GEODON was not marketed at the time these studies were performed, it is not known if GEODON is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

5.6 Rash

In premarketing trials with ziprasidone, about 5% of patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was related to dose of ziprasidone, although the finding might also be explained by the longer exposure time in the higher dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly with adjunctive treatment with antihistamines or steroids and/or upon discontinuation of ziprasidone, and all patients experiencing these reactions were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

5.7 Orthostatic Hypotension

Ziprasidone may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of the patients treated with ziprasidone.

Ziprasidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

5.8 **Leukopenia, Neutropenia, and Agranulocytosis**

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue Geodon at the first sign of decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue Geodon and have their WBC followed until recovery.

5.9 Seizures

During clinical trials, seizures occurred in 0.4% of patients treated with ziprasidone. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. As with other antipsychotic drugs, ziprasidone should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.10 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Ziprasidone and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Boxed Warning]*.

5.11 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, ziprasidone elevates prolactin levels in humans. Increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice; a similar effect was not observed in rats *[see Nonclinical Toxicology (13.1)]*. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

5.12 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction in patients treated with ziprasidone. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of patients on ziprasidone compared to 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since ziprasidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that ziprasidone therapy does not affect them adversely.

5.13 Priapism

One case of priapism was reported in the premarketing database. While the relationship of the reaction to ziprasidone use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that ziprasidone may share this capacity. Severe priapism may require surgical intervention.

5.14 Body Temperature Regulation

Although not reported with ziprasidone in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ziprasidone for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

5.15 Suicide

The possibility of a suicide attempt is inherent in psychotic illness or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ziprasidone should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

5.16 Patients with concomitant illnesses

Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.6),(8.7)]*

Ziprasidone has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QTc prolongation and orthostatic hypotension with ziprasidone, caution should be observed in cardiac patients *[see Warnings and Precautions (5.2), (5.7)]*

5.17 Laboratory Tests

Patients being considered for ziprasidone treatment that are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be replaced before proceeding with treatment. Patients who are started on diuretics during Ziprasidone therapy need periodic monitoring of serum potassium and magnesium. Ziprasidone should be discontinued in patients who are found to have persistent QTc measurements >500 msec. *[see Warnings and Precautions (5.2)]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical trials for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to one or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple-dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years. These patients include: (1) 4331 patients who participated in multiple-dose trials, predominantly in schizophrenia, representing approximately 1698 patient-years of exposure as of February 5, 2000; and (2) 472 patients who participated in bipolar mania trials representing approximately 133 patient-years of exposure. An additional 127 patients

with bipolar disorder participated in a long-term maintenance treatment study representing approximately 74.7 patient-years of exposure to ziprasidone. The conditions and duration of treatment with ziprasidone included open-label and double-blind studies, inpatient and outpatient studies, and short-term and longer-term exposure.

Clinical trials for intramuscular ziprasidone included 570 patients and/or normal subjects who received one or more injections of ziprasidone. Over 325 of these subjects participated in trials involving the administration of multiple doses.

Adverse reactions during exposure were obtained by collecting voluntarily reported adverse experiences, as well as results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Oral Ziprasidone

The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which ziprasidone was administered in doses ranging from 10 to 200 mg/day.

Commonly Observed Adverse Reactions in Short Term-Placebo-Controlled Trials

The following adverse reactions were the most commonly observed adverse reactions associated with the use of ziprasidone (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (ziprasidone incidence at least twice that for placebo):

Schizophrenia trials (*see Table 1*)

- Somnolence
- Respiratory Tract Infection

Bipolar trials (*see Table 2)*

- Somnolence
- Extrapyramidal Symptoms which includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.
- Dizziness which includes the adverse reaction terms dizziness and lightheadedness.
- Akathisia
- Abnormal Vision
- Asthenia
- Vomiting

SCHIZOPHRENIA

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone

Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 2.2% (6/273) on placebo. The most common reaction associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients *[See Warnings and Precautions (5.6)]*.

Adverse Reactions Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 6 weeks) in predominantly patients with schizophrenia, including only those reactions that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 1: Treatment-Emergent Adverse Reaction Incidence In Short-Term Oral Placebo-Controlled Trials – Schizophrenia

	Percentage of Patients Reporting Reaction	
Body System/Adverse Reaction	Ziprasidone (N=702)	Placebo (N=273)
Body as a Whole		
Asthenia	5	3
Accidental Injury	4	2
Chest Pain	3	2
Cardiovascular		
Tachycardia	2	1
Digestive		
Nausea	10	7
Constipation	9	8
Dyspepsia	8	7
Diarrhea	5	4
Dry Mouth	4	2
Anorexia	2	1
Nervous		
Extrapyramidal Symptoms*	14	8
Somnolence	14	7
Akathisia	8	7
Dizziness**	8	6
Respiratory		
Respiratory Tract Infection	8	3
Rhinitis	4	2

Cough Increased	3	1
Skin and Appendages		
Rash	4	3
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	3	2

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 5% in schizophrenia trials.

** Dizziness includes the adverse reaction terms dizziness and lightheadedness.

Dose Dependency of Adverse Reactions in Short-Term, Fixed-Dose, Placebo-Controlled Trials
An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision.

Extrapyramidal Symptoms (EPS) - The incidence of reported EPS (which included the adverse reaction terms extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching) for ziprasidone-treated patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo.

Dystonia - *Class Effect* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Vital Sign Changes - Ziprasidone is associated with orthostatic hypotension *[see Warnings and Precautions (5.7)*

Weight Gain - The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 4- and 6-week placebo-controlled schizophrenia clinical trials, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. In this set of clinical trials, weight gain was reported as an adverse reaction in 0.4% and 0.4% of ziprasidone and placebo patients, respectively. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain (>7% of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a “low” baseline BMI, no mean change for patients with a “normal” BMI, and a 1.3 kg mean weight loss for patients who entered the program with a “high” BMI.

ECG Changes - Ziprasidone is associated with an increase in the QTc interval *[see Warnings and Precautions (5.2)]*. In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients.

Other Adverse Reactions Observed During the Premarketing Evaluation of Oral Ziprasidone
Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone in schizophrenia trials at multiple doses >4 mg/day within the database of 3834 patients. All reported reactions are included except those already listed in Table 1 or elsewhere in labeling, those reaction terms that were so general as to be uninformative, reactions reported only once and that did not have a substantial probability of being acutely life-threatening, reactions that are part of the illness being treated or are otherwise common as background reactions, and reactions considered unlikely to be drug-related. It is important to emphasize that, although the reactions reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions:

Frequent - adverse reactions occurring in at least 1/100 patients (≥1.0% of patients) (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing);

Infrequent - adverse reactions occurring in 1/100 to 1/1000 patients (in 0.1-1.0% of patients)

Rare – adverse reactions occurring in fewer than 1/1000 patients (<0.1% of patients).

Body as a Whole
Frequent abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident

Cardiovascular System
Frequent tachycardia, hypertension, postural hypotension

Infrequent bradycardia, angina pectoris, atrial fibrillation

Rare first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis

Digestive System
Frequent anorexia, vomiting

Infrequent rectal hemorrhage, dysphagia, tongue edema

Rare gum hemorrhage, jaundice, fecal impaction, gamma glutamyl

transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena

Endocrine
Rare hypothyroidism, hyperthyroidism, thyroiditis

Hemic and Lymphatic System
Infrequent anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy

Rare thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia

Metabolic and Nutritional Disorders
Infrequent thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia

Rare BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis

Musculoskeletal System
Frequent myalgia

Infrequent tenosynovitis

Rare myopathy

Nervous System
Frequent agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy

Infrequent paralysis

Rare myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus

Respiratory System
Frequent dyspnea

Infrequent pneumonia, epistaxis

Rare hemoptysis, laryngismus

Skin and Appendages
Infrequent maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash

Special Senses
Frequent fungal dermatitis

Infrequent conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia

Rare eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis

Urogenital System
Infrequent impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria

Rare gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage

BIPOLAR DISORDER

Acute Treatment of Manic or Mixed Episodes

Adverse Reactions Associated with Discontinuation of Treatment in Short Term, Placebo-Controlled Trials
Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse reaction, compared with about 3.7% (5/136) on placebo. The most common reactions associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these reactions among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse reactions.

Adverse Reactions Occurring at an Incidence of 2% or More Among Ziprasidone-Treated Patients in Short-Term, Oral, Placebo-Controlled Trials
Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy (up to 3 weeks) in patients with bipolar mania, including only those reactions that occurred in 2% or more of patients treated with ziprasidone and for which the incidence in patients treated with ziprasidone was greater than the incidence in placebo-treated patients.

Table 2: Treatment-Emergent Adverse Reactions Incidence In Short-Term Oral Placebo-Controlled Trials – Manic and Mixed Episodes Associated with Bipolar Disorder

	Percentage of Patients Reporting Reaction	
Body System/Adverse Reaction	Ziprasidone (N=279)	Placebo (N=136)
Body as a Whole		
Headache	18	17
Asthenia	6	2
Accidental Injury	4	1
Cardiovascular		
Hypertension	3	2
Digestive		
Nausea	10	7
Diarrhea	5	4
Dry Mouth	5	4
Vomiting	5	2
Increased Salivation	4	0
Tongue Edema	3	1
Dysphagia	2	0
Musculoskeletal		
Myalgia	2	0
Nervous		
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Anxiety	5	4
Hypesthesia	2	1
Speech Disorder	2	0
Respiratory		
Pharyngitis	3	1
Dyspnea	2	1
Skin and Appendages		
Fungal Dermatitis	2	1
Special Senses		
Abnormal Vision	6	3

* Extrapyramidal Symptoms includes the following adverse reaction terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse reactions occurred individually at an incidence greater than 10% in bipolar mania trials.
** Dizziness includes the adverse reaction terms dizziness and lightheadedness.

Explorations for interactions on the basis of gender did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of this demographic factor.

Weight Gain – During a 6-month placebo-controlled bipolar maintenance study in adults with ziprasidone as an adjunct to lithium or valproate, the incidence of clinically significant weight gain (≥7% of body weight) during the double-blind period was 5.6% for both ziprasidone and placebo treatment groups who completed the 6 months of observation for relapse. Interpretation of these findings should take into consideration that only patients who adequately tolerated ziprasidone entered the maintenance phase of this study, and there were substantial dropouts by the 6 month endpoint.

INTRAMUSCULAR ZIPRASIDONE

Adverse Reactions Occurring at an Incidence of 1% or More Among Ziprasidone-Treated Patients in Short-Term Trials of Intramuscular Ziprasidone

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone (incidence of 5% or greater) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%).

Table 4: Treatment-Emergent Adverse Reaction Incidence In Short-Term Fixed-Dose Intramuscular Trials

	Percentage of Patients Reporting Reaction		
Body System/Adverse Reaction	Ziprasidone 2 mg (N=92)	Ziprasidone 10 mg (N=63)	Ziprasidone 20 mg (N=41)
Body as a Whole			
Headache	3	13	5
Injection Site Pain	9	8	7
Asthenia	2	0	0
Abdominal Pain	0	2	0
Flu Syndrome	1	0	0
Back Pain	1	0	0
Cardiovascular			
Postural Hypotension	0	0	5
Hypertension	2	0	0
Bradycardia	0	0	2
Vasodilation	1	0	0
Digestive			
Nausea	4	8	12
Rectal Hemorrhage	0	0	2
Diarrhea	3	3	0
Vomiting	0	3	0
Dyspepsia	1	3	2
Anorexia	0	2	0
Constipation	0	0	2
Tooth Disorder	1	0	0
Dry Mouth	1	0	0
Nervous			
Dizziness	3	3	10
Anxiety	2	0	0
Insomnia	3	0	0
Somnolence	8	8	20
Akathisia	0	2	0
Agitation	2	2	0
Extrapyramidal Syndrome	2	0	0
Hypertonia	1	0	0
Cogwheel Rigidity	1	0	0
Paresthesia	0	2	0
Personality Disorder	0	2	0
Psychosis	1	0	0
Speech Disorder	0	2	0
Respiratory			
Rhinitis	1	0	0
Skin and Appendages			
Furunculosis	0	2	0
Sweating	0	0	2
Urogenital			
Dysmenorrhea	0	2	0
Priapism	1	0	0

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of GEODON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following : *Cardiac Disorders* Tachycardia, torsade de pointes (in the presence of multiple confounding factors), *[See Warnings and Precautions (5.2)]*; *Digestive System Disorders* Swollen Tongue; *Reproductive System and Breast Disorders* Galactorrhea, priapism; *Nervous System Disorders* Facial Droop, neuroleptic malignant syndrome, serotonin

syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders* Insomnia, mania/hypomania; *Skin and subcutaneous Tissue Disorders* Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders* Enuresis, urinary incontinence; *Vascular Disorders* Postural hypotension, syncope.

7 DRUG INTERACTIONS

Drug-drug interactions can be pharmacodynamic (combined pharmacologic effects) or pharmacokinetic (alteration of plasma levels). The risks of using ziprasidone in combination with other drugs have been evaluated as described below. All interactions studies have been conducted with oral ziprasidone. Based upon the pharmacodynamic and pharmacokinetic profile of ziprasidone, possible interactions could be anticipated:

7.1 Metabolic Pathway

Approximately two-thirds of ziprasidone is metabolized via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase. Less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation.

7.2 In Vitro Studies

An *in vitro* enzyme inhibition study utilizing human liver microsomes showed that ziprasidone had little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and thus would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. There is little potential for drug interactions with ziprasidone due to displacement *[See Clinical Pharmacology (12.3)]*.

7.3 Pharmacodynamic Interactions

Ziprasidone should not be used with any drug that prolongs the QT interval *[See Contraindications (4.1)]*.

Given the primary CNS effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting drugs.

Because of its potential for inducing hypotension, ziprasidone may enhance the effects of certain antihypertensive agents.

Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

7.4 Pharmacokinetic Interactions

- Carbamazepine

Carbamazepine is an inducer of CYP3A4; administration of 200 mg twice daily for 21 days resulted in a decrease of approximately 35% in the AUC of ziprasidone. This effect may be greater when higher doses of carbamazepine are administered.

Ketoconazole

Ketoconazole, a potent inhibitor of CYP3A4, at a dose of 400 mg QD for 5 days, increased the AUC and Cmax of ziprasidone by about 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.

- Cimetidine

Cimetidine at a dose of 800 mg QD for 2 days did not affect ziprasidone pharmacokinetics.

- Antacid

The co-administration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

7.5 Lithium

Ziprasidone at a dose of 40 mg twice daily administered concomitantly with lithium at a dose of 450 mg twice daily for 7 days did not affect the steady-state level or renal clearance of lithium. Ziprasidone dosed adjunctively to lithium in a maintenance trial of bipolar patients did not affect mean therapeutic lithium levels.

7.6 Oral Contraceptives

In vivo studies have revealed no effect of ziprasidone on the pharmacokinetics of estrogen or progesterone components. Ziprasidone at a dose of 20 mg twice daily did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

7.7 Dextromethorphan

Consistent with *in vitro* results, a study in normal healthy volunteers showed that ziprasidone did not alter the metabolism of dextromethorphan, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio.

7.8 Valproate

A pharmacokinetic interaction of ziprasidone with valproate is unlikely due to the lack of common metabolic pathways for the two drugs. Ziprasidone dosed adjunctively to valproate in a maintenance trial of bipolar patients did not affect mean therapeutic valproate levels.

7.9 Other Concomitant Drug Therapy

Population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

7.10 Food Interaction

The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C - In animal studies ziprasidone demonstrated developmental toxicity, including possible teratogenic effects at doses similar to human therapeutic doses. When ziprasidone was administered to pregnant rabbits during the period of organogenesis, an increased incidence of fetal structural abnormalities (ventricular septal defects and other cardiovascular malformations and kidney alterations) was observed at a dose of 30 mg/kg/day (3 times the MRHD of 200 mg/day on a mg/m^2 basis). There was no evidence to suggest that these developmental effects were secondary to maternal toxicity. The developmental no-effect dose was 10 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis). In rats, embryofetal toxicity (decreased fetal weights, delayed skeletal ossification) was observed following administration of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD on a mg/m^2 basis) during organogenesis or throughout gestation, but there was no evidence of teratogenicity. Doses of 40 and 160 mg/kg/day (2 and 8 times the MRHD on a mg/m^2 basis) were associated with maternal toxicity. The developmental no-effect dose was 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis).

There was an increase in the number of pups born dead and a decrease in postnatal survival through the first 4 days of lactation among the offspring of female rats treated during gestation and lactation with doses of 10 mg/kg/day (0.5 times the MRHD on a mg/m^2 basis) or greater. Offspring developmental delays and neurobehavioral functional impairment were observed at doses of 5 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis) or greater. A no-effect level was not established for these effects.

There are no adequate and well-controlled studies in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of ziprasidone on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breastfeed.

8.4 Pediatric Use

The safety and effectiveness of ziprasidone in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of ziprasidone, 2.4 percent were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to ziprasidone, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients.

Ziprasidone intramuscular has not been systematically evaluated in elderly patients (65 years and over).

8.6 Renal Impairment

Because ziprasidone is highly metabolized, with less than 1% of the drug excreted unchanged, renal impairment alone is unlikely to have a major impact on the pharmacokinetics of ziprasidone. The pharmacokinetics of ziprasidone following 8 days of 20 mg twice daily dosing were similar among subjects with varying degrees of renal impairment (n=27), and subjects with normal renal function, indicating that dosage adjustment based upon the degree of renal impairment is not required. Ziprasidone is not removed by hemodialysis.

Intramuscular ziprasidone has not been systematically evaluated in elderly patients or in patients with hepatic or renal impairment. As the cyclodextrin excipient is cleared by renal filtration, ziprasidone intramuscular should be administered with caution to patients with impaired renal function *[see Clinical Pharmacology (12)]*.

8.7 Hepatic Impairment

As ziprasidone is cleared substantially by the liver, the presence of hepatic impairment would be expected to increase the AUC of ziprasidone; a multiple-dose study at 20 mg twice daily for 5 days in subjects (n=13) with clinically significant (Childs-Pugh Class A and B) cirrhosis revealed an increase in AUC $_{0\text{-}12}$ of 13% and 34% in Childs-Pugh Class A and B, respectively, compared to a matched control group (n=14). A half-life of 7.1 hours was observed in subjects with cirrhosis compared to 4.8 hours in the control group.

8.8 Age and Gender Effects

In a multiple-dose (8 days of treatment) study involving 32 subjects, there was no difference in the pharmacokinetics of ziprasidone between men and women or between elderly (>65 years) and young (18 to 45 years) subjects. Additionally, population pharmacokinetic evaluation of patients in controlled trials has revealed no evidence of clinically significant age or gender-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for age or gender are, therefore, not recommended.

8.9 Smoking

Based on *in vitro* studies utilizing human liver enzymes, ziprasidone is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of ziprasidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any significant pharmacokinetic differences between smokers and nonsmokers.

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

Ziprasidone has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which ziprasidone will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ziprasidone misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3,240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

Adverse reactions reported with ziprasidone overdose included extrapyramidal symptoms, somnolence, tremor, and anxiety. *[see Adverse Reactions (6.2)]*

10.2 Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Intravenous access should be established, and gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

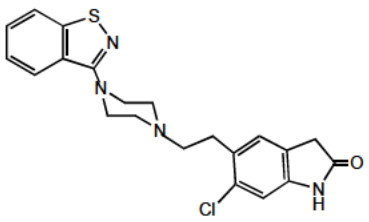
Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects that might be additive to those of ziprasidone.

Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, epinephrine and dopamine should not be used, since beta stimulation combined with α_1 antagonism associated with ziprasidone may worsen hypotension. Similarly, it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of ziprasidone, resulting in problematic hypotension.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. There is no specific antidote to ziprasidone, and it is not dialyzable. The possibility of multiple drug involvement should be considered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

GEODON is available as capsules (ziprasidone hydrochloride) for oral administration and as an injection (ziprasidone mesylate) for intramuscular use only. Ziprasidone is a psychotropic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. It has a molecular weight of 412.94 (free base), with the following chemical name: 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one. The empirical formula of $C_{21}H_{21}ClN_4OS$ (free base of ziprasidone) represents the following structural formula:



GEODON Capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Chemically, ziprasidone hydrochloride monohydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, monohydrochloride, monohydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot HCl \cdot H_2O$ and its molecular weight is 467.42. Ziprasidone hydrochloride monohydrate is a white to slightly pink powder.

GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. GEODON Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

GEODON for Injection contains a lyophilized form of ziprasidone mesylate trihydrate. Chemically, ziprasidone mesylate trihydrate is 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one, methanesulfonate, trihydrate. The empirical formula is $C_{21}H_{21}ClN_4OS \cdot CH_3SO_3H \cdot 3H_2O$ and its molecular weight is 563.09.

GEODON for Injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[See Dosage and Administration (2.3)]*. Each mL of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of ziprasidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. As with other drugs having efficacy in bipolar disorder, the mechanism of action of ziprasidone in bipolar disorder is unknown.

12.2 Pharmacodynamics

Ziprasidone exhibited high *in vitro* binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and α_1-adrenergic receptors (K_i s of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively), and moderate affinity for the histamine H_1 receptor (K_i=47 nM). Ziprasidone functioned as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and as an agonist at the $5HT_{1A}$ receptor. Ziprasidone inhibited synaptic reuptake of serotonin and norepinephrine. No appreciable affinity was exhibited for other receptor/binding sites tested, including the cholinergic muscarinic receptor (IC_{50} >1 μM). Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other therapeutic and side effects of ziprasidone. Ziprasidone's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug. Ziprasidone's antagonism of α_1-adrenergic receptors may explain the orthostatic hypotension observed with this drug.

12.3 Pharmacokinetics

Oral Pharmacokinetics

Ziprasidone's activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone are dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is predictable with multiple dosing. Elimination of ziprasidone is mainly via hepatic metabolism with a mean terminal half-life of about 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 mL/min/kg. Ziprasidone is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (<1%) or feces (<4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in two steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

Intramuscular Pharmacokinetics

Systemic Bioavailability The bioavailability of ziprasidone administered intramuscularly is 100%. After intramuscular administration of single doses, peak serum concentrations typically occur at approximately 60 minutes post-dose or earlier and the mean half-life ($T_{½}$) ranges from two to five hours. Exposure increases in a dose-related manner and following three days of intramuscular dosing, little accumulation is observed.

Metabolism and Elimination Although the metabolism and elimination of IM ziprasidone have not been systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted with ziprasidone in Long Evans rats and CD-1 mice. Ziprasidone was administered for 24 months in the diet at doses of 2, 6, or 12 mg/kg/day to rats, and 50, 100, or 200 mg/kg/day to mice (0.1 to 0.6 and 1 to 5 times the maximum recommended human dose [MRHD] of 200 mg/day on a mg/m^2 basis, respectively). In the rat study, there was no evidence of an increased incidence of tumors compared to controls. In male mice, there was no increase in incidence of tumors relative to controls. In female mice, there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested (50 to 200 mg/kg/day or 1 to 5 times the MRHD on a mg/m^2 basis). Proliferative changes in the pituitary and mammary glands of rodents have been observed following chronic administration of other antipsychotic agents and are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice at 100 and 200 mg/kg/day (or 2.5 and 5 times the MRHD on a mg/m^2 basis). Ziprasidone had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.11)]*.

Mutagenesis

Ziprasidone was tested in the Ames bacterial mutation assay, the *in vitro* mammalian cell gene mutation mouse lymphoma assay, the *in vitro* chromosomal aberration assay in human lymphocytes, and the *in vivo* chromosomal aberration assay in mouse bone marrow. There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the *in vitro* mammalian cell gene mutation assay and the *in vitro* chromosomal aberration assay in human lymphocytes.

Impairment of Fertility

Ziprasidone was shown to increase time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The effect on fertility appeared to be in the female since fertility was not impaired when males given 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis) were mated with untreated females. In a 6-month study in male rats given 200 mg/kg/day (10 times the MRHD on a mg/m^2 basis) there were no treatment-related findings observed in the testes.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of oral ziprasidone in the treatment of schizophrenia was evaluated in 5 placebo-controlled studies, 4 short-term (4- and 6-week) trials and one maintenance trial. All trials were in adult inpatients, most of whom met DSM III-R criteria for schizophrenia. Each study included 2 to 3 fixed doses of ziprasidone as well as placebo. Four of the 5 trials were able to distinguish ziprasidone from placebo; one short-term study did not. Although a single fixed-dose haloperidol arm was included as a comparative treatment in one of the three short-term trials, this single study was inadequate to provide a reliable and valid comparison of ziprasidone and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies. The Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second widely used assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS) was employed for assessing negative symptoms in one trial.

The results of the oral ziprasidone trials in schizophrenia follow:

- In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg twice daily) with placebo, only the 60 mg dose was superior to placebo on the BPRS total score and the CGI severity score. This higher dose group was not superior to placebo on the BPRS psychosis cluster or on the SANS.
- In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg twice daily) with placebo, both dose groups were superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the PANSS total and negative subscale scores. Although 80 mg twice daily had a numerically greater effect than 40 mg twice daily, the difference was not statistically significant.
- In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg twice daily) with placebo, all three dose groups were superior to placebo on the PANSS total score, the BPRS total score, the BPRS psychosis cluster, and the CGI severity score. Only the 100 mg twice daily dose group was superior to placebo on the PANSS negative subscale score. There was no clear evidence for a dose-response relationship within the 20 mg twice daily to 100 mg twice daily dose range.
- In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg twice daily), none of the dose groups was statistically superior to placebo on any outcome of interest.
- A study was conducted in stable chronic or subchronic (CGI-S $\leq$5 at baseline) schizophrenic inpatients (n=294) who had been hospitalized for not less than two months. After a 3-day single-blind placebo run-in, subjects were randomized to one of 3 fixed doses of ziprasidone (20 mg, 40 mg, or 80 mg twice daily) or placebo and observed for relapse. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of $\geq$6 (much worse or very much worse) and/or scores $\geq$6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in time to relapse, with no significant difference between the different dose groups. There were insufficient data to examine population subsets based on age and race. Examination of population subsets based on gender did not reveal any differential responsiveness.

14.2 Bipolar I Disorder

Acute Manic and Mixed Episodes Associated with Bipolar I Disorder

The efficacy of ziprasidone was established in 2 placebo-controlled, double-blind, 3-week monotherapy studies in patients meeting DSM-IV criteria for bipolar I disorder, manic or mixed episode with or without psychotic features. Primary rating instruments used for assessing manic symptoms in these trials were: (1) the Mania Rating Scale (MRS), which is derived from the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-CB) with items grouped as the Manic Syndrome subscale (elevated mood, less need for sleep, excessive energy, excessive activity, grandiosity), the Behavior and Ideation subscale (irritability, motor hyperactivity, accelerated speech, racing thoughts, poor judgment) and impaired insight; and (2) the Clinical Global Impression-Severity of Illness Scale (CGI-S), which was used to assess the clinical significance of treatment response.

The results of the oral ziprasidone trials in adult bipolar I disorder, manic/mixed episode follow**:** in a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg twice daily on Day 1 and 80 mg twice daily on Day 2. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of the study. Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 132 mg. In a second 3-week placebo-controlled trial (n=205), the dose of ziprasidone was 40 mg twice daily on Day 1. Titration within the range of 40-80 mg twice daily (in 20 mg twice daily increments) was permitted for the duration of study (beginning on Day 2). Ziprasidone was significantly more effective than placebo in reduction of the MRS total score and the CGI-S score. The mean daily dose of ziprasidone in this study was 112 mg.

Maintenance Therapy

The efficacy of ziprasidone as adjunctive therapy to lithium or valproate in the maintenance treatment of bipolar I disorder was established in a placebo-controlled trial in patients who met DSM-IV criteria for bipolar I disorder. The trial included patients whose most recent episode was manic or mixed, with or without psychotic features. In the open-label phase, patients were required to be stabilized on ziprasidone plus lithium or valproic acid for at least 8 weeks in order to be randomized. In the double-blind randomized phase, patients continued treatment with lithium or valproic acid and were randomized to receive either ziprasidone (administered twice daily totaling 80 mg to 160 mg per day) or placebo. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase. The primary endpoint in this study was time to recurrence of a mood episode (manic, mixed or depressed episode) requiring intervention, which was defined as any of the following: discontinuation due to a mood episode, clinical intervention for a mood episode (e.g., initiation of medication or hospitalization), or Mania Rating Scale score $\geq$ 18 or a MADRS score $\geq$18 (on 2 consecutive assessments no more than 10 days apart). A total of 584 subjects were treated in the open-label stabilization period. In the double-blind randomization period, 127 subjects were treated with ziprasidone, and 112 subjects were treated with placebo. Ziprasidone was superior to placebo in increasing the time to recurrence of a mood episode. The types of relapse events observed included depressive, manic, and mixed episodes. Depressive, manic, and mixed episodes accounted for 53%, 34%, and 13%, respectively, of the total number of relapse events in the study.

14.3 Acute Agitation in Schizophrenic Patients

The efficacy of intramuscular ziprasidone in the management of agitated schizophrenic patients was established in two short-term, double-blind trials of schizophrenic subjects who were considered by the investigators to be "acutely agitated" and in need of IM antipsychotic medication. In addition, patients were required to have a score of 3 or more on at least 3 of the following items of the PANSS: anxiety, tension, hostility and excitement. Efficacy was evaluated by analysis of the area under the curve (AUC) of the Behavioural Activity Rating Scale (BARS) and Clinical Global Impression (CGI) severity rating. The BARS is a seven point scale with scores ranging from 1 (difficult or unable to rouse) to 7 (violent, requires restraint). Patients' scores on the BARS at baseline were mostly 5 (signs of overt activity [physical or verbal], calms down with instructions) and as determined by investigators, exhibited a degree of agitation that warranted intramuscular therapy. There were few patients with a rating higher than 5 on the BARS, as the most severely agitated patients were generally unable to provide informed consent for participation in premarketing clinical trials.

Both studies compared higher doses of ziprasidone intramuscular with a 2 mg control dose. In one study, the higher dose was 20 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 4 hours. In the other study, the higher dose was 10 mg, which could be given up to 4 times in the 24 hours of the study, at interdose intervals of no less than 2 hours.

The results of the intramuscular ziprasidone trials follow:

(1) In a one-day, double-blind, randomized trial (n=79) involving doses of ziprasidone intramuscular of 20 mg or 2 mg, up to QID, ziprasidone intramuscular 20 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 4 hours, and by CGI severity at 4 hours and study endpoint.

(2) In another one-day, double-blind, randomized trial (n=117) involving doses of ziprasidone intramuscular of 10 mg or 2 mg, up to QID, ziprasidone intramuscular 10 mg was statistically superior to ziprasidone intramuscular 2 mg, as assessed by AUC of the BARS at 0 to 2 hours, but not by CGI severity.

16 HOW SUPPLIED/STORAGE AND HANDLING

GEODON Capsules are differentiated by capsule color/size and are imprinted in black ink with "Pfizer" and a unique number. GEODON Capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. They are supplied in the following strengths and package configurations:

GEODON Capsules			
Package Configuration	Capsule Strength (mg)	NDC Code	Imprint
Bottles of 60	20	NDC-0049-3960-60	396
Bottles of 60	40	NDC-0049-3970-60	397
Bottles of 60	60	NDC-0049-3980-60	398
Bottles of 60	80	NDC-0049-3990-60	399
Unit dose/80	20	NDC-0049-3960-41	396
Unit dose/80	40	NDC-0049-3970-41	397
Unit dose/80	60	NDC-0049-3980-41	398
Unit dose/80	80	NDC-0049-3990-41	399

GEODON Capsules should be stored at 25 C (77 F); excursions permitted to 15-30 C (59-86 F) [See USP Controlled Room Temperature].

GEODON for Injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted according to label instructions) *[see Dosage and Administration (2.3)]*. Each mL of ziprasidone mesylate for injection (when reconstituted) affords a colorless to pale pink solution that contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether β-cyclodextrin sodium (SBECD).

GEODON for Injection		
Package	Concentration	NDC Code
Single-use Vials	20 mg/mL	NDC-0049-3920-83

GEODON for Injection should be stored at 25 C (77 F); excursions permitted to 15-30 C (59-86 F) [See USP Controlled Room Temperature] in dry form. Protect from light. Following reconstitution, GEODON for Injection can be stored, when protected from light, for up to 24 hours at 15 -30 C (59 -86 F) or up to 7 days refrigerated, 2 -8 C (36 -46 F).

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling (17.3).*

Please refer to the patient package insert. To assure safe and effective use of GEODON, the information and instructions provided in the patient information should be discussed with patients.

17.1 Administration with Food

Patients should be instructed to take GEODON Capsules with food for optimal absorption. The absorption of ziprasidone is increased up to two-fold in the presence of food *[see Drug Interactions (7.8) and Clinical Pharmacology (12.3)]*.

17.2 QTc Prolongation

Patients should be advised to inform their health care providers of the following: History of QT prolongation; recent acute myocardial infarction; uncompensated heart failure; prescription of other drugs that have demonstrated QT prolongation; risk for significant electrolyte abnormalities; and history of cardiac arrhythmia *[see Contraindications (4.1) and Warnings and Precautions (5.2)]*.

Patients should be instructed to report the onset of any conditions that put them at risk for significant electrolyte disturbances, hypokalemia in particular, including but not limited to the initiation of diuretic therapy or prolonged diarrhea. In addition, patients should be instructed to report symptoms such as dizziness, palpitations, or syncope to the prescriber *[see Warnings and Precautions (5.2)]*.

17.3 FDA-Approved Patient Labeling

PATIENT SUMMARY OF INFORMATION ABOUT

GEODON® Capsules

(ziprasidone HCl)

Information for patients taking GEODON or their caregivers

This summary contains important information about GEODON. It is not meant to take the place of your doctor's instructions. Read this information carefully before you take GEODON. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about GEODON.

What Is GEODON?

GEODON is a type of prescription medicine called a psychotropic, also known as an atypical antipsychotic. GEODON can be used to treat symptoms of schizophrenia and acute manic or mixed episodes associated with bipolar disorder. GEODON can also be used as maintenance treatment of bipolar disorder when added to lithium or valproate.

Who Should Take GEODON?

Only your doctor can know if GEODON is right for you. GEODON may be prescribed for you if you have schizophrenia or bipolar disorder.

Symptoms of schizophrenia may include:

- hearing voices, seeing things, or sensing things that are not there (hallucinations)
- beliefs that are not true (delusions)
- unusual suspiciousness (paranoia)
- becoming withdrawn from family and friends

Symptoms of manic or mixed episodes of bipolar disorder may include:

- extremely high or irritable mood
- increased energy, activity, and restlessness
- racing thoughts or talking very fast
- easily distracted
- little need for sleep

If you show a response to GEODON, your symptoms may improve. If you continue to take GEODON there is less chance of your symptoms returning. Do not stop taking the capsules even when you feel better without first discussing it with your doctor.

It is also important to remember that GEODON capsules should be taken with food.

What is the most important safety information I should know about GEODON?

GEODON is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with a diagnosis of psychosis related to dementia treated with antipsychotics are at an increased risk of death when compared to patients who are treated with placebo (a sugar pill).

GEODON is an effective drug to treat the symptoms of schizophrenia and the manic or mixed episodes of bipolar disorder. However, one potential side effect is that it may change the way the electrical current in your heart works more than some other drugs. The change is small and it is not known whether this will be harmful, but some other drugs that cause this kind of change have in rare cases caused dangerous heart rhythm abnormalities**.** Because of this, GEODON should be used only after your doctor has considered this risk for GEODON against the risks and benefits of other medications available for treating schizophrenia or bipolar manic and mixed episodes.

Your risk of dangerous changes in heart rhythm can be increased if you are taking certain other medicines and if you already have certain abnormal heart conditions. Therefore, it is important to tell your doctor about any other medicines that you take, including non-prescription medicines, supplements, and herbal medicines. You must also tell your doctor about any heart problems you have or have had.

Who should NOT take GEODON?

Elderly patients with a diagnosis of psychosis related to dementia. GEODON is not approved for the treatment of these patients.

Anything that can increase the chance of a heart rhythm abnormality should be avoided. Therefore, do not take GEODON if:

- You have certain heart diseases, for example, long QT syndrome, a recent heart attack, severe heart failure, or certain irregularities of heart rhythm (discuss the specifics with your doctor)

- You are currently taking medications that should not be taken in combination with ziprasidone, for example, dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol or tacrolimus.

What To Tell Your Doctor Before You Start GEODON

Only your doctor can decide if GEODON is right for you. Before you start GEODON, be sure to tell your doctor if you:

- have had any problem with the way your heart beats or any heart related illness or disease
- any family history of heart disease, including recent heart attack
- have had any problem with fainting or dizziness
- are taking or have recently taken any prescription medicines
- are taking any over-the-counter medicines you can buy without a prescription, including natural/herbal remedies
- have had any problems with your liver
- are pregnant, might be pregnant, or plan to get pregnant
- are breast feeding
- are allergic to any medicines
- have ever had an allergic reaction to ziprasidone or any of the other ingredients of GEODON capsules. Ask your doctor or pharmacist for a list of these ingredients
- have low levels of potassium or magnesium in your blood

Your doctor may want you to get additional laboratory tests to see if GEODON is an appropriate treatment for you.

GEODON And Other Medicines

There are some medications that may be unsafe to use when taking GEODON, and there are some medicines that can affect how well GEODON works. While you are on GEODON, check with your doctor before starting any new prescription or over-the-counter medications, including natural/herbal remedies.

How To Take GEODON

- Take GEODON only as directed by your doctor.
- Swallow the capsules whole.
- Take GEODON capsules with food.
- It is best to take GEODON at the same time each day.
- GEODON may take a few weeks to work. It is important to be patient.
- Do not change your dose or stop taking your medicine without your doctor's approval.
- Remember to keep taking your capsules, even when you feel better.

Possible Side Effects

Because these problems could mean you're having a heart rhythm abnormality, contact your doctor ***IMMEDIATELY*** if you:

- Faint or lose consciousness
- Feel a change in the way that your heart beats (palpitations)

Common side effects of GEODON include the following and should also be discussed with your doctor if they occur:

- Feeling unusually tired or sleepy
- Nausea or upset stomach
- Constipation
- Dizziness
- Restlessness
- Abnormal muscle movements, including tremor, shuffling, and uncontrolled involuntary movements
- Diarrhea
- Rash
- Increased cough / runny nose

If you develop any side effects that concern you, talk with your doctor. It is particularly important to tell your doctor if you have diarrhea, vomiting, or another illness that can cause you to lose fluids. Your doctor may want to check your blood to make sure that you have the right amount of important salts after such illnesses.

For a list of all side effects that have been reported, ask your doctor or pharmacist for the GEODON Professional Package Insert.

What To Do For An Overdose

In case of an overdose, call your doctor or poison control center right away or go to the nearest emergency room.

Other Important Safety Information

A serious condition called neuroleptic malignant syndrome (NMS) can occur with all antipsychotic medications including GEODON. Signs of NMS include very high fever, rigid muscles, shaking, confusion, sweating, or increased heart rate and blood pressure. NMS is a rare but serious side effect that could be fatal. Therefore, tell your doctor if you experience any of these signs.

Adverse reactions related to high blood sugar (hyperglycemia), sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these reactions. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Dizziness caused by a drop in your blood pressure may occur with GEODON, especially when you first start taking this medication or when the dose is increased. If this happens, be careful not to stand up too quickly, and talk to your doctor about the problem.

Before taking GEODON, tell your doctor if you are pregnant or plan on becoming pregnant. It is advised that you don't breast feed an infant if you are taking GEODON.

Because GEODON can cause sleepiness, be careful when operating machinery or driving a motor vehicle.

Since medications of the same drug class as GEODON may interfere with the ability of the body to adjust to heat, it is best to avoid situations involving high temperature or humidity.

It is best to avoid consuming alcoholic beverages while taking GEODON.

Call your doctor ***immediately*** if you take more than the amount of GEODON prescribed by your doctor.

GEODON has not been shown to be safe or effective in the treatment of children and teenagers under the age of 18 years old.

Keep GEODON and all medicines out of the reach of children.

How To Store GEODON

Store GEODON capsules at room temperature (59°-86°F or 15°-30°C).

For More Information About GEODON

This sheet is only a summary. GEODON is a prescription medicine and only your doctor can decide if it is right for you. If you have any questions or want more information about GEODON, talk with your doctor or pharmacist. You can also visit www.geodon.com.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 19, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Geodon (ziprasidone) tablets for the maintenance treatment of bipolar I disorder, as an adjunct to lithium or valproate

TO: File NDA 20-825/S-034
[Note: This overview should be filed with the 1-21-09 original submission of this supplemental NDA.]

1.0 BACKGROUND

Geodon (ziprasidone) is an atypical antipsychotic that is approved for the treatment of schizophrenia and the acute treatment of bipolar mania. One of the post-marketing commitments for the bipolar mania approval was for a maintenance study in bipolar disorder. Study A1281137 was conducted to meet this goal and is the focus of this application. S-034 seeks an adjunctive bipolar maintenance claim in a dose range of 80-160 mg/day.

2.0 CHEMISTRY

The only CMC issue for this NDA would have been environmental assessment. However, the sponsor sought and was granted a categorical exclusion for EA. Thus, CMC recommends approval of this application from a CMC standpoint.

3.0 PHARMACOLOGY

Since the claim being sought is for the approved formulation of Geodon, there were no pharm/tox issues for review.

4.0 BIOPHARMACEUTICS

No new pharmacokinetic data were submitted as part of this application, however, OCP requested that the sponsor address a potential for a ziprasidone/valproate interaction. The sponsor provided an argument that an interaction between these two compounds was highly unlikely, and we have accepted this argument.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our review of this application focused on a single flexible-dose (80-160 mg/day) randomized withdrawal study (A1281137) involving ziprasidone as adjunctive therapy to either lithium or valproate in patients with bipolar I disorder and a recent manic or mixed episode. This was a multicenter study involving both US and non-US sites. There was an open-label run-in phase during which time patients who had not had an optimal response to lithium or valproate were given adjunctive ziprasidone in a dose range of 80-160 mg/day. Patients who were stable responders for at least 8 weeks were randomized to continue on lithium or valproate plus adjunctive ziprasidone (at the same dose they were stabilized on) or to lithium or valproate plus adjunctive placebo. The observation period for relapse (intervention for any type of affective episode: mania, mixed, or depression) was 6 months. The primary endpoint was time to relapse and the primary analysis was the log-rank test. The results were statistically significant in favor of adjunctive ziprasidone ($p=0.014$). There were 32% relapses on placebo+mood stabilizer compared to only 20% on drug+mood stabilizer. About half the relapses were depression and about half mania/mixed episodes. The results were generally robust to differences in gender, race, geograhpic distribution, and mood stabilizer. The sponsor has, in my view, provided sufficient evidence to support a (b) (4) claim of adjunctive maintenance efficacy for Geodon in the treatment of bipolar I disorder. We have made a number of changes to labeling regarding the description of the efficacy results. We have agreed to defer a requirement for a pediatric (10-17) maintenance study until after we have made a final judgment about the acute treatment for pediatric bipolar. In any case, a maintenance study in this population is unlikely to be conducted for ethical reasons.

5.2 Safety Data

The additional safety experience with Geodon as adjunctive treatment to lithium or valproate available from study A1281137 was incrementally quite small compared to the safety database we had available for our original reviews of this drug, however, I agree with the clinical team that no new, important safety information about this drug has been revealed in this NDA for maintenance treatment.

5.3 Clinical Sections of Labeling

As noted, we have made several modifications to the sponsor's proposed labeling, and we have now reached agreement with the sponsor on final labeling.

6.0 FOREIGN REGULATORY ACTIONS

It is my understanding that Geodon is not approved anywhere outside the US at this time for the adjunctive maintenance treatment of bipolar I disorder.

7.0 DSI INSPECTIONS

Inspections were conducted at 3 sites, and data from these sites were deemed to be acceptable. One of the sites did, however, have a number of deviations. A sensitivity analysis excluding patients from this site still favored ziprasidone.

8.0 LABELING AND APPROVAL LETTER

8.1 Labeling

As noted, we have reached agreement with the sponsor on final labeling.

8.2 Approval Letter

The approval letter includes the agreed upon final labeling.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Pfizer has submitted sufficient data to support the conclusion that Geodon is effective and acceptably safe in the adjunctive maintenance treatment of bipolar I disorder. We have reached agreement with the sponsor on final labeling. Thus, we will issue an approval letter for this application, with the agreed upon final labeling.

cc:
Orig NDA 20-825/S-034
HFD-130
HFD-130/TLaughren/MMathis/RLevin/FBecker/THarrison

DOC: Geodon_Bipolar LT_Laughren_AP_Memo.doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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

/s/

THOMAS P LAUGHREN
11/19/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 20-825/S-034; Geodon (ziprasidone) capsules

The following officers or employees of the FDA participated in the decision to approve this application and consented to be identified:

Thomas Laughren
Mitchell Mathis
Francis Becker
Kooros Mahjoob
Peiling Yang
George Kordzakhia
Julia Pinto

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	November 4, 2009
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/Supp #	20-825 S-034
Proprietary / Established (USAN) names	Geodon Ziprasidone hydrochloride
Dosage forms / strength	Oral capsules 20, 40, 60, and 80 mg
Indication	Maintenance treatment of bipolar I disorder, as adjunctive therapy to lithium or valproate
Recommended:	Approval

1. Introduction and Background

Ziprasidone is an atypical antipsychotic that was approved for the treatment of schizophrenia in adults on 5 February 2001. On 19 August 2004, it was approved as monotherapy for the treatment of acute manic or mixed episodes in bipolar I disorder, with or without psychotic features, in adults. The Bipolar Disorder approval letter (S-009) included a Postmarketing Commitment to submit the results of a clinical study or studies in adult patients, examining (1) the short-term efficacy and safety of ziprasidone as add-on therapy in bipolar patients currently taking mood stabilizers (e.g., lithium, valproate) and (2) the long-term efficacy and safety of ziprasidone in Bipolar Disorder. The sponsor met with FDA on January 12, 2005 to discuss a protocol design that would be consistent with these goals and would also support an indication. The design for the single study protocol in this submission (A1281137) was discussed at this meeting. A revised protocol design was sent to FDA on April 25, 2005, and FDA provided feedback to the sponsor on July 18, 2005. Following the Psychopharmacological Drugs Advisory Committee (PDAC) meeting of October 25, 2005, FDA indicated to the sponsor that in the proposed protocol a stabilization period long enough to ensure patients are in responder status for at least 8 weeks (i.e. over a period of 10- 12 weeks or longer) would be acceptable. The completed protocol was submitted on December 5. 2005.

2. CMC

There are no unresolved CMC issues. There were no new relevant data to review.

3. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical pharmacology/toxicology issues. There were no new relevant data to review.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer, Andre Jackson, Ph.D requested that the sponsor address the potential for clinical drug interactions between ziprasidone and valproic acid. The sponsor acknowledged that no formal study was conducted to examine potential pharmacokinetic interactions between ziprasidone and valproic acid. However, the sponsor notes that the two drugs do not have any common metabolic pathways, suggesting that pharmacokinetic interactions are unlikely. The major pathways of valproate biotransformation include mitochondrial ß- oxidation and conjugation with glucuronic acid. Less than 20% of metabolism occurs by other oxidative mechanisms such as CYP-dependent oxidation. The primary CYP pathways in valproate disposition involve CYP2C9 and CYP2A62.

In contrast, ziprasidone is metabolized by aldehyde oxidase (approximately two-thirds) and CYP3A4 (approximately one-third). Furthermore, as an inhibitor, ziprasidone has minimal effects on the activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in human liver microsomes. In the clinical trial, group mean lithium and valproic acid levels assessed at baseline and throughout both the open label and the double-blind periods were within the protocol specified therapeutic ranges [lithium (0.6 – 1.2 mEq/L), and valproic acid (50-125 µg/ml)].

5. Clinical/Statistical

5.1 Efficacy

5.1.1 Dose selection

The sponsor selected the dose range (80-160 mg/day) for the maintenance trial based on the identical ziprasidone dose range approved for the acute treatment of mania.

5.1.2 Clinical study essential to regulatory decision (design, analysis, results)

Trial A1281137 was a multicenter, randomized, double-blind, placebo-controlled maintenance study of ziprasidone (as adjunctive therapy to lithium or valproate) in 239 subjects with Bipolar I Disorder, recent manic or mixed or mixed episode. The study was conducted at 118 centers including 68 in the U.S. as well as centers in Chile, France, Germany, Guatemala, Hong Kong, India, Italy, Mexico, Russian Federation, Spain, Sweden, Taiwan, and Venezuela.

In order to enter the randomized withdrawal study, subjects with an acute manic or mixed episode first had to be stabilized for at least 8 weeks on open-label treatment with ziprasidone (80-160 mg/day) plus lithium or valproate. All subjects must have been treated with lithium or valproate before entering the open-label stabilization phase. Once stabilized on ziprasidone plus lithium or valproate, subjects were randomized to treatment with continued ziprasidone (plus lithium or valproate) or placebo (plus lithium or valproate). The ziprasidone dose in the controlled phase was the same as that used at the end of the stabilization phase. The protocol allowed for a reasonable adjustment of the ziprasidone dose during the controlled phase.

The primary endpoint of the controlled trial was the time to intervention/discontinuation (relapse) for any mood episode (manic, mixed, or depressed). Intervention or discontinuation was required if one or more of the following occurred: 1) the investigator judged that that discontinuation was in the best interest of the subject; 2) the subject had a loss of effect and/or the subject required an alteration in treatment; 3) the subject required hospitalization for treatment of a mood episode; or 4) the Mania Rating Scale score or MADRS score was $\geq$ 18 for 2 consecutive visits.

Based on the sponsor's primary survival analysis, the time to intervention for a mood episode (relapse) was statistically significantly different between treatment groups, in favor of ziprasidone (p=0.0104). The proportion of subjects with relapse of a mood episode was 19.7% (25/127) in the ziprasidone group and 32.4% (36/111) in the placebo group. The sponsor's table below illustrates the findings.

Table 1. Primary Efficacy Result

Table 3. Log-rank test for time to intervention for mood episode (ITT analysis- double-blind period).

	Ziprasidone + mood stabilizer	Placebo + mood stabilizer
Total number of patients	127	111
Patients with intervention for mood episode	25 (19.7%)	36 (32.4%)
p-value (vs placebo+mood stabilizer)	0.0104	

Source: Sponsor's Clinical Study Report A1281137; Table 13.4.2.1.1 (pg. 233)

For both treatment groups, the most common type of relapse observed was depressive episodes (64% and 44% for the ziprasidone and placebo group, respectively). For the study group as a whole, depressive relapse accounted for 53% of all relapses. These are numerical values observed, as opposed to results of a formal analysis. Manic relapses accounted for 28%, 39%, and 34% of the ziprasidone, placebo, and combined group, respectively. Mixed episodes accounted for 8%, 17%, and 13% of relapses, respectively. The results are illustrated in the table below.

Table 2. Types of Mood Episodes

Type of episode	Ziprasidone + mood stabilizer	Placebo + mood stabilizer	Treatment groups combined
Total episodes	25	36	61
Depressed episode	16 (64%)	16 (44%)	32 (53%)
Manic episode	7 (28%)	14 (39%)	21 (34%)
Mixed episode	2 (8%)	6 (17%)	8 (13%)

5.1.3 Discussion of primary reviewers' findings (clinical and statistical)

5.1.3.1 Clinical review findings

Francis Becker, M.D. conducted the clinical review. Dr. Becker concluded that Study A1281137 demonstrated the efficacy of ziprasidone as adjunctive therapy to lithium or

valproate in the maintenance treatment of bipolar I disorder. Ziprasidone was superior to placebo in preventing relapse of a mood episode. I agree with his conclusions.

Dr. Becker notes that this was not a fixed-dose study. Therefore, one cannot draw a conclusion about a possible dose-response relationship. The mean modal doses in the open-label and controlled phases were 111 mg/day and 109.2 mg/day, respectively.

Dr. Becker also notes that although randomization was not stratified by type of mood stabilizer, in both the lithium and valproate subgroups, there were numerically smaller proportions of relapses in the ziprasidone group compared to the placebo group (21% vs. 44% and 18.6% vs. 22.6% in the lithium and valproate subgroups, respectively).

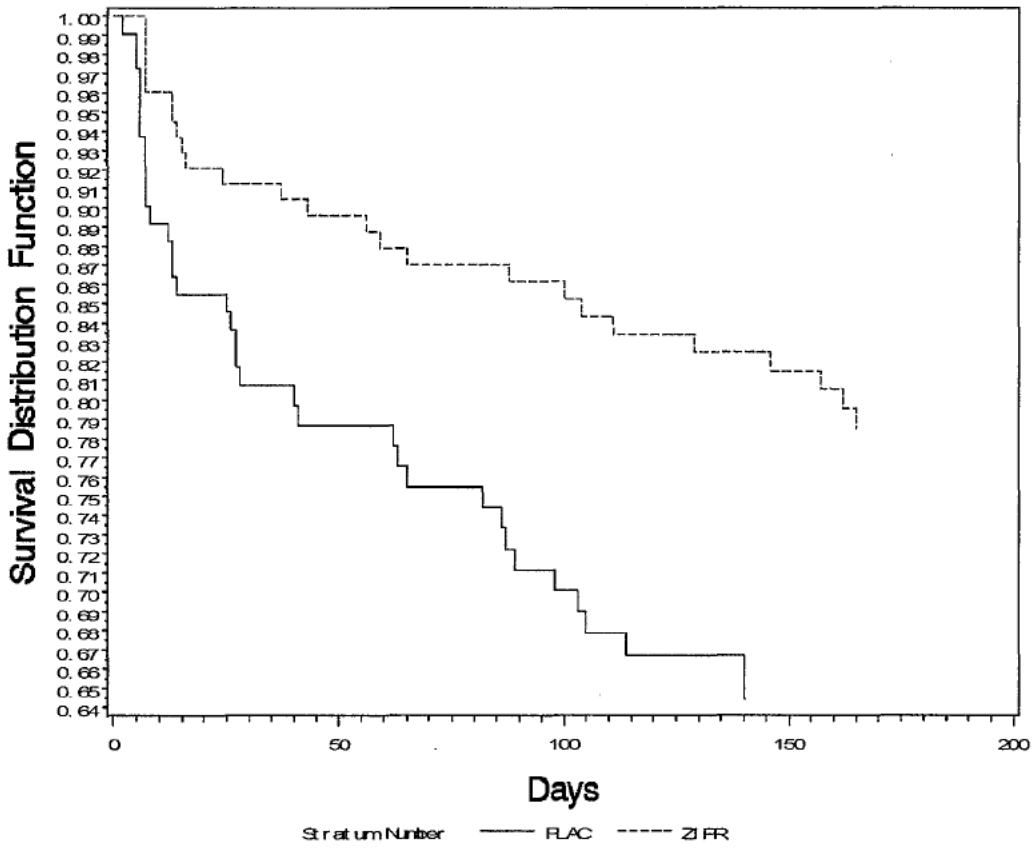
Table 3: Relapses by Mood Stabilizer

	Ziprasidone		Placebo	
Mood Stabilizer	N	n (%)	N	n (%)
Lithium	57	12 (21.1%)	49	22 (44.9%)
Valproic acid	70	13 (18.6%)	62	14 (22.6%)

5.1.3.2 Statistical Review Findings

George Kordzakhia, Ph.D. conducted the statistical analysis, and he confirmed the sponsor's primary efficacy results. He concluded that, based on the primary analysis (the log-rank test for equality of survival curves across treatment groups), the time to intervention for mood episode was statistically significant in favor of ziprasidone (p=0.0104). Only 19.7% of the ziprasidone subjects required intervention for a mood episode, compared with 32.4% of the placebo subjects. The Kaplan-Meier curves for time to intervention for mood episode support that the observed relapse rate was lower in the ziprasidone treatment group than in placebo treatment group during the entire double-blind relapse prevention phase (see Figure 1). I agree with his conclusions.

Figure 1. Kaplan-Meier curves of Time to Intervention for mood episode in the Double—Blind Treatment Phase (curves from top to bottom: Ziprasidone, Placebo)



[Source: Dr. Kordzakhia's results]

5.1.4 Pediatric use/PREA waivers and deferrals

The sponsor has requested a waiver for a bipolar disorder maintenance study in children younger than age 10. The basis for the waiver request is that it would not be feasible to recruit appropriate subjects, since the prevalence of bipolar disorder under the age of 10 is low, and the diagnosis is unstable in this age group. The sponsor has requested a deferral for ages 10 to 17. On October 27, 2009, the sponsor submitted a pediatric plan for a single, controlled maintenance study of ziprasidone as adjunctive therapy to lithium or valproate in pediatric subjects (ages 10 to 17) with Bipolar Disorder, recent manic episode. The waiver and deferral requests as well as the proposed pediatric plan were discussed at a PeRC meeting on October 27, 2009. The committee found the proposals acceptable.

5.2 Safety

5.2.1 General safety considerations

The safety database from Study A1281137 is adequate for assessing the safety of ziprasidone (as adjunctive therapy to lithium or valproate) in the maintenance treatment of bipolar. The exposure and the types of safety assessments are adequate. Dr. Becker concluded that there were no new or unexpected findings compared to the safety profile of ziprasidone treatment in other indications. I agree with his conclusion.

5.2.2 Safety findings from the clinical trial

5.2.2.1 Exposure

The total ziprasidone exposure in the open-label and controlled phase was 128.83 person-years (82.63 and 46.2, respectively). The number of subjects exposed to ziprasidone was 584 in the open-label phase and 127 in the controlled phase. The mean modal dose in the open-label and controlled phases were 111 mg/day and 109.2 mg/day, respectively. Overall, the median duration of ziprasidone treatment was 239.0 days for subjects randomized to ziprasidone (open-label ziprasidone + double-blind ziprasidone). During the controlled phase, the median duration of ziprasidone treatment was 167 days.

Table 4. Ziprasidone Exposure (person-years) for open-label and controlled phases

Treatment	**Open-label Patient Exposure (N)**	**Double-Blind Patient Exposure (N)**	**Total Patient Exposure**
Total	82.63 (584)	46.20 (127)	128.83
Ziprasidone/ Ziprasidone	28.50 (127)	46.20 (127)	74.70
Ziprasidone/ Placebo	25.76 (113)	NA	25.76
Ziprasidone/ Not randomized	28.37 (344)	NA	28.37

5.2.2.2 Adverse Events

There were no deaths in the open-label or controlled phase. In the open-label phase, only one serious adverse event was drug-related (dystonia). In the controlled phase, one SAE was possibly drug-related (arrhythmia, unspecified). In the controlled phase, three discontinuations due to adverse events were probably related to ziprasidone treatment (EPS, somnolence, and elevated transaminases). There were no other adverse events of particular concern.

5.2.3 Safety update

Dr. Becker reviewed the sponsor's postmarketing safety summary of ziprasidone in the treatment of bipolar disorder. He concluded that there are no new or unexpected findings based on this safety summary. I agree with his conclusion.
Description

6. Advisory Committee

The Division did not hold an advisory committee meeting, because there was no specific need to do so.

7. Labeling

The division has reviewed the sponsor's proposed labeling in detail. We have proposed precise labeling language in a separate label document. This includes conversion of approved Geodon labeling to the Physician's Labeling Rule (PLR) format. The main changes pertaining to this supplement for bipolar disorder maintenance treatment are included in the following sections: Indications and Usage, Dosing and Administration, and Clinical Studies. Generally, the sponsor's proposed language for the bipolar maintenance claim is acceptable.

8. DSI Audits

Lauren Iacono-Connors, Ph.D. (Good Clinical Practice Branch 2 Division of Scientific Investigations) conducted the review. Three clinical sites were inspected: Dr. Lydia Cohan, Site number 1027, Dr. Mariappa (Preeti) Srinivasa, Site number 1101, and Dr. Ranjive Mahajan, Site number 1104. These sites were selected for inspection because they are considered most important in demonstrating efficacy and safety claims made by the applicant. Dr. Iacono-Connors conclude that the data from these sites appear reliable, based on available information. The noted deficiencies are unlikely to impact data reliability.

Based on preliminary review of inspectional findings, the study data collected by Dr. Cohan, Dr. Srinivas and Dr. Mahajan appear reliable. All 3 sites were issued Form FDA 483s, Inspectional Observations; however, only the Cohan site raised concerns and required a more detailed assessment of the clinical impact of the inspectional observations on study outcome. There were numerous counts of protocol violations and record keeping errors. A copy of the Cohan Form FDA 483 was provided to the review division medical officer, Dr. Becker, on October 1, 2009. At that time DSI reviewer Lauren Iacono-Connors, proposed that while the list of inspectional observations was extensive with respect to protocol deviations and record keeping discrepancies, each specific observation did not appear to be clinically significant. The review division may consider the overall data from the Cohan site reliable. However, the review division may wish to consider each violation pertaining to protocol adherence and record keeping by subject, outlined in the Form FDA 483, and described in detail above. The review division may wish to censor subject-specific data from study analyses as appropriate.

In consultation with our statistician, the division conducted a sensitivity analysis, excluding the one site (1027). The efficacy results did not change.

9. Conclusions and Recommendations

I recommend approval for this supplemental NDA. In my opinion, the sponsor has demonstrated that ziprasidone, as adjunctive therapy to lithium or valproate, was effective and

reasonably safe as maintenance treatment of bipolar I disorder. The results of the primary survival analysis demonstrated that ziprasidone (as adjunctive treatment) was statistically superior to placebo in preventing relapse of mood episodes in subjects who had been stabilized on ziprasidone after a recent manic or mixed episode. Study A1281137 was adequate and well controlled.

The results of the study are probably generalizable to the population of patients with a diagnosis of bipolar I disorder, since the study appears to have included subjects who are representative of the bipolar disorder patient population. The safety and tolerability profile of ziprasidone in this study was quite similar to the safety profile of ziprasidone in other indications. There were no new or unexpected safety findings.

I recommend a deferral for a pediatric bipolar maintenance study, as discussed above. I do not recommend any specific risk management plan. Other than specific labeling proposals, I do not recommend any comments to the applicant.

Robert L. Levin, M.D.
November 4, 2009
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 20-825 S-34
HFD 130
T Laughren
M Mathis
F Becker
T Harrison

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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/s/

ROBERT L LEVIN
11/04/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	20-825 S-034
Submission Code	SE1-034 N000
Letter Date	December 19, 2008
Stamp Date	December 19, 2008
PDUFA Goal Date	November 21, 2009
Reviewer Name	Francis E. Becker, M.D.
Review Completion Date	October 2, 2009
Established Name	Ziprasidone
Trade Name	Geodon
Therapeutic Class	Atypical antipsychotic
Applicant	Pfizer, Inc.
Priority Designation	S
Formulation	20mg, 40mg, 60mg, & 80mg capsules
Dosing Regimen	40-80mg BID
Indication	Bipolar Disorder (adjunctive maintenance)
Intended Population	Adults with Bipolar I Disorder

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Tables

Figures

1 Recommendation/ Risk Benefit Assessments

1.1 Recommendation on Regulatory Action

I recommend that the Division take an approval action for supplemental NDA 20825 S-34 for the indication of maintenance treatment in Bipolar I Disorder as adjunct to mood stabilizer (lithium or valproate). In an adequate, well-controlled, 6-month, pivotal trial, the sponsor demonstrated that ziprasidone was superior to placebo in increasing the time to recurrence of a mood episode. In my opinion, the estimated treatment effect of ziprasidone was clinically significant.

The safety and tolerability profile of ziprasidone adjunctive maintenance (6 months) treatment in Bipolar I Disorder is acceptable. The profile is quite similar to ziprasidone's profile in the treatment of schizophrenic patients and patients with acute mania, and no new safety signals were identified. The incidence of adverse events was actually lower during the maintenance period of this trial compared to the open-label stabilization period. This is likely due to the fact that subjects experiencing significant adverse events in the open-label period were discontinued from the study and therefore were selected out of the double-blind maintenance period.

It seems reasonable to generalize the results of this trial to the general population of Bipolar Disorder patients, since the study population adequately represented the general population of patients with Bipolar Disorder requiring maintenance therapy.

1.2 Risk Benefit Assessment

Based on the review of the submitted safety data, long-term (6-10 month) treatment with ziprasidone as adjunct to lithium or valproate appears safe. During the open-label period of this trial, the most common adverse events associated with ziprasidone treatment were consistent with the adverse events reported in prior acute mania trials and included akathisia, dizziness, fatigue, headache, insomnia, nausea, sedation, somnolence, and tremor. During the maintenance period of this trial, the most common adverse events associated with ziprasidone treatment were headache, hypothyroidism, sedation, somnolence, tremor, and weight increased. In general, these adverse events are manageable. During the open-label period, there was one serious adverse event (SAE) of a severe dystonic reaction likely attributable to ziprasidone and, during the maintenance period, one SAE of cardiac arrhythmia may have been attributable to ziprasidone. Both of these SAEs resolved with discontinuation of ziprasidone. Seven SAEs of suicidal ideation (five in open-label period, two in double-blind period) and one SAE of suicide attempt (open-label period) occurred in subjects taking ziprasidone. It is not clear whether the SAEs of suicide ideation/attempt were attributable to ziprasidone. However, the risk of suicidality is inherent in Bipolar Disorder and is already addressed in current ziprasidone labeling. There were no deaths attributable to ziprasidone during the trial.

The following serious risks are associated with ziprasidone treatment and are listed in the **Warnings and Precautions** section of labeling: QT prolongation and risk of sudden death, Neuroleptic Malignant Syndrome, Tardive Dyskinesia, hyperglycemia and diabetes mellitus, rash, orthostatic hypotension, seizures, dysphagia, hyperprolactinemia, potential for cognitive and motor impairment, priapism, dysfunction of body temperature regulation, and risk of suicide.

However, ziprasidone's safety and tolerability compare reasonably well with other atypical antipsychotics (aripiprazole, risperidone, quetiapine, and olanzapine) currently approved for adjunctive maintenance treatment in subjects with Bipolar Disorder.

According to the World Health Organization, Bipolar Disorder is the sixth leading cause of disability among 15-44 year olds worldwide. The recurrent mood episodes seen in Bipolar Disorder have a significant impact on patients' quality of life, causing significant work and family disruptions. Associated features include acute agitation, psychosis, suicidal and dangerous behavior, grossly impaired judgment, grandiosity, impulsivity, risk-taking behavior, and thought disorder. Bipolar Depression is associated with the highest risk of suicide among all psychiatric or medical illnesses. Patients with Bipolar Disorder may experience a significant benefit in quality of life with adjunctive maintenance treatment with ziprasidone. Overall, the level of potential risk with long-term ziprasidone treatment is low, and the level of potential benefit of adjunctive maintenance treatment with ziprasidone is high.

1.4 Recommendations for Postmarket Requirements and Commitments

Currently, the Division does not have any specific recommendations or requests regarding ziprasidone treatment in the population studied.

2 Introduction and Regulatory Background

2.1 Product Information

Ziprasidone (Geodon) is an atypical antipsychotic belonging to the chemical class, benzisoxazole derivatives. The sponsor seeks an indication in adults for the use of oral ziprasidone as adjunctive treatment with a mood stabilizer (lithium or valproic acid) in the long-term maintenance treatment of Bipolar Disorder. For this indication, the sponsor proposes stable ziprasidone dosages of 40 – 80 mg BID (80 -160 mg per day).

Ziprasidone is currently approved by both the European Union and the United States for the treatment in adults of Schizophrenia and of manic or mixed episodes associated with Bipolar Disorder, with or without psychotic features. Currently approved formulations in adults for ziprasidone hydrochloride include the oral capsule (20, 40, 60, and 80 mg) and an oral solution (10 mg/ml). Ziprasidone mesylate is a rapid onset intramuscular injectable form (20 mg/ml) indicated for the treatment of acute agitation in schizophrenia patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of agitation.

Worldwide, ziprasidone has received marketing authorization in (b) (4) countries and is marketed in (b) (4) countries. There have been worldwide sales of over (b) (4) standard dosage units of ziprasidone corresponding to approximately (b) (4) patient-years of exposure. It is estimated that (b) (4) patients have received ziprasidone in clinical trials sponsored by the Marketing Authorization Holder (MAH) worldwide. To date, ziprasidone has not been approved in any country for use in the maintenance treatment of bipolar mania.

2.2 Currently Available Treatments for Proposed Indications

The table below summarizes the approved treatments for Bipolar Disorder:

Table 1: FDA-Approved Bipolar Treatment Regimens

Generic Name	Trade Name	Manic	Mixed	Maintenance (monotherapy)	Adjunctive (with lithium or valproate)	Depression
Valproate	*Depakote*	X				
Carbamazepine extended release	*Equetro*	X	X			
Lamotrigine	*Lamictal*			X		
Lithium		X		X		
Aripiprazole	*Abilify*	X	X	X	X	
Ziprasidone	*Geodon*	X	X			
Risperidone	*Risperdal*	X	X	X	X	
Quetiapine	*Seroquel*	X			X	X
Olanzapine	*Zyprexa*	X	X	X	X	
Olanzapine/fluoxetine	*Symbyax*					X

2.2.1 Atypical Antipsychotics

Several atypical antipsychotics are currently used in Bipolar Disorder:

Aripiprazole (Abilify)

Aripiprazole is indicated for acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and in pediatric patients 10 to 17 years of age. It is also indicated as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features in adults and in pediatric patients 10 to 17 years of age.

Olanzapine (Zyprexa)
Olanzapine is indicated for acute treatment of manic or mixed episodes associated with Bipolar I Disorder (monotherapy and adjunctive therapy with lithium or valproate) and maintenance treatment of Bipolar I Disorder (monotherapy) in adults.

Olanzapine is also approved in combination with the SSRI, fluoxetine, under the tradename, Symbyax, for the treatment of depressive episodes associated with Bipolar Disorder in adults.

Quetiapine (Seroquel)

Quetiapine is currently the only atypical antipsychotic approved for treatment of both acute depressive and manic episodes associated with Bipolar Disorder. It is also approved for adjunctive maintenance treatment with lithium or valproate

Risperidone (Risperdal)

Risperidone is indicated as monotherapy or as adjunctive therapy to lithium or valproate in the treatment of acute manic or mixed episodes associated with Bipolar Disorder. It is also approved as monotherapy or as adjunctive therapy to lithium or valproate in maintenance treatment of Bipolar Disorder.

Ziprasidone (Geodon)

As noted above, ziprasidone is currently approved for treatment of acute manic or mixed episodes associated with Bipolar Disorder, with or without psychotic features.

2.2.2 Lithium

Lithium, a mood stabilizer, has a role in the acute treatment of Mania, the acute treatment of Bipolar Depression, maintenance treatment of both Bipolar Mania and Bipolar Depression, and prophylaxis of Bipolar Manic and Depressive episodes. Although lithium can be effective as monotherapy in some cases, use of other medications in combination with lithium are frequently necessary to provide adequate treatment (e.g. antipsychotics, benzodiazepines, other mood stabilizers). The delayed onset of lithium's anti-manic effect (approximately 7 to 10 days) limits its utility in the treatment of acute mania, especially as monotherapy. Moreover, lithium does not adequately treat acute psychotic symptoms or acute agitation, common debilitating features of an acute manic episode. Hence, lithium is of greatest value in maintenance treatment and prophylaxis of affective episodes. Lithium has a relatively narrow therapeutic index regarding renal and neurocognitive dysfunction. Long term use of lithium poses the risks of renal dysfunction and thyroid dysfunction. In order to use lithium safely and effectively, one must regularly monitor serum lithium levels, renal function, and thyroid functions. Lithium toxicity can result in cognitive impairment, renal failure, and death. Common adverse events which can limit patients' adherence to lithium therapy include cognitive slowing, sedation, tremor, ataxia, nausea, diarrhea, and polyuria.

2.2.3 Valproate

Valproate (Depakote), an anticonvulsant and mood stabilizer, can effectively treat mania in some patients. However, valproate monotherapy is often inadequate to treat acute mania, requiring addition of the same classes of concomitant medications used with lithium. As with lithium, the onset of anti-manic effect is delayed. Valproate does not treat psychotic symptoms and often does not treat acute agitation adequately. It does not effectively treat or prevent depressive episodes of Bipolar Disorder and is not approved for maintenance therapy in Mania or for prophylaxis of manic episodes associated with Bipolar Disorder. Risks associated with valproate use include: hepatic dysfunction (sometimes severe, occasionally fatal); pancreatitis; weight gain; and ovarian dysfunction (polycystic ovary syndrome, irregular menses, and amenorrhea). One must monitor liver function and hematologic tests and valproate levels periodically.

2.2.4 Lamotrigine

Lamotrigine (Lamictal), an anticonvulsant and mood stabilizer, is approved for the maintenance treatment of Bipolar I Disorder. The effectiveness of lamotrigine in acute treatment has not been established.

2.2.5 Carbamazepine

Carbamazepine extended release (Equetro) is an anticonvulsant approved for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder.

2.3 Availability of Proposed Active Ingredient in the United States

Ziprasidone has been readily available in the United States since 2001. The drug has been used widely in the U.S. for the treatment of Schizophrenia and other psychotic disorders, and it has been used to treat mania (b) (4) .

2.4 Important Safety Issues with Consideration to Related Drugs

In general, the drugs categorized as atypical antipsychotics have similar pharmacodynamic profiles, benefits, and safety and tolerability profiles. As with ziprasidone, treatment with the other atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, and aripiprazole) has been associated with development of the following adverse events: extrapyramidal symptoms, sedation, orthostatic hypotension, weight gain, and hyperglycemia. Treatment with some of the atypical antipsychotics has been associated with proarrhythmic effects (primarily prolongation of the QTc interval). Ziprasidone may pose a higher risk of QTc prolongation than other antipsychotics. Treatment with quetiapine may be associated with development of cataracts. Risperidone treatment in elderly patients with dementia and agitation/psychosis appears to be associated with an increased risk of cerebrovascular adverse events. In addition, elderly patients with dementia-related psychosis treated with atypical antipsychotics have been found to be at an increased risk of death compared to placebo. Therefore, atypical antipsychotics are labeled with a boxed warning for the treatment of dementia-related psychosis in elderly patients.

Clozapine differs significantly from the other atypical antipsychotics. It is the only antipsychotic medication demonstrated to be effective in treating previously treatment-resistant schizophrenic patients. It is also approved for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Investigators hypothesize that clozapine's unique pharmacologic properties may confer its beneficial effects. Clozapine also has a different safety profile than other atypical antipsychotic drugs. Treatment with clozapine carries the risks of agranulocytosis, myocarditis, and seizures. Like other atypical antipsychotics, clozapine treatment can result in EPS, sedation, weight gain, hyperglycemia, and orthostatic hypotension.

In summary, ziprasidone and the other atypical antipsychotics (with the exception of clozapine) appear to have similar potential risks.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Geodon (ziprasidone HCl) Capsules were approved under NDA 20-825 on February 5, 2001 for the treatment of Schizophrenia in adults, and it was approved on August 19, 2004 (S-009) for use as monotherapy in the treatment of acute manic or mixed episodes of Bipolar I Disorder, with or without psychotic features. On March 29, 2006, Geodon (ziprasidone HCl) Oral Suspension was approved under NDA 21-483 for the treatment of schizophrenia and of acute manic or mixed episodes of Bipolar I Disorder, with or without psychotic features.

The Bipolar Disorder approval letter (S-009) included a Postmarketing Commitment to submit the results of a clinical study or studies in adult patients, examining (1) the short-term efficacy and safety of ziprasidone as add-on therapy in bipolar patients currently taking mood stabilizers (e.g., lithium, valproate) and (2) the long-term efficacy and safety of ziprasidone in Bipolar Disorder. The sponsor met with FDA on January 12, 2005 to discuss a protocol design that would be consistent with these goals and would also support an indication. The design for the single study protocol in this submission (A1281137) was discussed at this meeting. A revised protocol design was sent to FDA on April 25, 2005, and FDA provided feedback to the sponsor on July 18, 2005. Following the Psychopharmacological Drugs Advisory Committee (PDAC) meeting of October 25, 2005, FDA indicated to the sponsor that in the proposed protocol a stabilization period long enough to ensure patients are in responder status for at least 8 weeks (i.e. over a period of 10- 12 weeks or longer) would be acceptable. The completed protocol was submitted on December 5. 2005.

The sponsor intends that this submission will fulfill the Postmarketing Commitment (PMC) described above and support a new indication for oral ziprasidone as add-on therapy (to lithium or valproate) in the maintenance treatment of Bipolar Disorder.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of this submission are acceptable.

3.2 Compliance with Good Clinical Practices

It appears that this clinical trial was conducted in compliance with good clinical practice. This included all International Conference on Harmonization (ICH) Good Clinical Practice Guidelines (GCP) Guidelines. In addition, all local regulatory requirements were followed. The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centers participating in the trial.

3.3 Financial Disclosures

The sponsor provided documentation regarding financial disclosure and potential conflict of interest of investigators. None of the investigators in this study hold any form of propriety interest in Geodon. Six of the 463 investigators had financial information to disclose. The six investigators had significant payments of other sorts greater than $25,000. No investigator disclosed equity greater than $50,000. There does not appear to be any instances of conflict of interest which affected the conduct or results of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewers do not have any particular concerns regarding this submission and state that from their standpoint, this Supplement is recommended for approval.

4.3 Preclinical Pharmacology/Toxicology

Please see the original NDA review. No preclinical pharmacology or toxicology was included in this submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of ziprasidone in treating psychotic symptoms is unknown. However, it has been proposed that the drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonisms. The mechanism of action of ziprasidone in treating mania associated with Bipolar Disorder is unknown.

4.4.2 Pharmacodynamics

Ziprasidone is an atypical antipsychotic agent whose efficacy is likely mediated by combined antagonism of dopamine-D_2- and 5-hydroxytryptamine $5HT_{2A}$-receptors. In preclinical studies, ziprasidone has a high in vitro binding affinity for the dopamine D_2 and D_3, the serotonin $5HT_{2A}$, $5HT_{2C}$, $5HT_{1A}$, $5HT_{1D}$, and alpha-1-adrenergic receptors (Ki of 4.8, 7.2, 0.4, 1.3, 3.4, 2, and 10 nM, respectively). It has moderate affinity for the histamine H_1 receptor (Ki = 47 nM). Ziprasidone acts as an antagonist at the D_2, $5HT_{2A}$, and $5HT_{1D}$ receptors, and it acts as an agonist at the $5HT_{1A}$ receptor. Ziprasidone has no appreciable affinity for the cholinergic muscarinic receptor (IC50 > 1 μM).

4.4.3 Pharmacokinetics

The oral activity of ziprasidone is primarily due to the parent drug. The multiple-dose pharmacokinetics of ziprasidone is dose-proportional within the proposed clinical dose range, and ziprasidone accumulation is apparently predictable with multiple dosing. Elimination of

ziprasidone is mainly via hepatic metabolism (CYP3A4). The mean terminal half-life is approximately 7 hours within the proposed clinical dose range. Steady-state concentrations are achieved within one to three days of dosing. The mean apparent systemic clearance is 7.5 ml/min/kg. Ziprasidone is thought to be unlikely to interfere with metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Ziprasidone is well absorbed after oral administration, reaching peak plasma concentrations in 6 to 8 hours. The absolute bioavailability of a 20 mg dose under fed conditions is approximately 60%. The absorption of ziprasidone is increased up to two-fold in the presence of food.

Distribution: Ziprasidone has a mean apparent volume of distribution of 1.5 L/kg. It is greater than 99% bound to plasma proteins, binding primarily to albumin and α_1-acid glycoprotein. The *in vitro* plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is minimal.

Metabolism and Elimination: Ziprasidone is extensively metabolized after oral administration with only a small amount excreted in the urine (< 1%) or feces (< 4%) as unchanged drug. Ziprasidone is primarily cleared via three metabolic routes to yield four major circulating metabolites, benzisothiazole (BITP) sulphoxide, BITP-sulphone, ziprasidone sulphoxide, and S-methyl-dihydroziprasidone. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Unchanged ziprasidone represents about 44% of total drug-related material in serum. *In vitro* studies using human liver subcellular fractions indicate that S-methyl-dihydroziprasidone is generated in two steps. The data indicate that the reduction reaction is mediated by aldehyde oxidase and the subsequent methylation is mediated by thiol methyltransferase. *In vitro* studies using human liver microsomes and recombinant enzymes indicate that CYP3A4 is the major CYP contributing to the oxidative metabolism of ziprasidone. CYP1A2 may contribute to a much lesser extent. Based on *in vivo* abundance of excretory metabolites, less than one-third of ziprasidone metabolic clearance is mediated by cytochrome P450 catalyzed oxidation and approximately two-thirds via reduction by aldehyde oxidase. There are no known clinically relevant inhibitors or inducers of aldehyde oxidase.

4.5 Biostatistics

The biostatistician, George Kordzakhia, PhD, reviewed and replicated the sponsor's analysis from the single submitted trial (A1281137) and confirmed the accuracy of the sponsor's results. He reports that, "In Study A1281137, ziprasidone treatment arm was statistically superior to the corresponding placebo arm with respect to time to intervention to mood episode. The p-value obtained from the primary analysis, log-rank test was 0.0104." Dr. Kordzakhia therefore concludes that, "When used as an adjunctive therapy to a mood stabilizer (lithium or valproate), ziprasidone at a flexible dose of 80 to 160 mg daily showed positive effect in the maintenance treatment of manic or mixed episodes associated with bipolar disorder in adult patients."

Dr. Kordzakhia confirmed that the full analysis set consisted of the ITT population, defined as those subjects randomly assigned to treatment in the double-blind period who took at least 1 dose of double-blind medication and who had at least 1 post randomization observation. The full analysis set was the population for all efficacy analyses, and the Time to Intervention for a Mood Episode (manic, mixed, or depressed episode) during the double-blind maintenance period was the primary efficacy endpoint. As an exploratory analysis, the time to intervention for mood episode during Double-Blind Period 2 was analyzed by stratified log-rank test using the type of mood stabilizer as the stratification factor (randomization for the study was not stratified by the type of mood stabilizer).

Based on the primary analysis, the log-rank test for equality of survival curves across treatment groups, Dr. Kordzakhia confirms that the time to intervention to mood episode was statistically significant in favor of ziprasidone (p=0.0104) during the 6 months of double-blind treatment. Only 19.7% of the ziprasidone subjects required intervention for a mood episode compared with 32.4% of the placebo subjects. The Kaplan-Meier curves for time to intervention for a mood episode support that the observed relapse rate was lower in the ziprasidone treatment group than in the placebo treatment group during the entire double-blind relapse prevention phase.

Dr. Kordzakhia provides a table (copied and displayed below) showing the total number of mood episodes and types of mood episodes. He confirms that, "The proportions of patients with relapses into the depression, manic, and mixed type episodes were numerically lower in ziprasidone group, compared to placebo group:

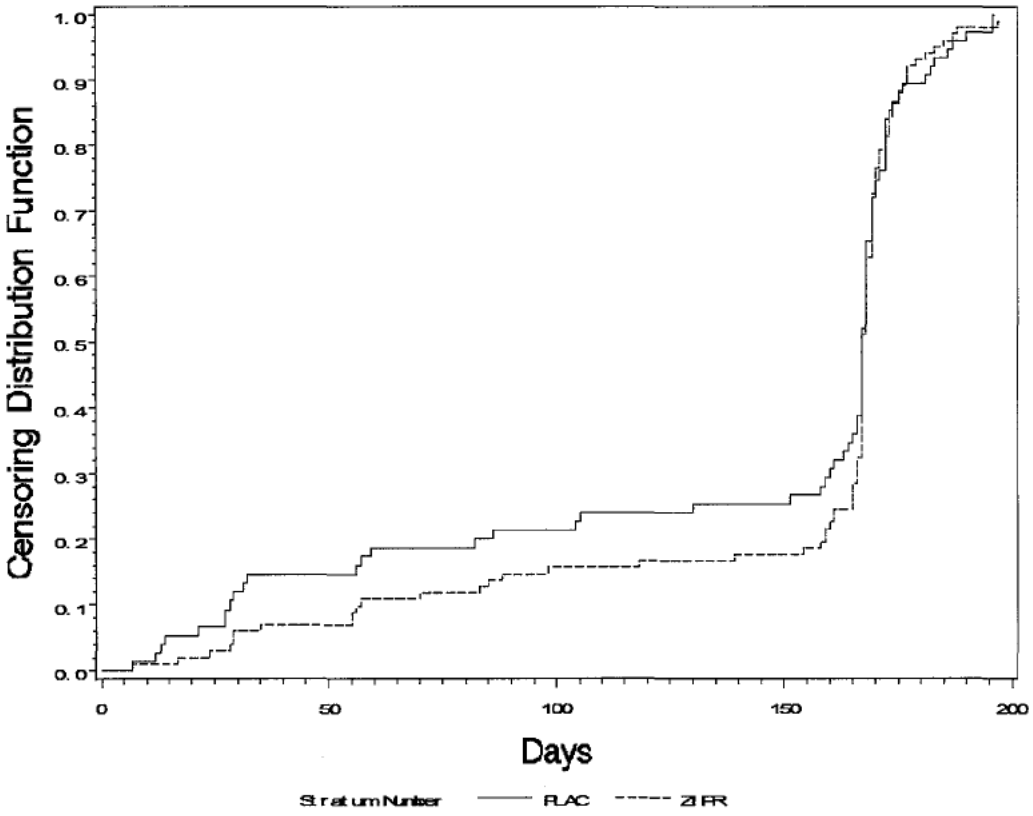
Table 2: Summary of Patients with Intervention for Mood Episodes (all Randomized Patients, Double-Blind Period)

	Ziprasidone + mood stabilizer	**Placebo + mood stabilizer**
Total number of patients	127	111
Patients with intervention for mood episode	25 (19.7%)	36 (32.4%)
Depression episode	14 (11.0%)	14 (12.6%)
Mania episode	6 (4.7%)	14 (12.6%)
Mixed episode	2 (1.6%)	6 (5.4 %)
Met MADRS or MRS discontinuation criteria (no mood episode)	3 (2.4%)	2 (1.8%)

Source: Dr. Kordzakhia review

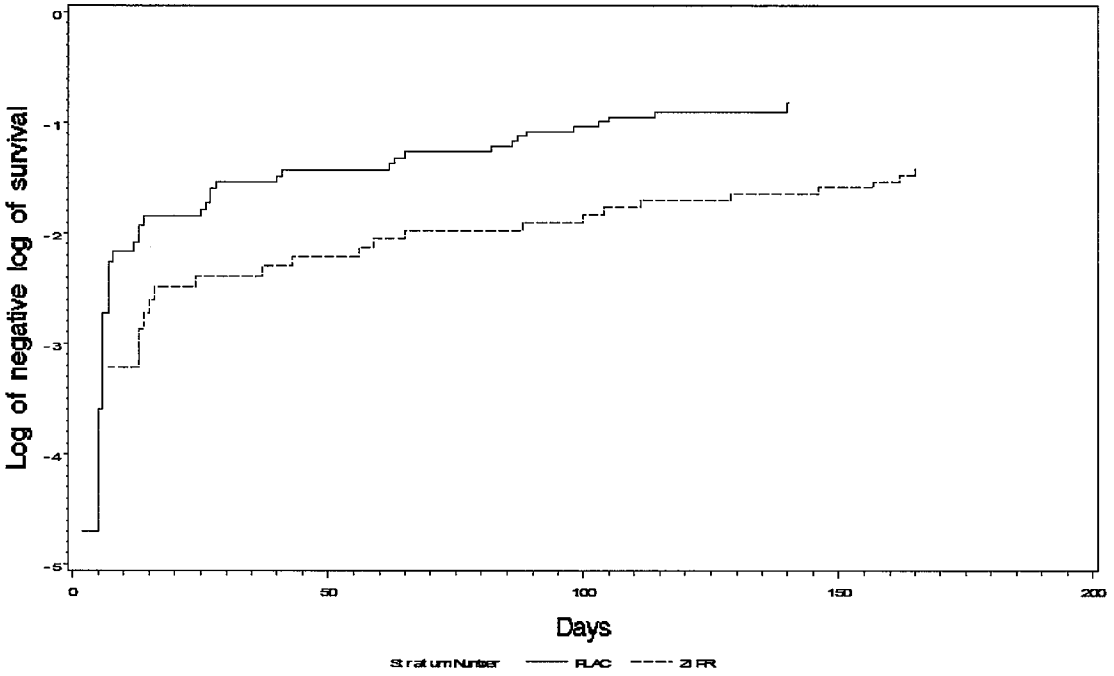
Biostatistics review also included exploration of cumulative distribution functions (CDF) of time to censor for subpopulation of patients who had no intervention for mood episode. For all censored patients, the CDF curves indicate the proportion of patients in each treatment arm who were censored by a given day. Dr. Kordzakhia reports that, "The plot suggests the time to censor was numerically larger in the ziprasidone treatment arm compared with the placebo arm," as shown in the figure below (electronically copied and reproduced from Dr, Kordzakhia's review):

Figure 1: **Study A1281137 Cumulative Distribution Function curves of censoring time in the Double—Blind Treatment Phase for all censored patient population (curves from top to bottom: Placebo, Ziprasidone)**



In addition, the log of negative log of survival function plot shows that in the duration of the study hazard rate was higher in the placebo group compared with the ziprasidone arm, as shown in the figure below (electronically copied and reproduced from Dr. Kordzakhia's review):

Figure 2: Study A1281137 Log of negative log of survival curves of Time to Intervention for mood episode in the Double—Blind Treatment Phase (curves from top to bottom: Placebo, Ziprasidone)



As an exploratory secondary analysis, the time to intervention for mood episode during Double-Blind Period 2 was analyzed by stratified log-rank test using the type of mood stabilizer as the stratification factor. The time to intervention for mood episode was statistically significant in favor of ziprasidone with p-value of 0.007.

Dr. Kordzakhia also conducted an exploratory Cox-proportional hazard analysis of time to intervention for mood episode for gender and race subgroups. Among all subgroups, the treatment effect appeared to be numerically in favor of ziprasidone when compared with placebo. The subgroup analysis by age was not performed since there was only one patient older than 65. Exploratory subgroup analysis of efficacy by country (US, Non US) and mood stabilizer (Lithium, Valproate) was also conducted. Dr. Kordzakhia reports that, "Among all subgroups, the treatment effect appeared to be numerically in favor of ziprasidone when compared with placebo."

4.6 Division of Scientific Investigation (DSI)

Preliminary comments from DSI have been conveyed to this reviewer via telephone and e-mail on October 1, 2009. Final report is not yet available. Concerning the few sites that were inspected, several problems were noted at a single site, Site 1027, located in Scottsdale, Arizona. Forty-five subjects were enrolled at this site, 11 of whom were randomized into the double-blind period. Four subjects completed the trial. Among the numerous problems identified at this site, there are several which are clinically significant. The clinically significant problems identified in this inspection are as follows:

1. Two subjects did not meet psychiatric inclusion criteria of having a therapeutic mood stabilizer level of either lithium (0.6-1.2 mEq/L) or divalproex sodium (50-125 ug/ml) for at least two weeks prior to the baseline visit.
2. Triplicate baseline ECGs were not performed at approximately two minute intervals for 9 subjects that were enrolled into the open label period.
3. ECGs were not performed at every visit for two subjects due to the site forgot to obtain them.
4. Clinical rating scales source documents did not match the eCRF on 14 subject's charts that were reviewed out of 24. For example, one subject (1001,(b) (6)) at Period 2/Week 2 was recorded as having a CGI-I score of 4 (no change) on source and 2 (much improved) on eCRF. At Period 2/Week 4, CGI-I was again recorded as a score of 4 (no change) on source and 2 (much improved) on eCRF. In addition, CGI-S for this subject at Period 2/Week 4 was recorded as 3 (mildly ill) on source and 2 (Borderline mentally ill) on eCRF. Another subject (1003, (b) (6) had baseline SADS-CB Score Sheet recording grandiosity as 2 on source and 1 on eCRF while Overt Anger was rated 1 on source and 2 on eCRF.
5. Site failed to report promptly to IRB a Serious Adverse Event within 3 business days. Specifically, the site became aware of a Serious Adverse Event (exposure in utero) that occurred in Subject 1029 (b) (6) and did not notify the IRB within 3 business days of becoming aware of the event.
6. Study drug unit's # 91519 and # 128317 shows that these two units were dispensed to two different subjects on two different days. The site only had one shipment showing that they received 1 unit for each of the two numbers. They could not explain how the other two numbers arrived to the site but they have them listed as being dispensed twice to two different subjects. According to the study coordinator the numbers are assigned by a Voice Interactive System called (b) (4) and that the system is only supposed to assign numbers once.

The irregularities outlined above are clearly clinically relevant. Failure to obtain ECGs in the manner specified by the protocol may have adversely effected inclusion or exclusion in the trial as well as safety assessments during the trial (for example, monitoring changes in QT interval compared to baseline). Inaccuracy regarding dispensing of study drug to certain subjects would obviously make interpretation of efficacy result difficult, and the failure of 2 subjects to have a therapeutic mood stabilizer level for at least 2 weeks prior to baseline may have allowed for their inappropriate inclusion in the study population. In addition, the clinical rating scales scores were important criteria for inclusion or exclusion in the trial, enrollment in the double-blind period, and discontinuation from the trial during the double-blind period. These problems could have adversely affected the efficacy outcome of this trial. However, the likelihood is low due to the small number of subjects involved.

5. Sources of Clinical Data

Clinical data were derived from the trial report for Trial A1281137 which included the full efficacy and safety database as well as Case Report Forms, tables, graphs, and JMP files from this trial. In addition, postmarketing safety data was derived from the sponsor's extensive global safety database.

5.1 Tables of Studies/ Clinical Trials

This application contained only one clinical trial, A1281137, which evaluated the effect of ziprasidone as adjunctive treatment with a mood stabilizer (Lithium or Valproate) in preventing relapse in adults with Bipolar Disorder who had responded to a minimum of 2 months treatment with both agents (ziprasidone plus mood stabilizer).

5.2 Review Strategy

This review entailed an examination of the efficacy results from Trial A1281137, an assessment of all safety data from this trial (adverse events, vital signs data, ECG data, and clinical laboratory data) as well as all updated safety data from postmarketing experience. The review also included an evaluation of the labeling revisions proposed by the sponsor to describe these findings in Geodon labeling. The review of efficacy also included extensive collaboration with the statistical reviewer, George Kordzakhia, Ph.D.

5.3 Discussion of Individual Studies/ Clinical Trials

The only clinical trial included in this submission, A1281137, was a 6-month, Phase 3, randomized, double-blind, placebo-controlled trial in subjects with Bipolar I Disorder to evaluate the continued safety and maintenance of effect of ziprasidone plus a mood stabilizer (vs. placebo plus a mood stabilizer) following a minimum of 2 months of response to open-label treatment with both agents.

6. Review of Efficacy

6.1 Rationale for Selection of Studies for Review

The maintenance claim for ziprasidone as adjunctive treatment in adults with manic or mixed episodes associated with Bipolar Disorder is based entirely on data from trial A1281137, the only clinical trial included in this submission. The primary efficacy endpoint of trial A1281137 was time to intervention for mood episode (TIME) during a 6-month, randomized, double-blind treatment period of ziprasidone versus placebo. This is reasonable and commonly utilized efficacy endpoint and trial duration for a randomized withdrawal maintenance trial.

6.2 Study Summary

6.2.1 Protocol A1281137

This clinical trial was a 6-month, Phase 3, randomized withdrawal, double-blind, placebo-controlled maintenance trial in subjects with Bipolar I Disorder to evaluate the continued safety and maintenance of effect of ziprasidone plus a mood stabilizer (vs. placebo plus a mood stabilizer) following a minimum of 2 months of response to open-label treatment with both agents. The trial, initiated on December 27, 2005 and completed on May 23, 2008, was conducted at 118 centers including 68 in the United States as well as centers in Chile, France,

Germany, Guatemala, Hong Kong, India, Italy, Mexico, Russian Federation, Spain, Sweden, Taiwan, and Venezuela.

Objectives

The primary objective of the trial was to evaluate the efficacy and safety of ziprasidone as adjunctive treatment with a mood stabilizer in the long-term maintenance treatment of Bipolar Disorder by comparing the time to intervention for a mood episode (TIME) in subjects receiving double-blind ziprasidone plus a mood stabilizer (lithium or valproate) vs. subjects receiving placebo plus a mood stabilizer.

The secondary objective was to evaluate time to discontinuation for any reason.

Additional secondary objectives were to assess changes in the following:

- Clinical Global Impression-Severity (CGI-S)
- Clinical Global Impression-Improvement (CGI-I)
- Mania Rating Scale (MRS)
- Montgomery Asberg Depression Rating Scale (MADRS)
- Positive and Negative Syndrome Scales (PANSS).

Study Population

Subjects enrolled in the open-label stabilization phase (Period 1) must have had a primary diagnosis of Bipolar I Disorder, with a recent or current manic or mixed episode as determined by Structured Clinical Interview for DSM-IV, with symptoms that began no more than 90 days prior to the screening visit. The subjects were to have an MRS score $\geq$14 if currently receiving lithium or valproic acid or an MRS score of $\geq$18 if not currently on lithium or valproic acid. All subjects were to have an MRS score $\geq$14 at the baseline visit prior to entry into the open-label period. MRS scores must include scores of 2 or higher on at least 4 items.

Subjects who began mood stabilizer (lithium or valproate) treatment at the screening visit were required to remain an additional 2-3 weeks in the screening phase of the trial to titrate to the therapeutic range and maintain it for at least 2 weeks prior to entry into the open-label stabilization phase (Period 1) of the study.

Key Inclusion Criteria:

- The subjects must have been on a documented therapeutic level of a mood stabilizer, either lithium (0.6-1.2 mEq/L) or valproic acid (50-125 μg/mL), for at least 2 weeks prior to the baseline visit of the open-label period.
- All subjects must have been willing and able to discontinue all psychotropic medications prior to the baseline visit, except lithium or divalproex sodium and lorazepam or zolpidem tartrate.
- Women of child bearing potential must have been using a reliable method of contraception.

Key Exclusion Criteria:

- Rapid cycling (defined as 8 or more mood episodes over the previous 12-month period).
- Been clinically stable on another treatment regimen that was also well tolerated (ie, clinical reason had to exist to discontinue current treatment and enter subject into protocol).
- Imminent risk of harm to self or to others.
- Mental retardation or organic brain syndrome.
- Substance abuse/dependence (excluding nicotine and caffeine) or positive urine drug screen.
- Received ziprasidone in a previous clinical trial.
- History of treatment resistance to at least 2 other antipsychotic medications.
- History of treatment resistance or intolerance to ziprasidone.
- Received clozapine within 12 weeks, a depot antipsychotic within 4 weeks or a monoamine oxidase inhibitor within 2 weeks prior to baseline.
- Pregnancy or breast feeding.
- Uncontrolled, unstable clinically significant medical condition (eg, renal, hepatic, endocrine, respiratory, cardiovascular, hematologic, immunologic, cerebrovascular disease, or malignancy), including extreme obesity (BMI >35 kg/m2) or anorexia (BMI <18.5 kg/m2).
- History of neuroleptic malignant syndrome or treatment-resistant tardive dyskinesia.
- Had a history of significant cardiovascular disease or significant concurrent cardiovascular disease, including uncontrolled hypertension (sitting diastolic pressure >95 mm Hg and/or sitting systolic pressure >170 mm Hg with or without treatment), hypotension, congestive heart failure, angina pectoris, bypass surgery, history of myocardial infarction or ischemic heart disease, uncompensated heart failure or recent acute myocardial infarction (within the past 6 months).
- Any clinically significant abnormal laboratory, vital sign, physical examination, or ECG finding that, in the opinion of the investigator, precluded trial participation.
- Had a clinically significant ECG abnormality at screening or baseline, a history of cardiac arrhythmias, conduction abnormalities or known history of QT prolongation (including congenital long QT syndrome).

  Note: Controlled essential hypertension (stable for at least 2 months by diet and/or pharmacotherapy) and nonclinically significant sinus bradycardia and sinus tachycardia were not considered significant medical illnesses and did not exclude a subject from the trial.

6.2.1.1 Study Design

The trial consisted of 2 periods, ie, a 2.5-4 month open-label stabilization period (Period 1) followed by a 6 month, double-blind maintenance period (Period 2). Throughout the trial, subjects had to be maintained within the therapeutic serum concentration of lithium or valproic acid.

Open-label Stabilization Phase (Period 1)

In the stabilization period (Period 1), open-label ziprasidone (80-160 mg daily) was added to a mood stabilizer, lithium or valproate, after the mood stabilizer had been maintained at a therapeutic blood level for at least 2 weeks. Stabilization started no earlier than Week 2 and not until symptoms had improved compared to baseline as measured by a CGI-I score ≤ 3.

On Day 1 of Period 1, open-label ziprasidone, 40 mg twice daily (BID) (80 mg/day), was added to the existing mood stabilizer. It was then increased to 60 mg BID or 80 mg BID on Day 2. Thereafter, the dose could be adjusted within the range of 40-80 mg BID on the basis of toleration and efficacy. Subjects who could not tolerate at least 80 mg/day were to be discontinued from the trial.

No dosage adjustments could be made to ziprasidone or the mood stabilizer during the 4 weeks prior to randomization (Period 2) except for documented safety reasons. In addition, an adjustment to the mood stabilizer to maintain the therapeutic range could occur if the level went below or above the required therapeutic range or if the plasma concentrations of lithium or valproic acid changed by at least 0.2 mEq/L or 25 μg/ml, respectively, from previous therapeutic levels.

Consideration was given to discontinuing a subject whose symptoms continued to worsen after an adjustment was made to the treatment regimen, and an adequate response time had elapsed, even if the 4-week or 2-week grace period had not elapsed, so as to prevent an imminent relapse. Although a CGI-I rating of 4 (no change) was not a discontinuation criterion, the rating should have occurred only at an occasional visit (if any) after the subject's treatment regimen had been optimized. In addition, a rating of ≥ 4 for 2 consecutive weeks re-started the 8-week stabilization clock because stabilization was based on a subject responding to treatment and being minimally improved or better (ie, CGI-I ≤ 3).

Discontinuation from open-label treatment was required if 1 or more of the following occurred:

- Investigator decided discontinuation was in the best interest of the subject.
- Subject did not exhibit symptomatic improvement within approximately 2 weeks after entering open-label or 2 weeks after the treatment regimen had been adjusted to optimum dose or serum concentration.
- Subject was hospitalized for disease under study.
- CGI-I rating was 5 (minimally worse) or 6 (much worse) for 4 consecutive weeks.
- CGI-I rating was 7 (very much worse) for 2 consecutive weeks.

Placebo-controlled Maintenance Phase (Period 2)

Following open-label treatment with both agents (mood stabilizer plus ziprasidone), subjects were eligible for entrance into Period 2 if they had achieved stability based on the following criteria:

1. Eight consecutive weeks on the adjunctive regimen (mood stabilizer plus ziprasidone)
2. Stable (ie fixed) treatment regimen for 4 consecutive weeks prior to entry into Period 2. Note that for the duration of the trial, ziprasidone or mood stabilizer dose could be

reduced for safety reasons and mood stabilizer dose could be adjusted to maintain a therapeutic serum concentration).

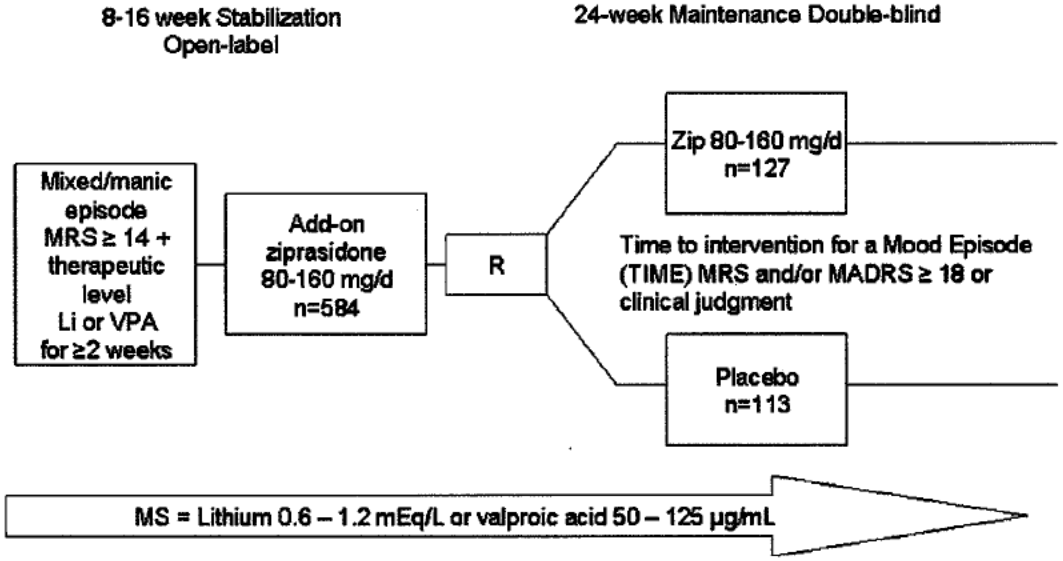
3. Continued CGI-I scores ≤3 (minimally improved) for 8 consecutive weeks on the adjunctive regimen. A CGI-I rating of 4 or higher was permitted at 1 visit within the 8-week stability period, but must have returned to < 3 within no more than 10 days and could not occur immediately prior to randomization. Note that a CGI-I rating of 3 was the minimum acceptable score in defining stabilization. The investigator was advised to use his/her clinical judgment in determining whether a subject who did not achieve a rating better than "minimally improved" had improved enough to remain in the protocol.
4. Factors such as improvement in the MRS and/or MADRS scores, the CGI-Severity score at Baseline and subsequent visits, etc were also to be taken into consideration in determining if a persistent CGI-I score of 3 is sufficient for a subject's continued participation in the protocol.

Subjects who achieved stability were randomized into Period 2 in a 1:1 ratio to 1 of 2 blinded treatment groups (ziprasidone plus the mood stabilizer or placebo plus the mood stabilizer) to evaluate the maintenance of effect of ziprasidone for up to an additional 6 months.

Subjects who were randomized in Period 2 to ziprasidone plus mood stabilizer remained on the dose level they received during the last 4 weeks of the open-label period. Subjects who were randomized to placebo plus the mood stabilizer were tapered off ziprasidone and onto matching placebo; the level of ziprasidone was decreased 20 mg BID every 2 days. The blind of the trial was maintained. After randomization, no adjustments to the treatment regimen were permitted for efficacy or symptom control; however, a down titration could have occurred for documented safety reasons.

Figure 3: Flow Chart for Study A1281137

(Electronically copied and reproduced from sponsor's submission)



MS=Mood Stabilizer

6.2.1.2 Efficacy Measures

Efficacy was assessed using the Schedule for Affective Disorders and Schizophrenia-Change Behavior Scale (SADS-CB) which contains the MRS, CGI-S, CGI-I, MADRS, and PANSS. Cognition and outcome measures were also performed. Only qualified raters were allowed to evaluate and rate subjects in this trial, and prior to the start of the study, rater certification was conducted by the central vendor for the SADS-CB and the MADRS.

The following rating scales were assessed:

- SADS-CB (MRS): A modified version of the Schedule for Affective Disorders and Schizophrenia- Change (SADS-C) was used to rate manic and depressive symptoms. The MRS is derived from the SADS-C with items grouped as the Manic Syndrome subscale, Behavior and Ideation subscale, and impaired insight.
- Investigator Clinical Global Impression, Severity and Improvement Scales (CGI-I and CGI-S): The subject's condition at baseline (prior to initiation of open-label study drug) was the comparator for judging CGI-I during the open-label period of the trial. The subject's condition at the final open-label visit was the comparator for judging CGI-I during the double-blind period of the trial.
- Montgomery Asberg Depression Rating Scale (MADRS): The MADRS assess 17 symptoms most commonly occurring in primary depressive illness and is designed to be particularly sensitive to the treatment effects of antidepressants.
- The Positive and Negative Syndrome Scale (PANSS) is a 30-item clinician-rated assessment designed to measure the severity of psychopathology in adults with psychotic disorders, emphasizing positive and negative symptoms.

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was the time to intervention for a mood episode (TIME) during the double-blind Maintenance Period. A mood episode could be depressed, manic, or mixed. Discontinuation from double-blind treatment was required if one or more of the following occurred and was counted as an intervention for mood episode:

- Investigator decided discontinuation was in the best interest of the subject.
- A loss of effect and/or requirement for an alteration to the treatment regimen (investigator judgment).
- Anytime a subject was hospitalized for disease under study.
- MRS rating was $\geq$18 for 2 consecutive visits.
- MADRS rating was $\geq$18 for 2 consecutive visits. If the MRS and/or MADRS score was $\geq$18 at any scheduled or unplanned visit, but the investigator felt that the clinical status of the subject merited remaining in the trial, the subject was required to return in $\leq$7 days, if at all possible, and no greater than 10 days for a follow-up visit. If either score remained at $\geq$18, the subject had to be discontinued from the trial.

Secondary Efficacy Endpoint

Time to discontinuation for any reason during the double-blind period was the key secondary endpoint. Other secondary endpoints included changes from baseline to the final visit in the double-blind period in CGI-S, CGI-I, MRS, MADRS and PANSS.

A Modified TIME endpoint was also defined and analyzed. In addition to discontinuations due to a mood episode requiring intervention, the Modified TIME included other discontinuations related to lack of persistent satisfactory effect, ie, discontinuations due to treatment related AEs, death due to treatment, or death due to disease under study. The sponsor states that Modified TIME may be thought of as an endpoint covering the ground between the primary variable and the key secondary variable. Withdrawals due to treatment-related adverse events (including treatment-related laboratory abnormalities) or death due to study drug or disease under study were counted as having met the criteria for an impending mood episode rather than as censored observations. This corresponds to the secondary analysis of Modified TIME.

Cognition and Outcome Measures

A computerized cognitive test battery, CNS Vital Signs, was administered to assess subjects' cognitive performance. The battery consisted of computerized tasks designed to assess the cognitive domains of working memory, verbal memory and learning, speed of processing, attention, and reasoning and problem solving. Due to minimal practice effects, this computerized battery could be used in repeated administrations to evaluate repeated administrations over time. The individual domain scores were also evaluated.

Other outcome measures were as follows:

- Changes in Sexual Functioning Questionnaire (CSFQ): Changes in sexual functioning were assessed using the self-report version of the 14-item CSFQ9, which measured sexual desire, sexual activity, and sexual satisfaction.
- Sheehan Disability Scale (SDS): The self-report SDS10 was used to measure the extent to which the subject's work/school, social life/leisure activities, and home life/family responsibilities were impaired by psychiatric illness.
- Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scales: Subjects completed the self-report 16-item short form of the Q-LES-Q11. The General Activities scale measures satisfaction with various areas of daily functioning such as physical health, social relationships, medication, and overall life satisfaction.

Subjects completed the CSFQ, SDS, and Q-LES-Q at the beginning of the office visit (after the computerized cognitive battery was completed).

6.2.1.3 Concomitant Medications

- A washout period between 3 and 5 half-lives was applied to most exclusion medications and/or their active metabolites.
- Prior antipsychotics were discontinued the day before the subject entered Period 1 or earlier, as determined by the investigator.

- Lorazepam (or a comparable dose of another benzodiazepine) was allowed to be administered for anxiety and insomnia at ≤2 mg/day, up to 4 days per week and for no more than 5 consecutive days. Lorazepam was not to be given within 4 hours prior to assessments.
- Diazepam was not to be used if the subject was receiving adjunctive valproic acid.
- Zolpidem (or other FDA-approved nonbenzodiazepine sleep aids) was allowed to be administered for insomnia at 5 or 10 mg/day (5 mg was preferred, with 10 mg being reserved for more severe insomnia), up to 4 days per week and for no more than 5 consecutive days.
- Zolpidem (or alternative) and lorazepam (or another benzodiazepine) could not be co-administered.
- Use of benztropine (or another anticholinergic) and/or propranolol was allowed during the trial to treat extrapyramidal symptoms (but not as a prophylactic measure).
- The chronic use of certain medications (some hormones, antihypertensives, diuretics, and oral hypoglycemics) was allowed if the subject was prescribed these medications at least 2 months prior to study entry, the subject's condition was stable, and the dose was stabilized prior to the screening visit.
- Please see table below (electronically copied and reproduced from the sponsor's submission):

Table 3: Concomitant Medications

First administration of these medications were discussed with sponsor or designated representative:

- Anorexics
- Antianginal Agents
- Antiarrhythmics
- Antihistamine: terfenadine, astemizole
- Anticoagulants
- Steroids (except topical)
- Theophylline
- Tryptophan
- Antihypertensivesa
- Diuretics [b]
- H2 Blockers [b]
- Metronidazole[c,d]
- ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers[b]
- Acetazolamide, urea, xanthine preparations, alkalinizing agents[b]
- NSAIDs, Indomethacin, Piroxicam, COX-2 inhibitors[b]
- Aspirind
- Meropenem, Rifampin, Tolbutamide[d]
- Hormones (replacement except insulin)[a]
- Oral hypoglycemicsa
- Antiinfectives
- Over the counter medications (see Use Allowed, below)

Use Prohibited:

- All other antipsychotic agents and antidepressants
- Diazepam[d]
- Antiemetic (dopamine antagonists such as prochloperazine and metoclopramide)
- Propranolol (for anti-hypertension use), reserpine, clonidine, and methyldopa
- Narcotic analgesic
- Any medications known to prolong the QTc interval (including, but not limited to, dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridizine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol and tacrolimus).
- Any medication cited in the Exclusion Criteria (5.2.2)

Use Allowed:

- Lorazepam (or alternate benzodiazepine), zolpidem tartrate, benztropine (or alternative anticholinergic) and/or propranolol

Abbreviations: ACE = angiotensin-converting enzyme, NSAID = Nonsteroidal anti-inflammatory drug, Cyclooxygenase-2
[a] If taken for at least 2 months before study and the dose was stabilized
[b] With adjunctive lithium
[c] With adjunctive aspirin
[d] With adjunctive divalproex sodium

6.2.1.4 Statistical Analysis Plan

Sample Size

Based on extrapolation of results from published studies with shorter periods prior to randomization, an expected relapse rate of 60% in the group randomized to placebo plus mood stabilizer and 40% in the group randomized to ziprasidone plus mood stabilizer was assumed. Based on these assumptions, the number of relapse events required to yield 80% power with a 5% Type I error was calculated to be 100. The sponsor therefore predicted that to allow for 15% subject discontinuation unrelated to the primary variable, a minimum of 115 subjects needed to be randomly assigned to each group for a total of 230 subjects entering the 6-month, double-blind phase of the trial.

It was planned to screen 1278 subjects with the expectation that 767 would be enrolled into the open-label period of the trial. If at least 30% of the subjects completed the open-label period and were available for randomization into the double-blind phase, then an estimated 230 subjects would be required for analysis.

The full analysis set consisted of the intent-to-treat (ITT) population, defined as those subjects randomly assigned to treatment in the double-blind period who took at least 1 dose of double-blind medication and who had at least 1 post randomization observation. The full analysis set was the population for all efficacy analyses.

The per protocol (PP) analysis was defined as all subjects in the full analysis set who did not have any protocol violations and was used in the analysis of: 1) TIME. 2) Time to Discontinuation for Any Reason, and 3) Modified Time to Intervention for Mood Episode (Modified TIME).

The safety population, also called the "All Subjects Treated" population, was defined as:

- Open-label stabilization period: all subjects who received at least one dose of adjunctive ziprasidone.
- Double-blind maintenance period: all subjects who received at least one dose of double-blind medication.

Statistical Analysis of Efficacy Parameters

Primary Endpoint

The primary efficacy endpoint was the Time to Intervention for a Mood Episode (TIME) during the double-blind maintenance period. The TIME was calculated as the number of days from the

day of randomization into the double-blind Period 2 of the study to the day of intervention for a mood episode. If the date of the intervention was missing, then it was assumed to have occurred on the date of the last subject visit. If the intervention was based on MRS or MADRS scores, TIME was calculated as the number of days from the day of randomization into the double-blind period of the study to the first observation of a score greater than or equal to 18.

The primary analysis was based on the Kaplan-Meier product-limit estimator. P-values were obtained from the log-rank test for equality of survival curves over treatment groups. Kaplan-Meier survival curves were presented and the median time to relapse was determined for each treatment group. The number of subjects at risk, number of events and number of censored observations were summarized, by treatment, at each visit.

Subjects discontinuing the trial early due to AE, laboratory abnormality, death, protocol deviation, lost to follow-up, not meeting entrance criteria, pregnancy, subject no longer willing to participate, study terminated by sponsor, or other reasons were considered censored observations. All censored cases were assumed to have relapsed immediately after censoring. This corresponds to the key-secondary analysis of time to discontinuation for any reason. Withdrawals due to treatment-related AEs (including treatment-related laboratory abnormalities) or death due to study drug or disease under study were counted as having met the criteria for an impending mood episode rather than as censored observations. This corresponds to the secondary analysis of modified TIME.

As an exploratory analysis, the TIME during Double-Blind Period 2 was analyzed by stratified log-rank test using the type of mood stabilizer as the stratification factor (randomization for the study was not stratified by the type of mood stabilizer). The analyses on the primary endpoint (including sensitivity) discussed above were done using both the ITT and PP analysis sets.

Secondary Endpoints

The Time to Discontinuation for Any Reason during the double-blind period (key-secondary) and the modified TIME during the double-blind period were analyzed using Kaplan-Meier product-limit estimator similar to that of the primary endpoint. P-values were obtained from the log-rank test for equality of survival curves over treatment groups. As an exploratory analysis, the Time to Discontinuation for Any Reason during the double-blind period was analyzed by stratified log-rank test using the type of mood stabilizer as the stratification factor. The key-secondary endpoint and modified TIME were analyzed using both ITT and PP analysis sets.

Analysis of change during the Double-Blind Period 2 from the final visit in the open-label period in each of the following rating scales, the MRS, MADRS, CGI-S and PANSS (total score, positive symptom score and negative symptom score) was conducted using SAS PROC MIXED to fit a mixed model, repeated measures analysis of covariance (ANCOVA), and baseline score (final open-label visit) as a covariate. Analysis of CGI-I scores (improvement relative to the final visit in the open-label period) was conducted using SAS PROC MIXED to fit a mixed model, repeated measures analysis of variance (ANOVA) with center and subject-within-center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects.

6.2.1.5 Safety Assessments

Safety monitoring included:

- Adverse event monitoring.
- Clinical laboratory: CBC, chemistries, urinalysis, T_4, TSH.
- Prolactin.
- Pregnancy test
- Serum lithium and divalproex levels.
- Urine drug screen.
- Physical examination.
- Vital signs, height, weight, waist circumference, and BMI.
- ECG monitoring. If a QTc interval of ≥500 msec was observed on any tracing at any time after the initiation of ziprasidone treatment, at least 3 additional ECGs had to be performed at 5-minute intervals to determine if the prolongation was persistent. If the QTc interval persisted at ≥500 msec, the subject was to be discontinued from the study and monitored every 4-8 hours (or more frequently if deemed necessary for safety) until the QTc returned to baseline.
- Movement disorder ratings: Simpson-Angus Rating Scale (S-ARS), Barnes Akathisia Determination Scale (BARS), and Abnormal Involuntary Movement Scale.
- Concomitant medication monitoring.

Table 4: Schedule of Activities- Double-blind Maintenance (Period 2)

Event	Double-blind Randomization Visits							
	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Physical exam					X			X
Weight & vital signs			X	X	X	X	X	X
ECG			X	X	X	X	X	X
Clinical labs			X		X			X
Prolactin			X					X
Lithium or valproate		X	X	X	X	X	X	X
Pregnancy test			X	X	X	X	X	X
Drug screen			X		X			X
MRS,MADRS,, CGI-I,CGI-S	X	X	X	X	X	X	X	X
PANSS			X	X	X	X	X	X
S-ARS,BARS,AIMS				X		X		X
Concomitant medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X

6.2.1.6 Results

Demographics

A total of 584 subjects were treated in the open-label stabilization period. In the double-blind randomization period, 127 subjects were treated with ziprasidone and 112 subjects were treated

with placebo. Age ranged from 18 to 71 years with a mean age of 38.8 years. The majority of subjects were white, female, and of non-Hispanic/Latino ethnicity. Please see table below:

TABLE 5
STUDY A1281137
BASELINE DEMOGRAPHIC FEATURES (DOUBLE-BLIND PHASE)

	Ziprasidone N=127	Placebo N=113
AGE (years)		
Mean	39.6	38.0
Age Range	18-64	18-71
GENDER		
% Males	40.2%	53.1%
% Females	59.8%	46.9%
RACE		
% Caucasian	64.6%	59.3%
% Black	3.9%	5.3%
% Asian	24.4%	25.7%
% Other*	7.1%	9.7%

* **Other** includes reasons that could not be captured under any other category (eg. Subject moved away from geographical area)

Baseline Characteristics

All subjects had a primary diagnosis of Bipolar I Disorder (manic or mixed). For all treatment groups, the current episode type was manic for a majority of subjects (ziprasidone = 73/126 and placebo = 60/113) and mixed for less than half of the subjects (ziprasidone = 53/126 and placebo = 53/113). Please see table below:

Table 6: Baseline Characteristics Study A1281137

		Total (N=583)	Randomized Total (N=239)	Randomized: Ziprasidone (N=126)	Randomized: Placebo (N=113)	Not Randomized (N=344)
Bipolar I, most recent episode manic						
Number of subjects		278	133	73	60	145
Duration of current episode (weeks)	Mean	5.3	5.1	4.5	5.9	5.6
	Range	1-65	1-65	1-18	1-65	1-48
	Unspecified(N)	0	0	0	0	0
Number of prior episodes	Mean	10.3	6.9	6.5	7.4	13.3
	Range	0-105	1-100	1-30	1-100	0-105
	Unspecified(N)	4	3	1	2	1
Bipolar I, most recent episode mixed						
Number of subjects		305	106	53	53	199
Duration of current episode (weeks)	Mean	7.1	6.7	6.2	7.2	7.3
	Range	0-72	0-26	0-17	0-26	1-72
	Unspecified(N)	0	0	0	0	0
Number of prior Episodes	Mean	12.2	14.5	19.2	9.9	10.9
	Range	0-100	0-100	0-100	0-100	0-99
	Unspecified(N)	5	3	2	1	2

There were no apparent differences between the ziprasidone and placebo treatment groups in age, race, ethnicity, or weight and height distributions. The ziprasidone treatment group had a higher proportion of female subjects (~60%) compared to the placebo treatment group (~47%). Approximately 57.5% had at least one current disease or syndrome in addition to the disease under study. The most frequently reported co-morbid medical conditions included hypertension, gastroesophageal reflux disease, hyperlipidemia, seasonal allergy, back pain, and hypercholesterolemia. Insomnia and depression were the most frequently reported co-morbid psychiatric disorders.

Patient Disposition

The number of subjects who completed the double-blind period of the study was 84 (66%) and 54 (48%) for ziprasidone and placebo groups, respectively. Please see table below:

TABLE 7: ENUMERATION (%) OF DROPOUTS BY REASON FOR DROPOUT; STUDY A1281137		
	Double-Blind Period	
Number (%) of Subjects	Ziprasidone	Placebo
Total Randomized*	127	113
Treated	127	112
Study Completers	84 (66.1)	54 (48.2)
Dropouts	43 (33.9)	58 (51.8)
Adverse Event	11 (8.6)	15 (13.4)
Laboratory abnormalities	1 (0.8)	0
Lack of Efficacy	9 (7.1)	22 (19.6)
Subject no longer willing to participate in study	9 (7.1)	9 (8.0)
Lost to Follow up	3 (2.4)	6 (5.4)
Other*	10 (7.9)	6 (5.4)

* Other includes reasons that could not be captured under any other category (eg. Subject moved away from geographical area).

Concomitant Medication Use

Since the protocol required subjects to receive lithium or valproic acid and allowed subjects to receive benzodiazepines, the two mood stabilizers and lorazepam were the most frequently reported concomitant psychotropic medication. During the double-blind period, the percentage of subjects reporting prior use of psychotropic medication was 98.4% (125/127) in the ziprasidone group and 99.1% (112/113) in the placebo group.

During the double-blind period, the mean weekly use of lorazepam in the ziprasidone-randomized subjects was 1.3 to 1.5 mg. In the placebo-randomized group, the mean weekly use was 1.3 to 1.8 mg, with use above 1.5 mg occurring during the last 4 weeks of the period.

Ibuprofen and paracetamol were the most frequently reported concomitant non-psychotropic medications during the open-label and double-blind periods. The percentage of subjects taking concomitant medications excluding psychotropics during the double-blind period was 59.1% (75/127) and 61.1% (69/113) in the ziprasidone and placebo groups, respectively.

Thus, concomitant medication use appeared similar in the ziprasidone group compared to the placebo group during the double-blind treatment period.

Important Protocol Violations

Protocol deviations recorded for this study included subjects who entered the study even though they did not strictly meet all entrance criteria and subjects who deviated from the protocol after the start of study drug.

One subject was randomized into the double-blind period at 2 different sites, 1024 and 1064. This subject inappropriately enrolled and participated in the open-label period in the second site while still participating in the double-blind period at the first site. The subject was ultimately randomized at the second site. The data associated with this subject (identification numbers 1024102 and 10641003) were excluded from the disposition summary, the ITT, PP, and safety analysis sets and are therefore not reflected in any tables, figures, or listings.

Subjects from Mexico site 1126 were excluded from the PP analysis set due to widespread protocol violations.

Please see table below (electronically copied and reproduced from the sponsor's submission):

Table 8: Protocol Deviations Study A1281137

Protocol Deviation	Number of Subjects
Inclusion / Exclusion Criteria	
Discontinued, drug screen	1
Missing therapeutic level of mood stabilizer for 2 weeks prior to baseline visit at open-label.	8
Positive urine drug screen	11
Actual episode >90 days	1
Laboratory Tests	
ECG was not repeated prior to randomizing the subject	2
Medical	
Body mass index >35 kg/m^2	4
Visit Schedule	
Out of window visits	14[a]
Other	
<60 days in Period 1	2
< 7-week stability	28
CGI-I >3 on last open-label visit	6
Compliance Period 2	5
Prohibited Meds	9
Site 1126 Quality Review (Section 5.9)	4
Subject randomized into double-blind phase at 2 sites (1024 and 1064)[b]	1

Source: Appendix B13
Abbreviations: ECG=electrocardiogram, CGI-I= Clinical Global Impression-Improvement
[a]One subject was counted twice; therefore, the number of subjects with out of window visits is 13.
[b] The data associated with this subject (identification numbers 10241012 and 10641003) were excluded from the disposition summary, the ITT, PP, and safety analysis sets

Dosing

Ziprasidone

Of the 127 subjects randomized to the ziprasidone plus mood stabilizer treatment group, 60 were stabilized in the open-label period on 40 mg BID, 40 subjects on 60 mg BID, and 27 subjects on 80 mg BID. As seen in the table below (electronically copied and reproduced from sponsor's

submission), the subjects on all three doses of ziprasidone maintained their dose through the double-blind treatment period with few exceptions (2/group). Specifically, 58 (96.7%) subjects receiving 40 mg BID, 38 (95.0%) subjects receiving 60 mg BID, and 25 (92.6%) subjects receiving 80 mg BID maintained their dose through the double-blind treatment period (Period 2).

Table 9: Maintenance Dose Report

	ZIPRASIDONE Total	ZIPRASIDONE 40MG BID	ZIPRASIDONE 60MG BID	ZIPRASIDONE 80MG BID
	N	n (%)	n (%)	n (%)
Subjects assigned (N)	127	60	40	27
Subjects that maintained dose through Double blind phase of study		58 (96.7%)	38 (95.0%)	25 (92.6%)
Subjects that did not maintain dose through Double blind phase of study		2 (3.3%)	2 (5.0%)	2 (7.4%)

The overall median and mean modal dose of ziprasidone in the last 4 weeks of the open-label (OL) period compared to the entire double-blind (DB) period is shown in the table below:

Table 10: Overall Ziprasidone BID Modal Doses (OL and DB)

Period	*N (%)*	*Median Modal Dose*	*Mean Modal Dose*
OL (last 4 weeks)	240 (100)	60	55.5
DB	127 (100)	60	54.6

In response to FDA query (8/31/09), the sponsor reports that only three subjects had a dose increase in at least one of the weeks of the controlled phase of the study relative to their dose in the last four weeks of stable dosing in the open-label phase of the study. Thus, median and mean BID modal dose showed minimal change during the 24 weeks of the double-blind period as shown in the table below:

Table 11: Ziprasidone BID Modal Dose by Visit- Double-Blind (DB) Period

Week	*N (%)*	*Median Modal Dose*	*Mean Modal Dose*
DB Day 1	127 (100)	60	54.8
DB Week 1	127 (100)	60	54.8
DB Week 2	124 (97.6)	60	54.7
DB Week 4	119 (93.7)	60	55.5
DB Week 8	113 (89)	60	54.9
DB Week 12	105 (82.7)	60	54.3
DB Week 16	99 (78)	60	55.2
DB Week 20	94 (74)	60	54.9
DB Week 24	89 (70.1)	60	55.1

Lithium and Valproate

The incidence of subjects who were not within the protocol required range of lithium (0.6 – 1.2 mEq/L) or valproic acid (50-125 µg/mL) on at least one observation during the trial was assessed. During the open-label period, for subjects with a normal baseline, 50% of subjects who received valproic acid and 62% of subjects who received lithium had at least one observation

that was not within range. The incidences were 64% and 69% for valproic acid and lithium, respectively, without regard to baseline abnormality.

Group mean lithium and valproic acid levels assessed at baseline and Weeks 2, 4, 8, 12, and 16 during the open-label period were within the therapeutic ranges. During the open-label period, mean valproic acid levels in subjects receiving valproic acid as a mood stabilizer were 64.7 ± 33.5 to 73.0 ± 30.1 μg/mL, and mean lithium levels in subjects receiving lithium as a mood stabilizer were 0.7 ± 0.3 to 0.8 ± 0.3 mEq/L.

The incidences of lithium and valproic acid abnormalities by mood stabilizer during the double-blind period were similar to those during the open-label period for subjects with a normal baseline as well as for those without regard to baseline abnormality. Twenty-six ziprasidone-randomized and 18 placebo-randomized subjects who entered the double-blind period had abnormal baseline values.

Group mean valproic acid and lithium levels assessed at Weeks 2, 4, 8, 12, 16, 20, and 24 during the double-blind period continued to remain within the therapeutic range. During the double-blind period, mean ± SD valproic acid levels in subjects receiving valproic acid as a mood stabilizer were 67.4 ± 33.8 to 72.8 ± 31.3 μg/mL, and mean ± SD lithium levels in subjects receiving lithium as a mood stabilizer were 0.7 ± 0.3 to 0.9 ± 0.3 mEq/L.

Efficacy Findings

Time to Intervention for Mood Episode During Double-Blind Period

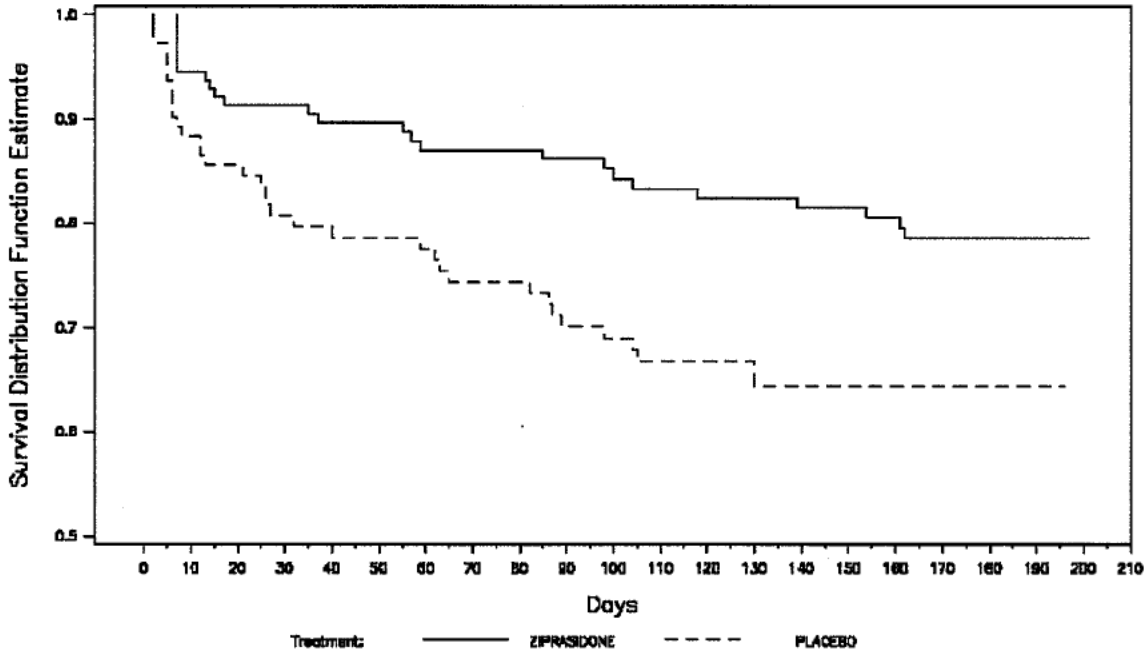
Based on the primary analysis, the TIME was statistically significant in favor of ziprasidone (p=0.0104) during the 6 months of Double-Blind Period 2 treatment. The ITT analysis revealed that 19.7% (25/127) of the ziprasidone subjects required intervention for a mood episode compared with 32.4% (36/111) of the placebo subjects as shown in the table below (electronically copied and reproduced from sponsor's submission):

Table 12: Primary Analysis- Log-Rank Test for Time to Intervention for Mood Episode (ITT Analysis- Double-Blind)

	Ziprasidone N=127	Placebo N=111
Subjects censored (%)	102 (80.3)	75 (67.6)
Subjects with Intervention for Mood Episode (%)	25 (19.7)	36 (32.4)
P-value (vs placebo)	0.0104	

The survival probability of the ziprasidone group was consistently higher than the placebo group during the 6 month double-blind period. Please see Kaplan-Meier Plot below (electronically copied and reproduced from sponsor's submission):

Figure 4: Kaplan-Meier Plot of Time to Intervention for Mood Episode (ITT Analysis Set)



The results from the PP Analysis Set were consistent with those of the ITT analysis, showing the TIME to be statistically significant in favor of ziprasidone (p=0.0123) during the 6 months of double-blind treatment (Period 2). Specifically, 22.2% (22/99) of ziprasidone subjects required intervention compared with 35.6% (32/90) of placebo subjects.

Time to Intervention for Mood Episode During Double-Blind Period: Sensitivity Analysis

As a result of the findings of the Division of Scientific Investigation (DSI) regarding numerous problems at Site 1027 (please see **Section 4.6**), a sensitivity analysis was performed by Dr. Kordzakhia (Biostatistics). As noted above, in the original ITT analysis, the TIME was statistically significant in favor of ziprasidone during the 6 months of Double-Blind Period 2 treatment, and the log-rank test p-value was 0.0104. In the sensitivity analysis, the data from Site 1027 was deleted, and the TIME was again statistically significant in favor of ziprasidone, demonstrating the log-rank test p-value to be 0.016. These results confirm that TIME was statistically significant in favor of ziprasidone compared to placebo, regardless of whether or not data from Site 1027 is included.

Time to Intervention: Mood Episode Type

A review of sponsor submitted JMP files (Mood Event Type; ITT analysis) provided data for descriptive analysis of Time to Intervention for Mood Episode based on mood episode type. Discontinuations by type of mood disorder as a percentage of all discontinuations due to mood episode are displayed in the table below. Although specific conclusions cannot be drawn, the following observations can be made. First, as shown in the table, a higher percentage of discontinuations due to mood episodes in the ziprasidone group were of depressive type (14/25,

56%), whereas in the placebo group the highest percentage of discontinuations for mood episode were equally divided between manic and depressed type (14/36, 38.9% in both groups):

Table 13: Discontinuations Due to Mood Episode (Double Blind Period) - ITT Analysis

Episode Type	Manic n (%)	Mixed n (%)	Depressed n (%)	Not Specified n (%)	Total N
Ziprasidone Group	6 (24.0)	2 (8.0)	14 (56.0)	3 (12)	25
Placebo Group	14 (38.9)	6 (16.7)	14 (38.9)	2 (5.6)	36

Second, the intervention for mood episode by mood episode type as a percentage of all randomized patients in the double-blind period is displayed in the table below and demonstrates that for all mood episode types (manic, mixed, or depressed), the percentage of subjects with relapse was lower in the ziprasidone group compared to the placebo group.

Table 14: Discontinuations due to Mood Episode (all Randomized Subjects)

Mood Episode	Ziprasidone Group (N=127)	Placebo Group (N=111)
Manic	6 (4.7%)	14 (12.6%)
Mixed	2 (1.6%)	6 (5.4%)
Depressed	14 (11.0%)	14 (12.6%)
Not Specified	3 (2.4%)	2 (1.8%)
Total	25 (19.7%)	36 (32.4%)

In response to FDA query (8/31/09), the sponsor confirms that all subjects included in the primary ITT analysis were either assigned a mood episode type (manic, mixed, or depressed) by the investigator or met the pre-specified protocol criteria of having 2 consecutive MADRS or MRS scores $\geq$ 18. Therefore, the 5 subjects listed in the tables above as Episode Type "Not Specified" did not have a mood episode type assigned by the investigator but were included in the primary ITT analysis because they met the MADRS or MRS criteria pre-specified by the protocol.

Among those who required intervention for mood episode (N=61), the median time to intervention was longer for the ziprasidone group (43.0 days, ITT and PP) compared to the placebo group (26.5 days [ITT], 20.0 days [PP]).

Time to Intervention: Mood Stabilizer Type

Randomization for this study was not stratified by type of mood stabilizer. However, among lithium treated subjects, a substantially greater proportion of placebo (44.9%) subjects experienced a mood episode requiring intervention than ziprasidone (21.1%) treated subjects. Among valproic acid treated subjects, a similar proportion of ziprasidone (18.6%) and placebo (22.6%) treated subjects experienced a mood episode requiring intervention. Please see table below (electronically copied and reproduced from sponsor's submission):

Table 15: Proportion of Subjects Requiring Intervention for a Mood Episode by Mood Stabilizer- ITT Analysis

	Ziprasidone		Placebo	
Mood Stabilizer	**N**	**n (%)**	**N**	**n (%)**
Lithium	57	12 (21.1%)	49	22 (44.9%)
Valproic acid	70	13 (18.6%)	62	14 (22.6%)

Among the 27 relapses on valproic acid, the median time to intervention for mood episode for subjects receiving ziprasidone (N=13) was 59.0 days compared to 9.5 days for subjects receiving placebo (N=14), and the mean time to intervention for mood episode for subjects receiving ziprasidone was 65.7 days (SD=52.7) compared to 31.2 days (SD=37.8) for subjects receiving placebo.

Among the 34 relapses on lithium, the median time to intervention for subjects receiving ziprasidone (N=12) was 20.0 days compared to 27.5 days for subjects taking placebo (N=22), and the mean time to intervention for mood episode for subjects receiving ziprasidone was 58.2 (SD=62.4) days compared to 51.6 (SD=44.9) days for subjects receiving placebo.

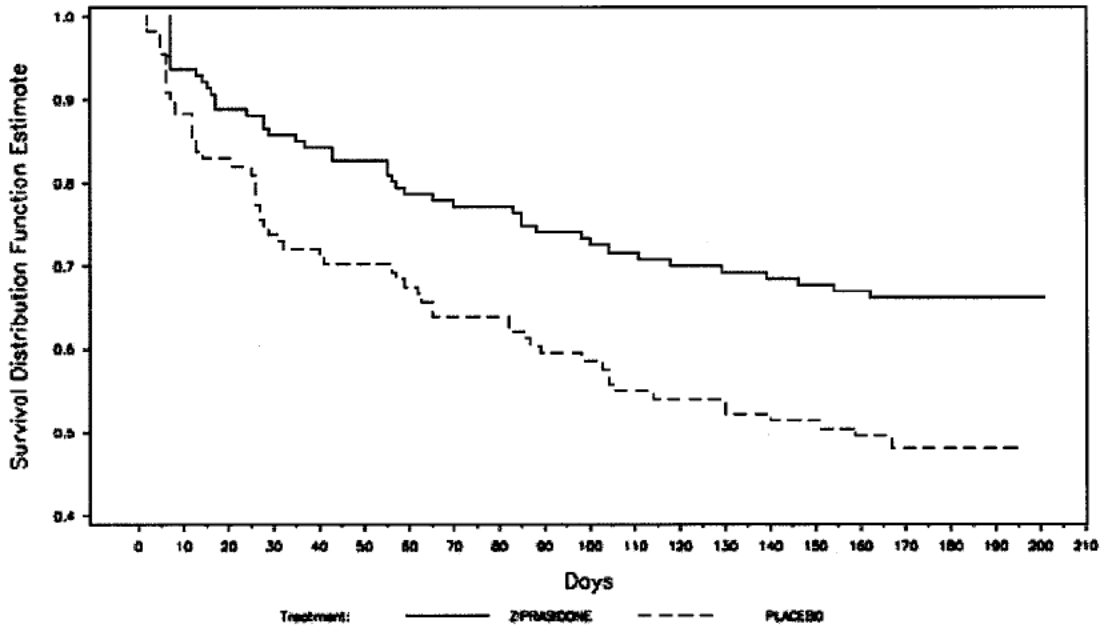
Time to Discontinuation for any Reason During Double-Blind Period

The time to discontinuation for any reason (defined as the key secondary endpoint) was statistically significant in favor of ziprasidone (p=0.0047) during the double-blind period, with 33.9% (43/123) of the ziprasidone subjects discontinued for any reason compared to 51.4% (57/111) of the placebo subjects. The survival probability of the ziprasidone group was consistently higher than the placebo group during the six month period (Period 2). The results of the PP analysis set were consistent with those from the ITT analysis. Please see table and Kaplan-Meier Plot below (electronically copied and reproduced from sponsor's submission):

Table 16: Key Secondary Analysis- Log-Rank Test for Time to Discontinuation for Any Reason during Double-Blind Period (ITT Analysis Set)

	Ziprasidone N=127	Placebo N=111
Subjects censored (%)	84 (66.1)	54 (48.6)
Subjects discontinued for any reason (%)	43 (33.9)	57 (51.4)
P-value (vs placebo)	0.0047	

Figure 5: Kaplan-Meir Plot of Time to Discontinuation for any Reason (ITT Analysis Set)



Modified Time to Intervention for Mood Episode During Double-Blind Period

The Modified TIME was defined as time to discontinuation from the trial due to lack of persistent satisfactory effect as well as discontinuations due to a mood episode requiring intervention. Therefore, Modified TIME included discontinuations due to adverse events believed to be treatment related. The Modified TIME was statistically significant in favor of the ziprasidone group (p=0.0205). In the ziprasidone-treated group, 22.8% (29/127) of the subjects discontinued per the Modified TIME criteria compared with 34.2% (38/111) of the subjects in the placebo group. The results of the PP analysis were consistent with those of the ITT analysis, with 24.2% of 99 ziprasidone treated subjects and 24.2% of 90 placebo treated subjects requiring intervention per Modified TIME criteria (p=0.0255). In the ziprasidone-treated group, the mean survival time to intervention per Modified TIME was 168.1 days and 167.1 days for the ITT and PP analysis set, respectively, while in the placebo group the mean survival time to intervention per Modified TIME was 140.3 days and 136.4 days for the ITT and PP analysis set, respectively.

Clinical Rating Scales

Efficacy was also assessed using SADS-CB (MRS), CGI-S, CGI-I, MADRS, and PANSS rating scales. For all summaries below, baseline for the double-blind period was defined as the last available observation from the open-label period. It is noteworthy that baseline clinical severity was similar overall in the subjects randomized to ziprasidone and the subjects randomized to placebo in Period 2. This would be consistent with the specified study protocol that all subjects had achieved the 8-week required clinical stability criteria prior to randomization into Period 2:

- SADS-CB (MRS): Descriptive statistics were used to analyze the change (by visit) in MRS score from baseline (Day 1) in Period 1 and the change in the final visit in the open-label Period 1 during the Double-Blind Period 2. At the end of open-label stabilization (Period 1), the mean ± standard deviation (SD) MRS score was 4.1 ± 4.6 in the group randomized to ziprasidone and 4.1 ± 4.8 in the group randomized to placebo. During the double-blind period (Period 2), for all visits beginning at Week 12, the decrease in baseline in MRS score for the ziprasidone group was statistically superior to the placebo group as shown it he table below (electronically copied and reproduced from sponsor's submission:

Table 17: Change in MRS Score during Double-Blind Period (ITT Analysis Set)

	ZIPRASIDONE		
Visit	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	P-value
Week 1	-0.85 (0.55)	(-1.93, 0.24)	0.1247
Week 2	-0.20 (0.62)	(-1.42, 1.02)	0.7515
Week 4	-0.63 (0.62)	(-1.84, 0.58)	0.3074
Week 8	-1.25 (0.71)	(-2.64, 0.13)	0.0758
Week 12	-1.98 (0.82)	(-3.59, -0.37)	0.0162
Week 16	-3.01 (0.83)	(-4.64, -1.38)	0.0003
Week 20	-2.21 (0.98)	(-4.13, -0.29)	0.0242
Week 24	-1.71 (0.71)	(-3.10, -0.32)	0.0161

LS Mean = Least Squares Mean; SE = Standard Error; CI = Confidence Interval.

- CGI: Descriptive statistics were used to analyze the change (by visit) in CGI-S and CGI-I scores from baseline in Period 1 and the change from final visit in the open-label period during the double-blind period. Both treatment groups had a mean CGI-I score of 1.8 and a mean CGI-S score of 2.2 at baseline (final visit in open-label) for the double-blind period. The CGI-I score for the ziprasidone group was significantly lower than the placebo group during Week 1 (p=0.0013), Week 4 (p=0.0188), and Week 16 (p=0.0085) of the double-blind period. Except for Week 1, when the ziprasidone-treated subjects had a significantly lower CGI-S severity score than the placebo-treated subjects (p=0.0088), there were no significant differences in the change from baseline in CGI-S scores between the ziprasidone and placebo groups. Please see tables below (electronically copied and reproduced from sponsor's submission:

Table 18: Change in CGI-I Score during Double-Blind Period (ITT Analysis Set)

	ZIPRASIDONE		
Visit	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	P-value
Week 1	-0.48 (0.15)	(-0.77, -0.19)	0.0013
Week 2	-0.27 (0.17)	(-0.61, 0.07)	0.1167
Week 4	-0.40 (0.17)	(-0.73, -0.07)	0.0188
Week 8	-0.15 (0.16)	(-0.46, 0.16)	0.3413
Week 12	-0.18 (0.16)	(-0.49, 0.14)	0.2760
Week 16	-0.51 (0.19)	(-0.89, -0.13)	0.0085
Week 20	-0.27 (0.18)	(-0.62, 0.08)	0.1317
Week 24	-0.25 (0.18)	(-0.61, 0.11)	0.1666

LS Mean = Least Squares Mean; SE = Standard Error; CI = Confidence Interval.

Table 19: Change in CGI-S Score during Double-Blind Period (ITT Analysis Set)

	ZIPRASIDONE		
Visit	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	P-value
Week 1	-0.24 (0.09)	(-0.41, -0.06)	0.0088
Week 2	-0.11 (0.13)	(-0.36, 0.13)	0.3677
Week 4	-0.18 (0.10)	(-0.39, 0.02)	0.0734
Week 8	-0.01 (0.11)	(-0.23, 0.21)	0.9166
Week 12	-0.14 (0.13)	(-0.41, 0.12)	0.2791
Week 16	-0.23 (0.16)	(-0.54, 0.08)	0.1460
Week 20	-0.05 (0.15)	(-0.35, 0.25)	0.7301
Week 24	-0.03 (0.14)	(-0.31, 0.24)	0.8162

LS Mean = Least Squares Mean; SE = Standard Error; CI = Confidence Interval.

- MADRS: Descriptive statistics were used to analyze the change (by visit) in MADRS total score from baseline (Day 1) and change from final visit in the open-label period during the double-blind period. At the end of open-label treatment period (Period 1), the mean ± SD MADRS score was 5.7 ± 6.6 in the group randomized to ziprasidone compared to 5.5 ± 7.0 in the group randomized to placebo. This indicates a comparable baseline level of severity of depressive symptoms upon their randomization into Period 2. In the double-blind period, with the exception of Week 1 when ziprasidone treated subjects had a significantly (p=0.0023) lower total MADRS score than placebo treated

subjects, there were no significant differences in the change from baseline in MADRS total score between the ziprasidone and placebo groups, as shown in the following table (electronically copied and reproduced from sponsor's submission:

Table 20: Change in MADRS Total Score during Double-Blind Period (ITT Analysis Set)

	ZIPRASIDONE		
Visit	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	P-value
Week 1	-2.29 (0.75)	(-3.76, -0.82)	0.0023
Week 2	-1.34 (0.91)	(-3.12, 0.45)	0.1412
Week 4	-1.49 (0.87)	(-3.19, 0.21)	0.0861
Week 8	-0.43 (0.82)	(-2.05, 1.18)	0.5992
Week 12	0.41 (0.76)	(-1.08, 1.90)	0.5873
Week 16	0.97 (0.78)	(-0.55, 2.49)	0.2116
Week 20	0.90 (0.68)	(-0.43, 2.23)	0.1847
Week 24	-0.00 (0.82)	(-1.62, 1.62)	0.9972

LS Mean = Least Squares Mean; SE = Standard Error; CI = Confidence Interval.

- PANSS: Descriptive statistics were used to analyze the change (by visit) in PANSS total score from baseline (Day 1) in Period 1 and change from final visit in the open-label period during the double-blind period. At the end of the open-label treatment period (Period 1), the mean ± SD total PANSS score in the group of subjects randomized to ziprasidone was 38.4 ± 9.3 and in the group of subjects randomized to placebo was 37.5 ± 8.9. During the double-blind period (Period 2), there were no significant differences in the change from baseline in PANSS total score between ziprasidone and placebo groups during any study visits as shown in the tables below:

Table 21: PANSS Total, Positive (Pos.), and Negative (Neg.) Score (Mean) by Visit during Double-Blind Period (ITT Analysis Set)

Visit	Ziprasidone				Placebo			
	N	Total	Pos.	Neg.	N	Total	Pos.	Neg.
Baseline	127	38.4	8.4	8.8	111	37.5	8.3	8.3
Week 4	123	39.0	8.4	9.0	98	38.6	8.3	8.6
Week 8	107	38.5	8.4	9.1	79	36.4	8.2	8.1
Week 12	98	38.1	8.0	9.0	70	37.3	8.6	8.2
Week 16	94	38.0	7.9	9.1	65	37.8	8.4	8.7
Week 20	84	37.5	8.0	8.8	58	35.4	8.1	7.7
Week 24	85	36.5	7.8	8.6	53	35.8	8.3	8.0

Table 22: Change in PANSS Total Score during Double-Blind Period (ITT Analysis Set)

	ZIPRASIDONE		
Visit	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	P-value
Week 4	-0.49 (0.93)	(-2.31, 1.32)	0.5954
Week 8	0.89 (0.93)	(-0.94, 2.71)	0.3414
Week 12	0.04 (1.23)	(-2.37, 2.45)	0.9745
Week 16	-0.85 (1.47)	(-3.73, 2.03)	0.5627
Week 20	0.36 (1.10)	(-1.79, 2.52)	0.7410
Week 24	-0.04 (0.88)	(-1.76, 1.68)	0.9632

LS Mean = Least Squares Mean; SE = Standard Error; CI = Confidence Interval.

Except for Week 16, there were no significant differences in the change from baseline in PANSS positive symptom subscale scores between ziprasidone and placebo groups. There were also no significant differences in the change from baseline in PANSS negative symptom subscale scores between the ziprasidone and placebo groups, with the exception of Week 8. Please see tables below (electronically copied and reproduced from sponsor's submission):

Table 23: Change in PANSS Positive Scale during Double-Blind Period (ITT Analysis Set)

	ZIPRASIDONE		
Visit	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	P-value
Week 4	0.01 (0.22)	(-0.41, 0.44)	0.9538
Week 8	0.05 (0.25)	(-0.45, 0.54)	0.8541
Week 12	-0.52 (0.32)	(-1.16, 0.12)	0.1084
Week 16	-0.56 (0.27)	(-1.08, -0.03)	0.0380
Week 20	-0.39 (0.35)	(-1.08, 0.30)	0.2649
Week 24	-0.32 (0.27)	(-0.86, 0.21)	0.2394

LS Mean = Least Squares Mean; SE = Standard Error; CI = Confidence Interval.

Table 24: Change in PANSS Negative Scale during Double-Blind Period (ITT Analysis Set)

	ZIPRASIDONE		
Visit	Difference from Placebo LS Mean (SE)	95% CI for the Difference from Placebo	P-value
Week 4	0.07 (0.29)	(-0.50, 0.64)	0.8117
Week 8	0.51 (0.26)	(0.01, 1.02)	0.0443
Week 12	0.29 (0.28)	(-0.26, 0.83)	0.3039
Week 16	0.00 (0.46)	(-0.91, 0.91)	0.9953
Week 20	0.44 (0.32)	(-0.18, 1.07)	0.1653
Week 24	0.18 (0.32)	(-0.45, 0.81)	0.5771

LS Mean = Least Squares Mean; SE = Standard Error; CI = Confidence Interval.

6.2.1.7 Conclusions

Study A1281137 demonstrates that ziprasidone is superior to placebo as adjunctive treatment with a mood stabilizer (Lithium or Valproate) in maintaining a response and preventing relapse of a mood episode in adults with Bipolar Disorder who had responded to a minimum of 2 months treatment with both agents (ziprasidone plus mood stabilizer). Furthermore, descriptive analysis suggests that ziprasidone is superior to placebo as adjunctive treatment with a mood stabilizer (Lithium or Valproate) in maintaining a response and preventing relapse of all mood episode types (manic, mixed, or depressed).

7 Review of Safety

7.1 Methods

7.1.1 Studies/ Clinical Trials Used to Evaluate Safety

The safety database and safety results summary from the single clinical trial accompanying this submission (A1281137) were reviewed in detail.

7.2 Adequacy of Safety Assessments

The parameters and frequency of safety assessments were appropriate for the drug, the population, and the duration of the trial.

7.2.1 Overall Exposure at Appropriate Doses/Durations

During the open-label period, the median number of treatment days (ie, days subject received study drug; days of missed dosing are excluded from the analysis) for all subjects enrolled was 59.5 days, while the median number of treatment days for subjects who were ultimately randomized into the double-blind period was 77.0 days.

During the double-blind period, the median number of treatment days for subjects randomized to ziprasidone was 167.0 days. Overall, the subjects randomized to ziprasidone had a median number of treatment days of 239.0 (open-label ziprasidone + double-blind ziprasidone). This represents approximately 74.7 patient-years of exposure to ziprasidone, as shown in the table below:

Table 25: Ziprasidone Patient Exposure (patient-years) for Open-Label and Double-Blind Periods

Treatment	*Open-label Patient Exposure (N)*	*Double-Blind Patient Exposure (N)*	*Total Patient Exposure*
Ziprasidone/ Ziprasidone	28.50 (127)	46.20 (127)	74.70
Ziprasidone/ Placebo	25.76 (113)	NA	25.76
Ziprasidone/ Not randomized	28.37 (344)	NA	28.37
Total	82.63 (584)	46.20 (127)	128.83

7.2.2 Explorations for Dose Response

This was not a fixed dose study. Therefore, explorations for dose-response cannot be accurately assessed.

7.2.4 Routine Clinical Testing

In addition to standard clinical and laboratory assessments, the sponsor conducted careful assessment of other specific parameters that would be of particular interest during treatment with ziprasidone or other atypical antipsychotics. The following parameters were monitored thoroughly: EPS (with directed ratings), 12-lead ECG (including various interval calculations and corrections), pulse, blood pressure, weight gain, serum glucose, lipid profile, prolactin levels, and pregnancy testing. Adverse events were coded according to the Medical Dictionary of Drug Regulatory Activities. Investigators appeared to provide the appropriate follow-up and treatment, as indicated, for specific adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pharmacokinetic and pharmacodynamic evaluations were not done in this trial.

7.3 Major Safety Results

Adverse events that occurred during treatment or within 6 days after the last dose of study drug were considered treatment-emergent and were summarized according to body system, preferred term, and investigator assessment of severity and causality. During the double-blind period, there were 177 adverse events (in 79 subjects) in the ziprasidone group compared to 142 adverse events (in 64 subjects) in the placebo group as shown in the table below (electronically copied and reproduced from sponsor's submission):

Table 26: Summary of Treatment-Emergent Adverse Events (All Causalities) for Open-Label and Double-Blind Periods

	Open-Label Period	Double-Blind Period	
	Total	Ziprasidone	Placebo
Number (%) of subjects:			
Subjects evaluable for adverse events	584	127	112
Number of adverse events	1423	177	142
Subjects with adverse events	463 (79.3)	79 (62.2)	64 (57.1)
Subjects with serious adverse events	15 (2.6)	3 (2.4)	2 (1.8)
Subjects with severe adverse events	84 (14.4)	11 (8.7)	6 (5.4)
Subjects discontinued due to adverse events	145 (24.8)	16 (12.6)	16 (14.3)
Subjects with dose reduced or temporary discontinuation due to adverse events	179 (30.7)	2 (1.6)	1 (0.9)

Definition of Serious Adverse Events (SAE)

1. Resulted in death
2. Were life-threatening
3. Required in-patient hospitalization or prolongation of existing hospitalization
4. Resulted in a persistent or significant disability/incapacity
5. Resulted in congenital anomaly/birth defect
6. Jeopardized the subject or required medical or surgical intervention to prevent one of the outcomes listed in this definition.
7. Were considered serious by the investigator

7.3.1 Deaths

There were no deaths in the open-label or controlled phases of the study.

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Open-Label Period

During the open-label period, a total of 21 subjects were reported to have a serious adverse event (SAE) while on ziprasidone. Fifteen of the 21 subjects experienced SAEs related to psychiatric symptoms, including 4 subjects with suicidal ideation, 1 subject with suicidal depression, and 1 subject with a suicidal attempt. Of the remaining 7 subjects, 2 became pregnant during open-label treatment, reported an in utero exposure, and ultimately experienced a spontaneous abortion. One subject experienced a serious dystonic reaction. Twelve subjects permanently discontinued study drug due to the events, and all of the SAEs eventually resolved. The case of the dystonic reaction was possibly related to study drug. It is difficult to determine whether the cases of suicidal ideation and suicide attempt are related to ziprasidone. The rest of the SAEs were either unrelated to study drug or, in the case of the psychiatric events, related to the disease under study.

Table 27: SAE Line Listing by Mood Stabilizer (Open-label Period I)

Study Drug & Mood Stabilizer Assignment	Subject Number	MedDRA Preferred Term	Action Taken	Outcome
Ziprasidone + Valproic Acid	10111009	Psychiatric decompensation	Discontinued	Resolved
	10311001	Suicidal ideation	Discontinued	Resolved
		Bipolar disorder	Discontinued	Resolved
	10331008	Bipolar disorder	Discontinued	Resolved
	10451018	Thrombophlebitis	Discontinued	Resolved
	10511025	Chronic obstructive pulmonary disease	None	Resolved
	10511029	Suicidal ideation	None	Resolved
	10541017	Influenza	Treatment given	Resolved
	10621003	Dystonia	None	Resolved
	10831001	Depression	Discontinued	Resolved
	10981006	Bipolar I disorder	None	Resolved
		Bipolar I disorder	None	Resolved
	11381002	Affect lability	None	Resolved
	11391011	Pregnancy	Discontinued	Resolved
	11491001	Mania	Discontinued	Resolved
Ziprasidone + Lithium	10131028	Suicidal ideation	Discontinued	Resolved
	10241002	Suicide attempt	Ziprasidone dose increased	Resolved
	10271029	Pregnancy	Discontinued	Resolved
	10401002	Bipolar I disorder	Discontinued	Resolved
	10511005	Psychotic Disorder	None	Resolved
	10521012	Anxiety	Discontinued	Resolved
		Depression, suicidal	Discontinued	Resolved
	10731001	Mania	Discontinued	Resolved
		Psychotic disorder	Discontinued	Resolved
	11231001	Suicidal ideation	Treatment given	Resolved

The following are narratives of serious adverse event cases experienced by subjects during the open-label period (Period 1):

Suicidal Ideation:

1. A suicide attempt occurred in a 39 year old white male (10241002) on ziprasidone 60 mg BID and lithium. After feeling depressed for a few days, he took two handfuls of lithium (300 mg) tablets, but vomited them up 20 minutes later. He did not report the event until his follow-up visit several days later, at which time the ziprasidone was increased to 80 mg BID. The subject was considered recovered and remained in the study.
2. A 26 year old white female (10521012) with Bipolar I Disorder most recent episode mixed on lithium and ziprasidone developed worsening depression with suicidal ideation and psychotic anxiety after the dose of ziprasidone was decreased from 80 mg BID to 60 mg BID due to intolerable somnolence. The patient was hospitalized for one day, and study drug was discontinued. SAE was recorded as depression, suicidal.
3. A 23 year old white male (10131028) reported suicidal ideation with a plan to overdose on his medication 17 days after starting lithium 1200 mg BID and ziprasidone 40 mg BID. Subject was hospitalized and study drug was discontinued.

4. A 41 year old male (10311001) on ziprasidone 80 mg BID plus divalproex sodium had onset of suicidal ideation and exacerbation of Bipolar Disorder after several weeks of open-label treatment. The subject had a plan to hang himself or overdose on his medications. The subject was hospitalized and study drug discontinued.
5. A 31 year old white female (10511029) who was taking ziprasidone and Depakote ER since 5/30/07 reported suicidal ideation on (b) (6) with a plan to cut herself. She had apparently been non-compliant and did not take study medication from (b) (6) to (b) (6). She was hospitalized and discontinued from the study.
6. A 30 year old female (11231001) on lithium 900 mg daily received ziprasidone 40 mg BID for 14 days (b) (6) Ziprasidone was then discontinued due to the non-serious adverse events of akathisia and drowsiness. On follow-up visit (b) (6), akathisia was still present, and the patient began a moderate to severe depressive episode. On a second follow-up visit (b) (6), the akathisia had resolved, but the patient appeared to have suicidal ideation. The subject was eventually hospitalized.

Chronic Obstructive Pulmonary Disease:

1. A 34 year old white male (10511025) with a history of COPD was hospitalized in the intensive care unit for COPD exacerbation and pneumonia. The patient rapidly improved and was discharged. The subject had signed consent for the study prior to hospitalization but did not enter screening visit or take study medication until after discharge.

Dystonia:

1. A 26 year old white male (10621003) with a bipolar-mixed history presented on (b) (6) with an acute dystonic reaction characterized by significant lateral torsion in the hand and neck and symptoms of difficulty breathing. The patient, who had been on Depakote ER and ziprasidone (80 mg BID) since (b) (6) was given 75 mg Benadryl orally without response. On route to the emergency room, he received intramuscular Benadryl and subsequently recovered. The event was considered possibly related to study drug, and study drug was discontinued.

7.3.2.2 Double-Blind Period

During the double-blind period (Period 2), a total of 7 subjects reported serious adverse events (SAEs). Three of these subjects had been randomized to ziprasidone, and the other four had been randomized to placebo. Two of the ziprasidone subjects experienced suicidal ideation and one subject experienced an arrhythmia (ventricular extrasystole). In the case of the arrhythmia, it is possible that the event was related to treatment with ziprasidone. In the 2 cases of suicidal ideation, it is difficult to determine whether or not the adverse events were related to treatment with ziprasidone. All SAEs in the placebo-randomized subjects were related to mania or hypomania. Six subjects permanently discontinued study drug for the events. All of the SAEs resolved.

Table 28: Serious Adverse Events by Study Drug Assignment and Mood Stabilizer (Double-Blind Period 2)

Study Drug & Mood Stabilizer Assignment	Subject Number	MedDRA Preferred Term	Action Taken	Outcome
Ziprasidone +Valproic Acid	10131017	Suicidal ideation	Discontinued	Resolved
	11351008	Suicidal ideation	Discontinued	Resolved
	11421014	Arrhythmia	Discontinued	Resolved
Placebo + Lithium	11031003	Mania	Discontinued	Resolved
	11381004	Mania	Discontinued	Resolved
	11421001	Mania	Discontinued	Resolved
Placebo + Valproic Acid	11381002	Hypomania	None	Resolved

The following narratives describe the serious adverse event cases in the ziprasidone- randomized group during the double-blind period (Period 2):

Suicidal Ideation:

1. A 45 year old white male (Subject 10131017) taking Depakote ER (1250-1500 mg/day) since December 22, 2006 experienced suicidal ideation 7 days after being randomized to ziprasidone 60 mg BID. He reported suicidal thoughts and stated he did not feel safe. The study drug was permanently discontinued, and the subject was hospitalized. He gradually improved and was discharged from the hospital 7 days later. The patient had a history of several previous hospitalizations for suicidal ideation. The sponsor concluded that the adverse event was not related to study drug but instead was most likely related to the acute psychosocial stressor of the patient becoming homeless at approximately the same time as double-blind study medication was begun.
2. A 41 year old white female (Subject 11351108) was admitted to the hospital in (b) (6) for suicidal ideation. The subject had been on Depakote ER 500 mg BID since February 19, 2007 and started the double-blind randomization period June 6, 2007, receiving ziprasidone 40 mg BID. Study drug was discontinued when the subject was hospitalized (b) (6) The sponsor concluded that since the life situation of the subject's husband and daughter leaving her played a contributory role towards the adverse event, it was unlikely to be related to study drug.

Cardiac Arrhythmia:

A 39 year old white female (Subject 11421014) started ziprasidone on February 16, 2007. On October 19, 2007, a local cardiologist noted ventricular extrasystole on an ECG done on October 11, 2007. The subject was taking ziprasidone 40 mg BID and valproic acid (dose not reported) at that time. A follow-up ECG on October 24, 2007 did not show ventricular extrasystole but still had an abnormal arrhythmia. No information is provided as to the exactly what the "abnormal arrhythmia" was. The study medication was discontinued on October 23, 2007, and ECG on November 8, 2007 was normal and unchanged compared to baseline ECG. The subject never had symptoms of cardiac arrhythmia.

7.3.3 Dropouts and/or Discontinuations

The following reasons could be used by the investigator for discontinuing the subject:

- Insufficient clinical response
- AE
- Laboratory abnormality
- Subject death
- Protocol violation
- Lost to follow-up
- Did not meet entrance criteria
- Subject no longer willing to participate
- Withdrawn due to pregnancy
- Study terminated by sponsor
- Other reasons that could not be captured under any other category

Most discontinuations from the trial were for reasons not related to the study drug. The majority of these nonrelated reasons were attributed to "Subject not willing to participate" in the open-label period, and "Other" in the double-blind period. The majority of discontinuations that were considered to be related to study treatment were attributed to AEs in the open-label period and "Lack of efficacy" in the double-blind period. Please see table below (electronically copied and reproduced from sponsor's submission):

Table 29: Subject Disposition

	Open-Label Period	Double-Blind Period	
Number (%) of Subjects	**Total**	**Ziprasidone**	**Placebo**
Screened 1088			
Assigned to Study Treatment[a]	586	127	113
Treated	584	127	112
Completed	241 (41.3)	84 (66.1)	54 (48.2)
Discontinued	343 (58.7)	43 (33.9)	58 (51.8)
Reason for discontinuation			
Related to study drug	158 (27.1)	15 (11.8)	28 (25.0)
Lack of efficacy	31 (5.3)	9 (7.1)	22 (19.6)
Laboratory abnormality	1 (0.2)	1 (0.8)	0
Adverse event	126 (21.6)	5 (3.9)	6 (5.4)
Not related to study drug	189 (32.4)	28 (22.0)	30 (26.8)
Other	54 (9.2)	10 (7.9)	6 (5.4)
Laboratory abnormality	2 (0.3)	-	-
Adverse event	22 (3.8)	6 (4.7)	9 (8.0)
Lost to follow-up	35 (6.0)	3 (2.4)	6 (5.4)
Subject no longer willing to participate in study	76 (13.0)	9 (7.1)	9 (8.0)

During the double-blind period, a total of 16 subjects (12.6%) randomized to ziprasidone and 16 subjects (14.3%) randomized to placebo discontinued the study drug due to all-causality adverse events (AEs). One ziprasidone subject (10641021) discontinued the study due to a severe, treatment-related elevation of liver enzymes. The most common reason for discontinuation from the study by system organ class was psychiatric disorders in both the ziprasidone and placebo groups. There were no temporary discontinuations in the double-blind period; however, 17 subjects had a reduction in dose of the study drug: 8 in the ziprasidone group, and 9 in the placebo group.

Table 30: Discontinuations Due to Adverse Events (Double Blind Treatment Period)

Adverse Event	Ziprasidone (N=127) n (%)	Placebo (N=112) n (%)
Psychiatric Disorders	**6 (4.8)**	**11 (9.2)**
Suicidal Ideation	2 (1.6)	1 (0.8)
Mania	1 (0.8)	5 (4.4)
Depression	3 (2.4)	2 (1.6)
Psychosis	0 (0.0)	1 (0.8)
Self-injurious Ideation	0 (0.0)	1 (0.8)
Bipolar Disorder Exacerbation	0 (0.0)	1 (0.8)
Nervous System Disorders	**3 (2.4)**	**3 (2.4)**
Somnolence/sedation	2 (1.6)	0 (0.0)
Tremor	1 (0.8)	0 (0.0)
Dysarthria	0 (0.0)	1 (0.8)
Dyskinesia	0 (0.0)	2 (1.6)
Gastrointestinal Disorders	**0 (0.0)**	**3 (2.4)**
Bleeding Ulcer	0 (0.0)	1 (0.8)
Glossodynia	0 (0.0)	1 (0.8)
Dysphagia	0 (0.0)	1 (0.8)
Cardiac Disorders	**1 (0.8)**	**0 (0.0)**
Cardiac Arrhythmia	1 (0.8)	0 (0.0)
Endocrine Disorders	**2 (1.6)**	**0 (0.0)**
Goiter	1 (0.8)	0 (0.0)
Elevated TSH	1 (0.8)	0 (0.0)
Abnormal clinical Labs	**1 (0.8)**	**2 (1.6)**
Elevated Liver Enzymes	1 (0.8)	1 (0.8)
Hepatitis e antibody reactive	0 (0.0)	1 (0.8)
Dermatologic disorders	**0 (0.0)**	**1 (0.8)**
Worsening Psoriasis	0 (0.0)	1 (0.8)

7.3.3.1 Ziprasidone Discontinuations Due to Adverse Events (Double-Blind Period)

The following narratives describe some of the discontinuation due to adverse event cases in the ziprasidone- randomized group during the double-blind period, selected based on clinical relevance:

Suicidal Ideation:

Please see narratives in **Section 7.3.2**

Cardiac Arrhythmia:

Please see narrative in **Section 7.3.2**

Goiter/Elevated TSH:

A 32 year old white female (subject 10481006) was withdrawn from the study after 12 weeks of double-blind treatment due to severe thyroid stimulating hormone (TSH) increased and severe enlarged thyroid. The subject was assigned to ziprasidone 160 mg and lithium at the time of discontinuation. At Week 16 of Period 1, TSH was 4.98 ng/dl (normal range: 0.35 – 5.5 ng/dl). On Week 4 of Period 2, TSH was found to be 137.92 ng/dl. On Week 12 of Period 2, TSH was 136.28 ng/dl and "enlarged thyroid" was reported. The causality was felt to be due to study drug. TSH had decreased to 10.97 ng/dl by Period 2, Week 24 (12 weeks after discontinuation of study drug), but thyroid remained enlarged. TSH subsequently returned to normal. Free T4 (thyroxine) remained normal throughout the study. The subject also reported dizziness, dry mouth, sedation, and peripheral edema.

Elevated Liver Enzymes:

A 40 year old Hispanic male (subject 10641021) assigned to ziprasidone plus lithium withdrew from the study after Week 6 of Period 2. At screening (prior to Period 1), Aspartate Aminotransferase (GOT), Alanine Aminotransferase (GPT), and Lactate Dehydrogenase (LDH) were normal, and Hepatitis B Surface Antigen was nonreactive. Total bilirubin and alkaline phosphatase remained normal throughout the study. Subsequent GOT, GPT and LDH levels were as follows:

Table 31: Subject 10641021 Liver Enzyme Data

Period 1				**Period 2**			
						Last Dose of Study Drug	
Week	**0**	**4**	**16**	**4**	**5**	**6**	**24**
GOT (normal: 0-41 U/L)	33	29	47	117	120		93
GPT (normal: 0-45 U/L)	38	31	42	241	209		156
LDH (normal: 100-242 U/L)	162	132	276	140	148		135

The causality of this event was felt to be "unknown or treatment related." No other adverse events were reported, but a history of alcohol dependence was noted. The patient also had a Hepatitis C Antibody reported as "reactive" at screening.

7.3.4 Significant Adverse Events

7.3.4.1 Nervous System Disorders

During the open-label period, nervous system disorders that occurred in ≥ 5% of subjects included akathisia (7.5%), dizziness (8.4%), headache (5.5%), sedation (22.9%), somnolence (17.0%), and tremor (12.5%).

During the double-blind period, nervous system disorders that occurred more frequently in the ziprasidone-treated group compared to placebo included sedation (2.4% vs. 0.9%), somnolence (4.7% vs. 0.9%), and tremor (6.3% vs. 3.6%). One adverse event each of dyskinesia, extrapyramidal disorder, and Parkinsonian rest tremor were reported in the ziprasidone group. In the placebo group, three adverse events of dyskinesia and one adverse event each of areflexia, bradykinesia, extrapyramidal disorder, and tardive dyskinesia were reported.

7.3.4.2 Suicidality

The incidence of suicidal ideation and suicide attempt during the open-label period (Period 1) was 0.7% (n=4) and 0.2% (n=1), respectively. Two of the 4 subjects with suicidal ideation and the 1 subject with a suicide attempt were ultimately randomized.

The incidence of suicidal ideation during the double-blind period was 1.6% (n=2) for ziprasidone subjects and 1.8% (n=2) for placebo subjects. One placebo subject also experienced self-injurious ideation.

It is difficult to determine whether the adverse events of suicide ideation and suicide attempt were treatment-related. Concerning the cases in the open-label period, non-compliance with study medication may have been a factor in one (10511029). In another case (11231001), the subject was already off study medication for almost 2 weeks prior to the onset of suicidal ideation and was also suffering from akathisia which could have been a contributing factor. Concerning the 2 subjects in the ziprasidone group who experienced suicidal ideation during the double-blind treatment period, one was noted to have a history of several previous hospitalizations for suicidal ideation, and in both subjects, an acute psychosocial stressor coincided with the onset of suicidal ideation and was felt to be a contributing factor. Please see **Section 7.3.2** for narratives. None of the cases were attributed to ziprasidone by the sponsor.

7.3.4.3 Cardiac Adverse Events

Cardiac disorders were reported in 1.7% (n=10) of all open-label subjects. One subject (11031104) was reported to have an old myocardial infarction; however, this subject was not randomized. Although the event was considered to have occurred prior to study entry, at an undetermined age, the causality of the event was reported as "treatment-related."

During the double-blind period (Period 2), cardiac disorders were reported in 1.6% (n=2) of ziprasidone subjects and 2.7% (n=3) of placebo subjects. Of the cardiac events, one subject was

reported to have an arrhythmia that was reported as an SAE, was considered related to study drug, and led to discontinuation from the study (please see **Section 7.3.2** for narrative).

7.3.4.4 Weight Gain

For all subjects in the open-label period, 5.5% experienced >7% increase in body weight and 3.2% experienced >7% decrease in body weight.

During the double-blind period, the incidence of clinically significant weight gain (≥7% of body weight) was 5.6% in both the ziprasidone and placebo treatment groups. However, 12.8% of ziprasidone-randomized subjects lost > 7% of body weight compared to 5.6% of placebo-randomized subjects. Overall, the ziprasidone group lost a mean of 0.8 kg and the placebo group gained a mean of 0.5 kg during the double-blind period.

7.3.4.5 Metabolic Disorders

During the open-label period, one adverse event each of blood glucose increased, hyperglycemia, and hypertriglyceridemia were reported, and 2 adverse events of hyperlipidemia were reported.

During the double-blind period, one adverse event each of blood cholesterol increased, blood glucose increased, dyslipidemia, and hyperglycemia were reported in the ziprasidone group, and one adverse event each of diabetes mellitus and hypercholesterolemia were reported in the placebo group. The mean change from baseline at week 24 for fasting glucose was +0.3 ± 22.9 mg/dl in the ziprasidone treated patients (N=65) and +2.6 ± 22.9 mg/dl in the placebo treated patients (N=37). The mean changes from baseline in fasting levels of total cholesterol (+0.7 ± 22.1 vs. +5.0 ± 30.0 mg/dl; N = 64 vs. N = 37), LDL (-0.1 ± 19.0 vs. +3.7 ± 23.2 mg/dl; N = 63 vs. N = 36), HDL (-0.7 ± 7.6 vs. -0.8 ± 9.5 mg/dl; N = 65 vs. N = 37), and triglycerides (+5.2 ± 61.0 vs. -0.8 ± 82.8 mg/dl; N = 64 vs. N = 37) were similar in the ziprasidone and placebo patients.

7.4.1 Common Adverse Events

During the open-label period (Period 1), the majority of all-causality adverse events (AEs) were judged to be mild (627 AEs) or moderate (625 AEs). A total of 126 severe all-causality AEs occurred. Organ systems with the highest frequency of all causality events included nervous system disorders (61.3%), psychiatric disorders (26.4%), gastrointestinal disorders (18.8%), general disorders and administrative site conditions (13.9%), and musculoskeletal and connective tissue disorders (12.0%). Within these organ systems, the AEs that occurred with ≥ 10% incidence included sedation, somnolence, tremor, and insomnia. The tables below summarize the incidence of all causality, treatment-emergent AEs that occurred at a rate of ≥5% and at a rate of ≥ 2% in the open-label period. None of these commonly reported adverse events are new or unexpected with ziprasidone treatment.

Table 32: Treatment-Emergent Adverse Events Experienced by ≥ 5% of Subjects during the Open-Label Period (N=584)

Adverse Event	n (%)
Akathisia	47 (8.0)
Dizziness	49 (8.4)
Fatigue	44 (7.5)
Headache	32 (5.5)
Insomnia	59 (10.1)
Nausea	42 (7.2)
Sedation	134 (22.9)
Somnolence	99 (17.0)
Tremor	73 (12.5)

Table 33: Treatment-Emergent Adverse Events Experienced by ≥ 2% of Subjects during the Open-Label Period (N=584)

Adverse Event	n (%)
Anorexia	13 (2.2)
Akathisia	47 (8.0)
Diarrhea	24 (4.1)
Dizziness	49 (8.4)
Dry mouth	13 (2.2)
Extrapyramidal syndrome	14 (2.4)
Fatigue	44 (7.5)
Headache	32 (5.5)
Hypersomnia	14 (2.4)
Insomnia	59 (10.1)
Irritability	12 (2.1)
Lethargy	16 (2.7)
Nausea	42 (7.2)
Restlessness	18 (3.1)
Sedation	134 (22.9)
Somnolence	99 (17.0)
Tremor	59 (10.1)
Vision blurred	20 (3.4)
Vomiting	21 (3.6)
Weight increased	14 (2.4)

The highest frequency of all causality adverse events by body system in ziprasidone versus placebo subjects during the double-blind period (Period 2) were similar to the open-label period and included gastrointestinal disorders (11.0% vs. 7.1%), infections and infestations ((16.5% vs. 9.8%), investigations (13.4% vs. 3.6%), nervous system disorders ((20.5% vs. 15.3%), and psychiatric disorders (18.1% vs. 27.7%). Insomnia (10.7%) in the placebo subjects was the only

adverse event that occurred in ≥ 10% of subjects. The majority of AEs were classified as mild or moderate in severity.

Among the treatment-emergent adverse events that occurred at a rate of ≥ 5% in either treatment group during the double-blind period, tremor was the only event that occurred at a higher incidence in the ziprasidone group (6.3%; n=8) compared to the placebo group (3.6%; n=4). Nervous system disorders were the most frequently reported AEs in the ziprasidone treatment group, while psychiatric disorders were the most frequently reported AEs in the placebo treatment group.

The adverse event reporting rates in the double-blind period may have been biased by the previous open-label ziprasidone treatment (21.6% of subjects during the open-label period were discontinued due to adverse events). The table below summarizes adverse events reported in greater than 2% of subjects in the ziprasidone group and at a higher proportion than the placebo group. The adverse events listed are probably related to treatment with ziprasidone because these AEs occur commonly with ziprasidone treatment at a rate considerably higher than in the placebo group. Furthermore, all of these common AEs are known to be associated with ziprasidone, from pre-marketing and postmarketing experience.

Table 34: Adverse Events Reported in ≥ 2% of the Ziprasidone group (and at a Higher Proportion than in the Placebo Group) During Double-Blind Treatment Period

Adverse Event	Ziprasidone (N= 127) n(%)	Placebo (N=112) n(%)
Headache	4(3.2)	3(2.7)
Hypothyroidism	4(3.2)	1(0.9)
Sedation	3(2.4)	1(0.9)
Somnolence	6(4.7)	1(0.9)
Tremor	8(6.3)	4(3.6)
Weight increased	4(3.1)	2(1.8)

7.4.2 Laboratory Findings

During the double-blind period, laboratory abnormalities were reported in 81% of ziprasidone-randomized subjects and 81% of placebo-randomized subjects. The majority of these abnormalities was transient in nature, resolved with continued treatment, and was regarded as minor deviations which were not clinically significant. The events in the ziprasidone-randomized group were mostly related to changes in liver enzymes, thyroid function, and glucose. In the ziprasidone-randomized group, 1 subject had an ALT > 3 x upper limit of normal (ULN), 1 subject had a fasting glucose < 0.6 x lower limit of normal (LLN), 1 subject had a fasting glucose > 1.5 x ULN, and 1 subject had a random glucose > 1.5 x ULN. Among the placebo-randomized group, 1 subject had an ALT > 3 x ULN and 1 subject had an elevated creatinine (> 1.3 x ULN).

Elevated prolactin (> 1.1 x ULN) during the double-blind period was reported in 12% (10/81) of ziprasidone subjects and 6% (5/83) of placebo subjects. Hyperprolactinemia was reported as a treatment-related adverse event in 1 ziprasidone-randomized subject.

A review of the mean and median values at baseline and post-baseline visits during the open-label and double-blind periods did not reveal any clinical trends or abnormal laboratory results that were unexpected.

7.4.3 Vital Signs

Median baseline sitting blood pressure and pulse rate were similar throughout the open-label period (Period 1) for all subjects who entered the trial and for subjects who were ultimately randomized into Period 2. For the double-blind period (Period 2), median baseline sitting blood pressure and pulse rate were comparable to the open-label period, remained similar throughout the period, and were similar across treatment groups. No relevant trends or differences between the lithium- and valproic acid-treated subjects were observed. There were no adverse events related to blood pressure. Tachycardia was reported in one placebo-randomized subject.

7.4.4 Electrocardiograms (ECGs)

7.4.4.1 Open-Label Period

The sponsor notes that the magnitude of the prolongation in QTc interval observed in the open-label period when all subjects received adjunctive ziprasidone was generally comparable to that reported previously in clinical trials for oral ziprasidone alone in subjects with schizophrenia and acute bipolar mania. Five subjects during the open-label period had adverse event of prolonged QTc, and one of the 5 subjects was discontinued from the study for this adverse event. None of the QTcF values were > 500 msec. Please see tables below (electronically copied and reproduced from sponsor's submission):

Table 35: QT and QTc Intervals: Mean Baseline and Week 16 Values (msec) and Mean Change from Baseline to Week 16 (msec) During the Open-Label Treatment Period 1

	Baseline (N=574)		Week 16 (N =294)		Week 16 (N = 287)	
	Mean	Range	Mean	Range	Mean Change	Range
QT interval (msec)	383.2	295.3-476.3	390.3	308.0-473.0	9.3	-79.0-97.7
QTcB	414.3	348.0-484.0	418.4	343.0-490.0	4.2	-81.3-86.7
QTcF	403.3	344.0-463.3	408.4	345.0-482.0	5.9	-46.0-90.7

Table 36: Incidence of Categorical Increases in QTc Intervals during the Open-Label Treatment Period 1: Number (%) of Subjects

	Fridericia	Bazett
Incidence[a]		
QTc ≥450 msec	51 (8.7)	169 (28.9)
QTc ≥480 msec	5 (0.9)	19 (3.3)
QTc ≥500 msec	0	5 (0.9)
Increase from Baseline[a]		
≥30 msec	97 (18.2)	139 (26.0)
≥60 msec	5 (0.9)	10 (1.9)
≥75 msec	2 (0.4)	3 (0.6)
Percent change ≥20%	2 (0.4)	3 (0.6)

7.4.4.2 Double-Blind Period

Mean changes in QT, QTcB, and QTcF from baseline of the double-blind treatment period to Week 24 were greater in the ziprasidone group than in the placebo group as shown in the table below:

Table 37: QT and QTc Intervals: Mean Baseline and Week 24 Values (msec) and Mean Change from Baseline to Week 24 (msec) During the Double-Blind Treatment Period 2

Parameter	Treatment Group	Baseline Mean	Final Mean	Change in Mean
QT interval (msec)	Ziprasidone	393.2	386.2	-3.3
	Placebo	389.4	378.8	-8.7
QTcB	Ziprasidone	420.2	422.1	2.1
	Placebo	415.9	410.8	-2.0
QTcF	Ziprasidone	410.6	409.4	0.2
	Placebo	406.5	399.5	-4.3

In the ziprasidone-treated group, 1 subject had a QTcF interval ≥ 500 msec. In the placebo group 1 subject had a QTcF ≥ 480 msec, and no subject had QTcF interval ≥ 500 msec. The ziprasidone-treated group had 3 subjects with an increase from baseline in QTcF ≥ 60 msec, and 2 subjects had an increase from baseline in QTcF ≥ 75 msec, compared with none in the placebo group. Please see table below (electronically copied and reproduced from sponsor's submission):

Table 38: Incidence of Categorical Increases in QTc Intervals during the Double-Blind Treatment Period 2: Number (%) of Subjects

	Ziprasidone (N= 127)		Placebo (N =112)	
	Fridericia	Bazett	Fridericia	Bazett
Incidence				
QTc ≥450 msec	17 (13.4)	40 (31.5)	4 (3.6)	21 (18.8)
QTc ≥480 msec	2 (1.6)	7 (5.5)	1 (0.9)	1 (0.9)
QTc ≥500 msec	1 (0.8)	1 (0.8)	0	0
Increase from Baseline[a]	N = 125	N = 125	N = 105	N = 105
≥30 msec	17 (13.6)	34 (27.2)	7 (6.7)	13 (12.4)
≥60 msec	3 (2.4)	7 (5.6)	0	1 (1.0)
≥75 msec	2 (1.6)	2 (1.6)	0	0
Percent change ≥20%	2 (1.6)	1 (0.8)	0	1 (1.0)

N=125 for increase from baseline (ziprasidone), N=105 for increase from baseline (placebo)

In the subgroup of subjects receiving valproic acid as a mood stabilizer, the mean changes in QTcB and QTcF were greater than in the placebo group. One subject in this subgroup randomized to ziprasidone had a QTcF ≥ 480 msec compared to none in the placebo group, and 1 subject in the ziprasidone-treated group had an increase from baseline in QTcF ≥ 60 msec compared to none in the placebo group.

Table 39: QT and QTc Intervals in Subjects on Valproic Acid: Mean Baseline and Week 24 Values (msec) and Mean Change from Baseline to Week 24 (msec) During the Double-Blind Treatment Period 2

Parameter	Treatment Group	Baseline Mean	Final Mean	Change in Mean
QT interval (msec)	Ziprasidone	392.9	383.1	-5.9
	Placebo	382.6	373.0	-7.4
QTcB	Ziprasidone	414.9	416.6	4.1
	Placebo	409.7	406.6	-1.0
QTcF	Ziprasidone	407.1	404.8	0.7
	Placebo	400.1	394.9	-3.2

Ziprasidone: N=69 at baseline, N-45 at Week 24, N=43 Mean change
Placebo: N=62 at baseline, N=34 at Week 24, N=34 Mean change

In the subgroup of subjects receiving lithium as a mood stabilizer, the QT, QTcB, and QTcF intervals were on average slightly decreased in the ziprasidone-treated subjects, but the magnitude of the decrease in these intervals observed in the placebo-treated subjects was greater. One subject (subject 10171001) in the ziprasidone-treated group had an increase in QTcF ≥ 500 msec. This occurred on only one occasion (Week 8; 556 msec), and subsequent values were ≤ 450 msec. No subjects in the placebo-treated group had an increase in QTcF ≥ 500 msec. In the ziprasidone-treated group, 2 subjects had an increase from baseline in QTcF ≥ 60 msec and 2 had an increase from baseline in QTcF ≥ 75 msec. No subjects in the placebo group had an increase from baseline in QTcF ≥ 60 msec or QTcF ≥ 75 msec.

Table 40: QT and QTc Intervals in Subjects on Lithium: Mean Baseline and Week 24 Values (msec) and Mean Change from Baseline to Week 24 (msec) During the Double-Blind Treatment Period 2

Parameter	Treatment Group	Baseline Mean	Final Mean	Change in Mean
QT interval (msec)	Ziprasidone	393.5	389.9	-0.5
	Placebo	398.3	391.0	-11.6
QTcB	Ziprasidone	426.5	428.4	-0.1
	Placebo	424.0	419.4	-4.3
QTcF	Ziprasidone	414.9	414.8	-0.3
	Placebo	414.9	409.3	-7.0

Ziprasidone: N=57 at baseline, N=39 at Week 24, N=39 Mean change
Placebo: N=47 at baseline, N=16 at Week 24, N=15 Mean change

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

This was not a fixed dose study. Therefore, explorations for dose dependency for adverse events could not be assessed.

7.5.3 Drug-Demographic Interactions

No analysis according to age, race, or gender was included in this submission.

7.5.4 Drug-Disease Interactions

In this submission, only one disease population (Bipolar Disorder) was under study. Therefore, drug-disease interactions could not be assessed.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted specifically in support of this application. Previous *in vitro* enzyme inhibition studies in human liver microsomes suggest that ziprasidone has little inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Thus, ziprasidone treatment would not likely interfere with the metabolism of drugs primarily metabolized by these enzymes. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium. Furthermore, population pharmacokinetic analysis of schizophrenic patients enrolled in controlled clinical trials has not revealed evidence of clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam.

In vivo studies have revealed a 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, a 35-40% increase in ziprasidone AUC by concomitantly administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid. Since carbamazepine is used to treat mania in some patients, this potential interaction is clinically relevant. Treatment with ketoconazole, a potent inhibitor of CYP3A4, increased the

AUC and Cmax of ziprasidone by about 35-40%. Thus, inhibitors of this enzyme may have a clinically significant effect on the pharmacokinetics of ziprasidone.

Lithium

As noted above, *in vivo* studies showed no effect of ziprasidone on the pharmacokinetics of lithium. Specifically, ziprasidone at a dose of 40 mg BID administered concomitantly with lithium at a dose of 450 mg BID for 7 days did not affect the steady-state level or renal-clearance of lithium.

Valproate

No formal study has been conducted to examine the potential pharmacokinetic interaction of ziprasidone and valproic acid. In response to written FDA requests ("Comments in lieu of Pre-Submission Meeting letter of 01 October 2008 and queries in Filing Letter of March 2009), the sponsor has provided justification for the lack of a formal study and further rationale as to whether or not ziprasidone and valproic acid would affect the *in vivo* steady state concentrations of each other when coadministered. The sponsor's rationale is as follows:

First, ziprasidone and valproic acid lack any common metabolic pathways. The major pathways of valproate biotransformation are mitochondrial β-oxidation and conjugation with glucuronic acid. Less than 15-20% of metabolism occurs by other oxidative mechanisms such as CYP dependent oxidation. The primary CYP pathways are CYP2C9 and CYP2A6. In contrast, ziprasidone is metabolized by aldehyde oxidase (about two-thirds) and CYP3A4 (about one-third). As noted above, ziprasidone has been shown to have little effect on activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes.

Second, in the current clinical trial (A1281137), group mean lithium and valproic acid levels assessed at baseline and frequent post-baseline intervals throughout both the open label and the double-blind periods of the study were within the protocol specified therapeutic range [lithium (0.6 – 1.2 mEq/L); valproic acid (50-125 μg/ml)] .

The sponsor therefore concludes that pharmacokinetic interactions between ziprasidone and valproate are unlikely and that a formal ziprasidone-valproate interaction study is not necessary.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of ziprasidone treatment in pregnant women. Ziprasidone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and mother. The effect of ziprasidone on labor and delivery is unknown. Furthermore, it is unknown whether, and if so in what amount, ziprasidone and its metabolites are excreted in human milk. It is recommended that women treated with ziprasidone should not breast feed.

During the open-label period, two subjects became pregnant and reported an in utero exposure to ziprasidone. Both of these subjects were reported as having the SAE of pregnancy, and both subjects ultimately experienced a spontaneous abortion. Neither subject was randomized to enter the double-blind period of the study. During the double-blind period, one subject became pregnant, was discontinued from the study, and underwent elective abortion. Please see narratives below:

1. A 35 year old white female (subject 11391011) with Bipolar Disorder was started on valproic acid on August 1, 2006 and took oral ziprasidone 40-60 mg BID from 9/11/06 to (b) (6). Study drug was discontinued on (b) (6) upon confirmation of pregnancy. Urine and serum pregnancy tests were positive. The subject's last menstrual period was (b) (6) On (b) (6) the subject had a spontaneous abortion due to a blighted ovum. A dilatation and curettage (D&C) was performed post-miscarriage.
2. A 34 year old black female (subject 10271029) with Bipolar Disorder and taking lithium carbonate 900 mg daily since 9/13/06 and ziprasidone 40 mg BID since 10/11/06 was found to have a positive urine pregnancy test at Week (b) (6) at which time study drug was discontinued. Urine pregnancy test had been negative at Week (b) (6) The subject telephoned the study center on (b) (6) to report a spontaneous miscarriage.
3. A 21 year old white female (subject 10071019) with Bipolar I Disorder randomized to ziprasidone plus divalproex sodium was withdrawn from the study (study drug discontinued (b) (6) during Week 4 of Period 2 (double-blind period) due to onset of pregnancy. The subject underwent elective abortion on (b) (6).

7.6.4 Overdose

There were no reports of overdose during the open-label or double-blind periods of this trial. However, in premarketing trials involving more than 5400 patients and/or normal subjects, accidental or intentional overdose of oral ziprasidone was documented in 10 patients. All of these patients survived without sequelae. In the patient taking the largest confirmed amount, 3,240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension. In postmarketing use, adverse events reported in association with ziprasidone overdose generally included extrapyramidal symptoms, somnolence, tremor, and anxiety.

7.7 Additional Submissions/ Safety Issues

No additional submissions and safety updates are required since the application involves a single study that has been completed.

8 Postmarket Experience

8.1 Sponsor's Methodology

The sponsor/Marketing Authorization Holder's (MAH) global safety database contains cases of adverse events reported spontaneously to the sponsor/MAH, cases reported from health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and marketing programs sponsored by the sponsor/MAH (solicited cases).

The database contains 12,670 non-clinical study cases for ziprasidone during the reporting period of February 5, 1998 through September 15, 2008.

The database was searched for adverse events reported with ziprasidone coding to the Medical Dictionary for Regulatory Activities (MedDRA) and meeting the following criteria:

- Age $\geq$ 18 years
- Source from non-clinical study (spontaneous, medical literature, health authority cases, and solicited cases)
- Reporting period of February 5, 1998 through September 15, 2008

The cases/reports were then grouped as follows:

- Bipolar cases (Preferred Term: Bipolar Disorder, Bipolar I Disorder, Bipolar II Disorder, Hypomania, Mania, or Mood Disorder NOS)
- Non-Bipolar cases (all cases not reporting Preferred Terms above)
- Bipolar cases that also reported a mood stabilizing drug (carbamazepine, gabapentin, Lamotrigine, lithium, oxacarbazepine, topiramate, and valproic acid) as a suspect or concomitant medication were considered "with mood stabilizers." All other bipolar cases were considered "without mood stabilizers."

8.2 Results and Analysis

8.2.1 General Analysis

A search of the sponsor/MAH's global safety database for ziprasidone non-clinical cases of adults with an indication of Bipolar or related disorders identified 973 cases. This represents 8% of the total ziprasidone non-clinical cases (12,670) in the sponsor/MAH's global safety database. There were 4,566 non-Bipolar cases. The case characteristics (age, gender, case seriousness, and case outcome) were generally similar between the 2 groups. No new safety information was identified based on this analysis.

There were no differences identified in the case seriousness, AEs, and SAEs reported among the Bipolar group when compared to the non-Bipolar group. There were 35 deaths (3.6%) in the Bipolar Disorder group and 251 deaths (5.5%) in the non-Bipolar group. A similar proportion of serious adverse events (SAE) between the 2 groups (43.1% of the Bipolar Disorder cases and 41.6% of the non-Bipolar cases) were noted.

At the System Organ Class (SOC) level, the reporting proportion and the distribution of serious and non-serious events were similar in the Bipolar group compared to the Non-Bipolar group. Forty (40) % of the events in the Bipolar group and 38% of the events in the Non-Bipolar group were assessed as serious. The SOCs reporting the greatest number of Preferred Terms (PTs) in both groups were Psychiatric disorders, Nervous system disorders, and General disorders.

8.2.2 Adverse Events

The sponsor has presented tables of adverse events and serious adverse events reported in $\geq$ 2% cases with Bipolar and/or Non-Bipolar diagnoses. The following AEs were reported with a $\geq$ 5%

reporting proportion in the Bipolar group (listed in order of decreasing reporting proportion): Somnolence, Insomnia, Anxiety, Depression, Dizziness, Tremor, Mania, Fatigue, and Nausea.

8.2.3 Serious Adverse Events

The following SAEs were reported with a ≥ 5% reporting proportion in the Bipolar group (listed in order of decreasing reporting proportion): Mania, Bipolar Disorder, Tardive dyskinesia, Loss of consciousness, and Electrocardiogram QT prolonged. The SAEs with ≥ 2% reporting proportion that were > 3 fold higher in the Bipolar group as compared to the Non-Bipolar group were Loss of Consciousness, Mania, Swollen tongue, and Weight increased. The higher reporting of these AEs likely does not suggest a safety signal among the bipolar patients as the events are associated with the disease under study or are not new or unexpected based on the current labeling for ziprasidone. Please see table below:

Table 41: Serious Adverse Events Reported in ≥ 2% of Bipolar and Non-Bipolar Cases (Postmarketing Data)

Adverse Event	Bipolar Cases (N=391) n (%)	Non-Bipolar Cases (N=1,718) n (%)
Agitation	7 (1.8)	37 (2.1)
Akathisia	3 (0.8)	36 (2.1)
Anxiety	11 (2.8)	35 (2.0)
Bipolar Disorder	23 (5.9)	5 (0.3)
Cardiac arrest	14 (3.6)	57 (3.3)
Completed suicide	5 (1.3)	54 (3.2)
Convulsion	16 (4.1)	59 (3.5)
Death	2 (0.5)	49 (2.8)
Depression	11 (2.8)	22 (1.3)
Dyskinesia	7 (1.8)	34 (2.0)
Dyspnea	12 (3.1)	39 (2.2)
Dystonia	18 (4.6)	73 (4.2)
ECG QT prolonged	20 (5.2)	91 (5.3)
Extrapyramidal disorder	8 (2.0)	60 (3.5)
Hypersensitivity	8 (2.1)	21 (1.2)
Intentional Overdose	8 (2.1)	46 (2.5)
Loss of Consciousness	21 (5.3)	28 (1.6)
Mania	25 (6.4)	25 (1.4)
Myocardial Infarction	7 (1.8)	38 (2.2)
Nausea	8 (2.0)	16 (0.9)
Neuroleptic Malignant Syndrome	5 (1.3)	87 (5.0)
Overdose	3 (0.8)	34 (2.0)
Psychotic Disorder	6 (1.6)	58 (3.3)
Schizophrenia	0 (0.0)	41 (2.4)
Suicidal Ideation	15 (3.8)	40 (2.3)
Suicide Attempt	12 (3.1)	44 (2.6)
Swollen Tongue	15 (3.8)	21 (1.8)
Syncope	7 (1.8)	35 (2.1)
Tardive Dyskinesia	21 (5.4)	75 (4.4)
Tremor	10 (2.6)	21 (1.2)
Vomiting	8 (2.0)	18 (1.0)
Weight Increased	9 (2.3)	11 (0.6)

8.2.4 Concomitant Mood Stabilizers

The most commonly reported mood stabilizers were lithium (17%), lamotrigine (16%), and valproic acid (12%). The following AEs were reported in ≥ 5% in the group with mood stabilizers (listed in order of decreasing reporting proportion): Somnolence, Anxiety, Dizziness, Insomnia, Feeling abnormal, and Restlessness. The AEs reported in the bipolar patients taking concomitant ziprasidone and mood stabilizers were similar in proportion as compared to those reported in Bipolar patients who did not take concomitant mood stabilizers. There were no AEs with reporting proportion of > 3-fold in the group with mood stabilizers as compared to the group without mood stabilizers.

8.2.5 Reviewer's Conclusions

Based on review of the postmarketing adverse events data submitted, it appears that ziprasidone treatment (with or without concomitant mood stabilizers) in patients with Bipolar Disorder and related disorders is not associated with any new safety signals or new, unexpected adverse events compared to ziprasidone treatment in patients with non-bipolar disorders. However, the data submitted and the review of postmarketing adverse events are somewhat limited in that the sponsor has not provided line listings or narratives for the cases in which death or other serious adverse events were reported.

9 Appendices

9.1 Literature Review/ References

The sponsor has provided references from the literature relevant to this submission. A bibliography is provided.

9.2 Labeling Recommendations

This labeling review was based on the labeling provided by the sponsor in the 12/19/09 submission and focused on those clinical sections directly pertinent to the maintenance claim supported by study A1281137.

9.2.1 Highlights of Prescribing Information

Under **Highlights of Prescribing Information,** the sponsor's submitted labeling is as follows:

(b) (4)

3 Pages Immediately Following Withheld - Draft Labeling b(4)

(b) (4)

[redacted]

9.3 Advisory Committee Meeting

No advisory committee meeting is planned for this application.

Francis E. Becker, M.D., F.A.C.P.
October 2, 2009
Medical Officer,
FDA CDER ODE1 DPP HFD 130

cc: NDA 20825 S-34
HFD 130
T Laughren
M Mathis
R Levin

T Harrison
A Jackson
G Kordzakhia
L Iacono-Connor

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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/s/

FRANCIS E BECKER
10/02/2009

ROBERT L LEVIN
10/05/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

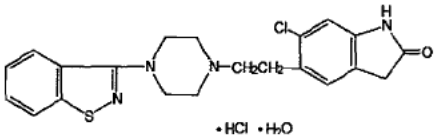
CHEMISTRY REVIEW(S)

Division of Post Approval Marketing Evaluation IV
Chemist Review of Supplement

1. Division of Post Approval Marketing IV
2. NDA Number: 20825
3. Supplement Numbers/Dates: SE1-034
   Letter Date: December 19, 2008
   Stamp Date: December 19, 2008
4. Amendments/Reports/Dates:
5. Received by Chemist: February 2, 2009

6. Applicant Name and Address: Pfizer Inc.
235 East 42nd Street
New York, NY 10017

7. Name of the Drug: GEODON®
8. Nonproprietary name: ziprasidone HCl
9. Chemical Structure/ Chemical Name: 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro (b) (4)



10: Dosage Form: Capsules
11. Potency: 20, 40, 60 and 80mg
12. Pharmacological Category: Psychosis

13. How Dispensed:	XXX (RX)	____(OTC)
14. Records and Reports current	XXX (yes)	____(No)
15. Related IND/NDA/DMF:	____(yes)	XXX (No)

17. **Comments:** This efficacy supplement provides for a new indication in adults for (b) (4). CMC information is cross-referenced to the original NDA, with no new information provided in this submission. The Sponsor requests Categorical Exclusion to an environmental assessment under 21 CFR Part 25.31 (b) based on a prepared environmental analysis wherein the estimated concentration of the drug substance at the point of entry into the aquatic system is below 1 ppb.

Conclusions: From the CMC standpoint, this Supplement is recommended for approval.

19. Reviewer Name Julia C. Pinto, Ph.D., Chemist

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/s/

Julia Pinto
4/23/2009 04:53:49 PM
CHEMIST

Nallaperumal Chidambaram
4/23/2009 04:56:04 PM
CHEMIST
For Dr. James D. Vidra

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-825 / S#034
Drug Name:	Geodone (Ziprasidone)
Indication(s):	Bipolar
Applicant:	Pfizer
Date(s):	Initial submission date: December 19, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.; Kooros Mahjoob, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Frank Becker, M.D., Reviewer Bob Levin, M.D., Team Leader
Project Manager:	Terry Harrison, Pharm. D.
Key Words	Log-rank test

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

When used as an adjunctive therapy to a mood stabilizer (lithium or valproic acid), ziprasidone at a flexible dose of 80 to 160 mg daily showed positive effect in the maintenance treatment of manic or mixed episodes associated with bipolar disorder in adult patients.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted results of one pivotal study A1281137 in support of long-term efficacy of ziprasidone as an adjunctive treatment with a mood stabilizer of mania associated with bipolar disorder.

Study A1281137 was an 8-10 month, Phase 3, double-blind, placebo-controlled trial to evaluate the maintenance of effect of ziprasidone plus adjunctive lithium or valproic acid in symptomatic subjects with a recent or current manic or mixed episode of Bipolar I Disorder. The study was conducted at 118 centers: 68 in the United States (US), 41 in Asia/Europe, and 9 in Latin America.

The trial consisted of 2 periods, ie, a 2.5-4 month, open-label stabilization period (Period 1) followed by a 6 month, double-blind maintenance period (Period 2). A total of 1088 subjects were screened for this study, of which 586 entered the open-label stabilization period and 584 were treated. Of the 584 treated subjects, 241 (41%) completed the open-label period. Two hundred forty (240) subjects were randomized into the double-blind period (127 ziprasidone plus open-label mood stabilizer, and 113 placebo plus open-label mood stabilizer) and 239 subjects were treated (127 ziprasidone plus open-label mood stabilizer, and 112 placebo plus open-label mood stabilizer). The number of subjects who completed the double-blind period of the study was 84 (66%) and 54 (48%) for ziprasidone and placebo groups, respectively.

1.3 STATISTICAL ISSUES AND FINDINGS

In Study A1281137, ziprasidone treatment arm was statistically superior to the corresponding placebo arm with respect to time to intervention for mood episode. The p-value obtained from the primary analysis, log-rank test, was 0.0104.

2 INTRODUCTION

2.1 OVERVIEW

The sponsor submitted results of one pivotal phase III study (A1281137) to evaluate the maintenance of effect of ziprasidone plus a mood stabilizer (lithium or valproic acid) in patients with a recent or current manic or mixed episode of Bipolar I Disorder

2.2 DATA SOURCES

Data used for review are from the electronic submission received on December 19, 2008. The network path is \\Cdsesub1\evsprod\NDA020825\0038 in the EDR.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 OBJECTIVE

The primary objective of this trial was to achieve a long-term maintenance indication for bipolar disorder by comparing the time to intervention for a mood episode in patients receiving double-blind ziprasidone plus a mood stabilizer versus patients receiving placebo plus a mood stabilizer.

3.1.2 STUDY DESIGN

Study A1281137 was an 8-10 month, Phase 3, double-blind, placebo-controlled trial.
to evaluate the maintenance of effect of ziprasidone plus adjunctive lithium or valproic acid in symptomatic subjects with a recent or current manic or mixed episode of Bipolar I Disorder.

The trial consisted of 2 periods, ie, a 2.5-4 month, open-label stabilization period (Period 1) followed by a 6 month, double-blind maintenance period (Period 2). In the stabilization period, open-label ziprasidone (80-160 mg daily) was added to lithium or valproic acid after the mood stabilizer had been maintained at a therapeutic serum concentration for at least 2 weeks. Following open-label treatment with both agents, subjects who achieved stability for 8 consecutive weeks on the adjunctive regimen (based on investigator judgment as assessed by the CGI-I scale and the establishment of a stable treatment regimen) were randomized into Period 2 in a 1:1 ratio to 1 of 2 blinded treatment groups (ziprasidone plus the mood stabilizer or placebo plus the mood stabilizer), to evaluate the maintenance of effect of adjunctive ziprasidone for up to an additional 6 months. Subjects randomized to double-blind ziprasidone were maintained on the treatment regimen received during the final 4 weeks of open-label treatment; subjects randomized to placebo were tapered off ziprasidone to placebo. All subjects remained on the mood stabilizer during the double-blind period.

The total duration of the trial per subject was 8.5-10 months including 10-16 weeks in open-label Period 1 and up to Week 24 in double-blind Period 2. Subjects who began mood stabilizer treatment at the screening visit were required to remain an additional 2-3 weeks in the screening phase of the trial to titrate to the therapeutic range and maintain it for at least 2 weeks prior to entry into Period 1 and the addition of open-label ziprasidone.

To be included in the study subjects had to have a recent or current manic or mixed Bipolar I episode with manic symptoms that began no more than 90 days prior to the screening visit; an MRS score ≥14 (with scores of 2 or higher on at least 4 items) if currently receiving the therapeutic level of a lithium or valproic acid for at least 2 weeks at the screening visit or have an MRS score of ≥18 (with scores of 2 or higher on at least 4 items), if not currently on lithium or valproic acid at the screening visit, or on a mood stabilizer other than lithium or valproic acid. Subjects on a different mood stabilizer had to be willing and be appropriate to switch to either lithium or valproic acid. Subjects had to receive 2 weeks of mood stabilizer exposure in the therapeutic range, and after 2 weeks treatment within that range had to have an MRS score ≥14 (with scores of 2 or higher on at least 4 items).

Open-label stabilization phase:
Subjects remained in Period 1 for at least 10 weeks and up to 16 weeks prior to randomization into Period 2. Subjects were titrated to an optimal treatment regimen (for safety and efficacy) of open-label ziprasidone plus mood stabilizer during Period 1, and the regimen was to remain fixed for the 4 weeks prior to randomization. Stabilization started no earlier than Week 2 and not until symptoms had improved compared to baseline as measured by a CG-I score ≤3. Continued stabilization required that subjects have CGI-I scores ≤3 for 8 consecutive weeks prior to randomization. A CGI-I rating of 4 or higher was permitted at 1 visit within the 8-week stability period, but must have returned to < 3 within no more than 10 days and could not occur immediately prior to randomization.

Double-Blind Maintenance phase:
At the end of the open-label period, randomization numbers were assigned sequentially to the subjects as they were determined to be eligible for the double-blind treatment period. Each subject was assigned in a blinded fashion to 1 of 2 parallel, double-blind, treatment arms in a 1:1 ratio to receive ziprasidone plus the mood stabilizer or placebo plus the mood stabilizer for up to 6 months. Subjects who were randomized to ziprasidone plus mood stabilizer remained on the dose level they received during the last 4 weeks of the open-label period. After randomization, no adjustments to the treatment regimen were permitted for efficacy or symptom control; however, a down titration could occur for documented safety reasons. Subjects who were randomized to placebo plus the mood stabilizer were tapered off ziprasidone and onto matching placebo; however, the blind of the trial was maintained. For placebo-randomized subjects, the level of ziprasidone was decreased 20 mg BID every 2 days so subjects who were receiving 80 mg BID, 60 mg BID and 40 mg BID in open-label were tapered to placebo over 6, 4 and 2 days, respectively, during the first week of Period 2.

Discontinuation from the double-blind period was required if 1 or more of the following occurred and was to be counted as an intervention for a mood episode:
- Investigator decided discontinuation was in the best interest of the subject.
- An alteration to the treatment regimen was required.
- Subject was hospitalized for disease under study.
- MRS rating was ≥18 for 2 consecutive visits scheduled no more than 10 days apart.
- MADRS rating was ≥18 for 2 consecutive visits scheduled no more than 10 days apart.

3.1.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Study A1281137 was conducted at 118 centers: 68 in the United States (US), 41 in Asia/Europe, and 9 in Latin America. A total of 1088 subjects were screened for this study, of which 586 entered the open-label period and 584 were treated. Of the 584 treated subjects, 241 (41%) completed the open-label period. Two hundred forty (240) subjects were randomized into the double-blind period (127 ziprasidone plus open-label mood stabilizer, and 113 placebo plus open-label mood stabilizer) and 239 subjects were treated (127 ziprasidone plus open-label mood stabilizer, and 112 placebo plus open-label mood stabilizer). The number of subjects who completed the double-blind period of the study was 84 (66%) and 54 (48%) for ziprasidone and placebo groups, respectively. Subject disposition for the double-blind period is summarized in Table 1.

The sponsor states that one subject was randomized into the double-blind period at 2 different sites, 1024 and 1064. The subject's participation overlapped, in that the subject inappropriately enrolled and participated in the open-label period at the second site while still participating in the double-blind period at the first site. The subject was ultimately randomized at the second site. The data associated with this subject (identification numbers 10241012 and 10641003) were excluded from the disposition summary, the ITT, PP, and safety analysis sets and therefore are not reflected in any tables, figures, listings.

Table 1. Study Patient Disposition (Double-Randomized Treatment Phase)

	Ziprasidone+Mood Stabilizer	**Placebo+Mood Stabizer**
Patients Randomized: N=	127	113
Patients treated: N=	127	112
ITT Population: N=	127 (100%)	111 (99.1%)
Discontinued	43 (33.9%)	58 (51.8%)
Discontinued for reason related to study drug	15 (11.8%)	28 (25.0%)
Lack of efficacy	9 (7.1%)	22 (19.6%)
Laboratory abnormality	1 (0.8%)	0
Adverse event	5 (3.9%)	6 (5.4%)
Discontinued for reason not related to study drug:	28 (22.0%)	30 (26.8%)
Other	10 (7.9%)	6 (5.4%)
Adverse event	6 (4.7%)	9 (8.0%)
Lost to follow up	3 (2.4%)	6 (5.4%)
Subject no longer willing to participate in study	9 (7.1%)	9 (8.0%)
Completed treatment	84 (66.1%)	54 (48.2%)

Source: Sponsor's Clinical Study Report A1281137, Corresponds to Table 6 (pg. 73)

Table 2 below summarizes the demographics for subjects randomized to ziprasidone and placebo in the double-blind period. The ziprasidone treatment group had a higher proportion of female subjects (about 60%) compared to the placebo treatment group (approximately 47%). The age for randomized subjects ranged from 18 to 71 years, with a mean age of 38.8 years. The majority of subjects were white, female, and of non-Hispanic/Latino ethnicity.

Table 2. Demographic and Baseline characteristics for patients in the double-blind relapse prevention phase

Variable	Ziprasidone + Mood Stabilizer N=127	Placebo+ Mood Stabilizer N=113
Gender		
Male	51 (40.2%)	60 (53.1%)
Female	76 (59.8%)	53 (46.9%)
Age (years)		
18-44	79 (62.2%)	81 (71.7%)
45-64	48 (37.8%)	31 (27.4%)
>=65	0 (0%)	1 (0.9%)
Mean (SD)	39.6 (12.3)	38.0 (11.6)
Range	18-64	18-71
Race		
White	82 (64.6%)	67 (59.3%)
Black	5 (3.9%)	6 (5.3%)
Asian	31 (24.4%)	29 (25.7%)
Other	9 (7.1%)	11 (9.7%)
Weight (kg)		
Mean (SD)	78.4 (19.1)	79.4 (23.9)
Range	40-133.6	35.0-150.0

Source: Sponsor's Clinical Study Report A1281137, Corresponds to Table 9 (pg. 77)

3.1.4 STATISTICAL METHODOLOGIES

The full analysis set consisted of the ITT population, defined as those subjects randomly assigned to treatment in the double-blind period who took at least 1 dose of double-blind medication and who had at least 1 post randomization observation. The full analysis set was the population for all efficacy analyses.

The primary efficacy endpoint was Time to Intervention for a Mood Episode (manic, mixed, or depressed episode) during the double-blind maintenance period. This variable was calculated as the number of days from the day of randomization into the double-blind Period 2 of the study to the day of intervention for a mood episode. If the date of the intervention was missing, then it was assumed to have occurred on the date of the last subject visit. The investigator made the determination of whether a patient was to be discontinued for a mood episode based on the need for the initiation of alternate therapy, hospitalization for a mood episode, MRS score $\geq$18 at two consecutive assessments no more than 10 days apart, or Montgomery Asberg Depression Rating Scale (MADRS) score $\geq$18 at two consecutive assessments no more than 10 days apart. The primary analysis was based on the log-rank test for equality of survival curves over treatment groups. Survival curves were constructed using the Kaplan-Meier product limit method.

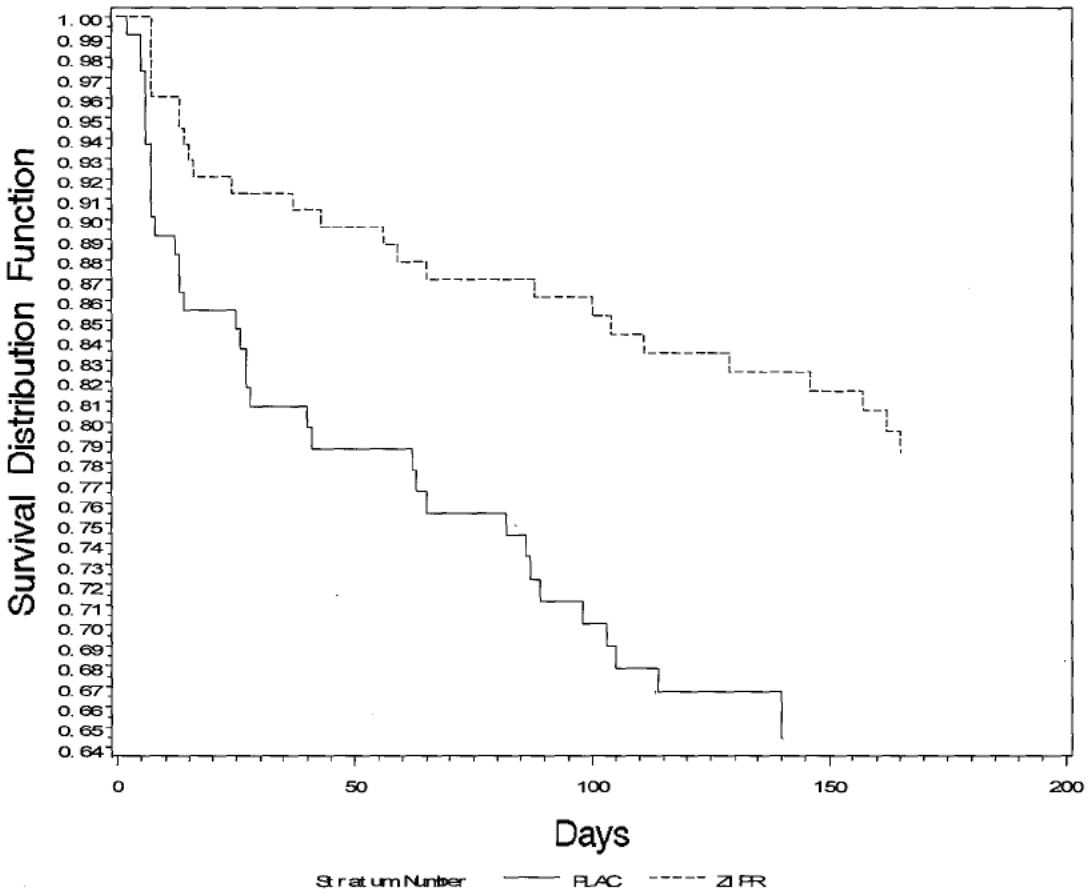
As an exploratory analysis, the time to intervention for mood episode during Double-Blind Period 2 was analyzed by stratified log-rank test using the type of mood stabilizer as the stratification factor (randomization for the study was not stratified by the type of mood stabilizer).

3.1.5 RESULTS OF EFFICACY ANALYSES

Primary Analysis

This reviewer confirmed the sponsor's primary efficacy results. Based on the primary analysis, the log-rank test for equality of survival curves across treatment groups, the time to intervention for mood episode was statistically significant in favor of ziprasidone (p=0.0104) during 6 months of double-blind treatment (see Table 3). Only 19.7% of the ziprasidone subjects required intervention for a mood episode compared with 32.4% of the placebo subjects. The Kaplan-Meier curves for time to intervention for mood episode support that the observed relapse rate was lower in the ziprasidone treatment group than in placebo treatment group during the entire double-blind relapse prevention phase (see Figure 1).

Figure 1. Kaplan-Meier curves of Time to Intervention for mood episode in the Double—Blind Treatment Phase (curves from top to bottom: Ziprasidone, Placebo)



[Source: Reviewer's results]

Table 3. Log-rank test for time to intervention for mood episode (ITT analysis- double-blind period).

	Ziprasidone + mood stabilizer	Placebo + mood stabilizer
Total number of patients	127	111
Patients with intervention for mood episode	25 (19.7%)	36 (32.4%)
p-value (vs placebo+mood stabilizer)	0.0104	

Source: Sponsor's Clinical Study Report A1281137, Table 13.4.2.1.1 (pg. 233)

Table 4 displays the total number of mood episodes and types of episodes. The proportions of patients with relapses into depression, manic and mixed types of episodes were numerically lower in ziprasidone group, compared to the placebo group.

Table 4. Summary of patients with intervention for mood episodes (all randomized patients, double-blind period).

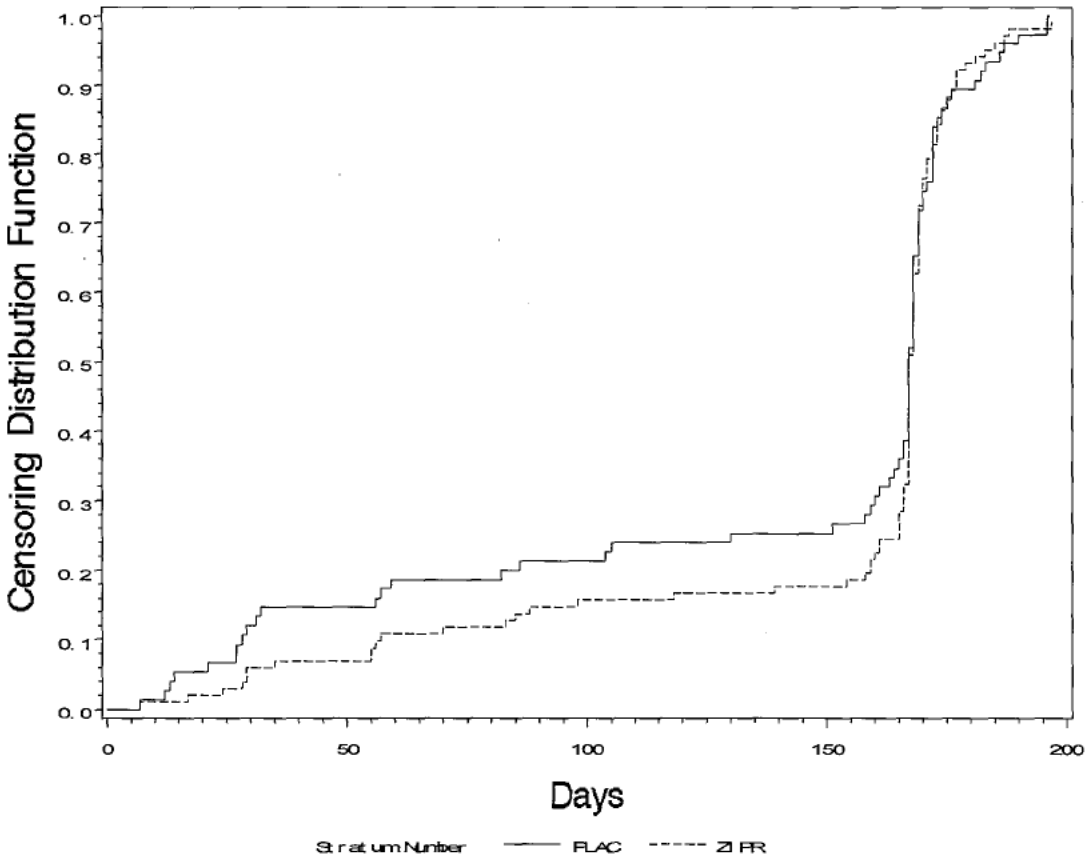
	Ziprasidone + mood stabilizer	Placebo + mood stabilizer
Total number of patients	127	111
Patients with intervention for mood episode	25 (19.7%)	36 (32.4%)
Depression episode	14 (11.0%)	14 (12.6%)
Mania episode	6 (4.7%)	14 (12.6%)
Mixed episode	2 (1.6%)	6 (5.4 %)
Met MADRS or MRS discontinuation criteria (no mood episode)	3 (2.4%)	2 (1.8%)

Source: Reviewer's results

Supportive Analyses

This reviewer also explored empirical cumulative distribution functions (CDF) of time to censor for subpopulation of patients who had no intervention for mood episode. In Figure 2, for all censored patients the CDF curves indicate the proportion of patients in each treatment arm who were censored by a given day. For example, by Day 150, approximately 25% of patients were censored in the placebo group and approximately 16% were censored in ziprasidone arm. The plot suggests that time to censor was numerically larger in the ziprasidone treatment arm compared with placebo arm.

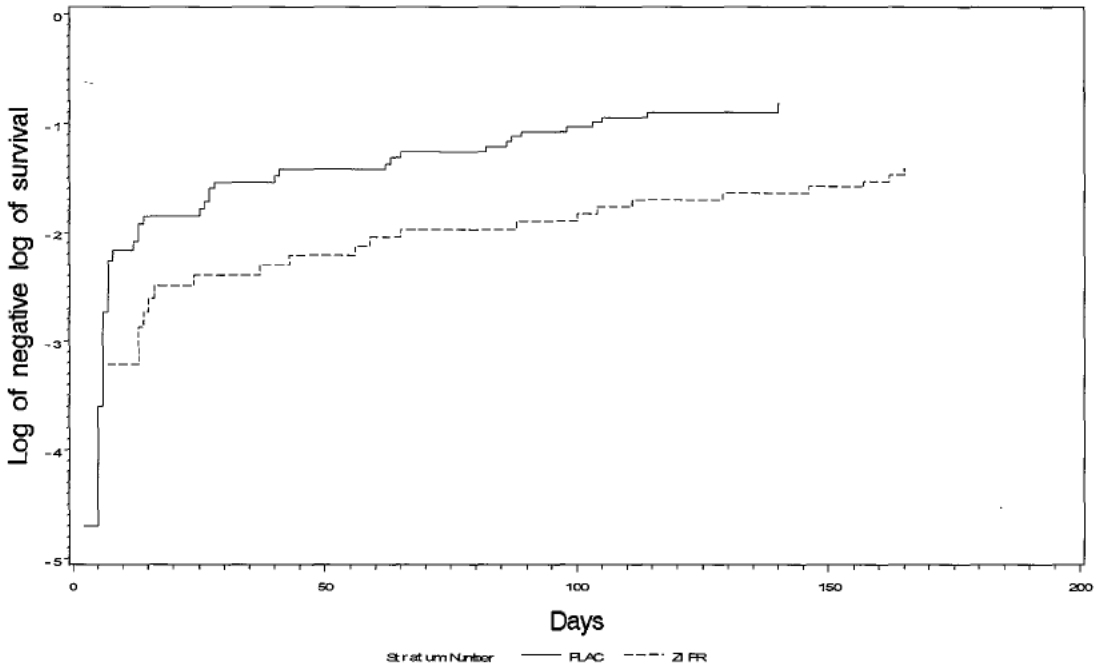
Figure 2. Study A1281137 Cumulative Distribution Function curves of censoring time in the Double—Blind Treatment Phase for all censored patient population (curves from top to bottom: Placebo, Ziprasidone)



[Source: Reviewer's results]

The log of negative log of survival function plot shows that in the duration of the study hazard rate was higher in the placebo group compared with the ziprasidone arm.

Figure 3. Study A1281137 Log of negative log of survival curves of Time to Intervention for mood episode in the Double—Blind Treatment Phase (curves from top to bottom: Placebo, Ziprasidone)



[Source: Reviewer's results]

As an exploratory secondary analysis, the time to intervention for mood episode during Double-Blind Period 2 was analyzed by stratified log-rank test using the type of mood stabilizer as the stratification factor. The time to intervention for mood episode was statistically significant in favor of ziprasidone with p-value of 0.007.

3.1.6 REVIEWER'S COMMENTS.

In Study A1281137, ziprasidone treatment arm was statistically superior to the corresponding placebo arm with respect to time to intervention for mood episode. The p-value obtained from the primary analysis, log-rank test, was 0.0104.

3.2 EVALUATION OF SAFETY

Not evaluated by this reviewer. Please refer to clinical review of this application for a detailed safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

This reviewer conducted an exploratory Cox-proportional hazard analysis of time to intervention for mood episode for gender and race subgroups (see Table 5 and Table 6). Among all subgroups, the treatment effect appeared to be numerically in favor of ziprasidone when compared with placebo. The subgroup analysis by age was not performed since there was only one patient older than 65 (refer to Table 2).

Table 5. Subgroup Analysis by Gender: Cox-proportional Hazard Analysis of Time to Intervention for Mood Episode

	Ziprasidone	Placebo	Placebo vs Ziprasidone	
Male			**Hazard Ratio (HR)**	**95% CI for HR**
Total number of patients	51	59		
Patients with relapse	8 (15.7%)	15 (25.4%)	0.53	(0.22, 1.25)
Female				
Total number of patients	76	52		
Patients with relapse	17 (22.4%)	21 (40.1%)	0.48	(0.25, 0.91)

Source: Reviewers Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 6. Subgroup Analysis by Race: Cox-proportional Hazard Analysis of Time to Intervention for Mood Episode.

	Ziprasidone	Placebo	Placebo vs Ziprasidone	
White			**Hazard Ratio (HR)**	**95% CI for HR**
Total number of patients	82	66		
Patients with relapse	18 (22.0%)	24 (36.4%)	0.49	(0.27, 0.91)
Asian				
Total number of patients	31	29		
Patients with relapse	5 (16.1%)	9 (31.0%)	0.50	(0.17, 1.50)
Other				
Total number of patients	14	16		
Patients with relapse	2 (14.3%)	3 (18.8%)	0.67	(0.11, 4.00)

Source: Reviewers Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

This reviewer conducted exploratory subgroup analysis of efficacy by country (US, Non US) and mood stabilizer (Lithium, Divalproex). The results are summarized in Table 7 and Table 8. Among all subgroups, the treatment effect appeared to be numerically in favor of ziprasidone when compared with placebo.

Table 7. Subgroup Analysis by Country: Cox-proportional Hazard Analysis of Time to Intervention for Mood Episode

	Ziprasidone	Placebo	Placebo vs. Ziprasidone	
US			**Hazard Ratio (HR)**	**95% CI for HR**
Total number of patients	73	64		
Patients who had mood event	19 (26.0%)	23 (35.9%)	0.577	(0.314, 1.062)
Non US				
Total number of patients	54	47		
Patients who had mood event	6 (11.1%)	13 (27.7%)	0.392	(0.149, 1.033)

Source: Reviewers Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 8. Subgroup Analysis by Mood Stabilizer: Cox-proportional Hazard Analysis of Time to Intervention for Mood Episode

	Ziprasidone	Placebo	Placebo vs. Ziprasidone	
Lithium			**Hazard Ratio (HR)**	**95% CI for HR**
Total number of patients	57	49		
Patients who had mood event	12 (21.1%)	22 (44.9%)	0.352	(0.173, 0.714)
Divalproex Sodium				
Total number of patients	70	62		
Patients who had mood event	13 (18.6%)	14 (22.6%)	0.767	(0.360, 1.631)

Source: Reviewers Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In Study A1281137, ziprasidone treatment arm was statistically superior to the corresponding placebo arm with respect to time to intervention for mood episode. The p-value obtained from the primary analysis, log-rank test, was 0.0104.

5.2 CONCLUSIONS AND RECOMMENDATIONS

When used as an adjunctive therapy to a mood stabilizer (lithium or valproic acid), ziprasidone at a flexible dose of 80 to 160 mg daily showed positive effect in the maintenance treatment of manic or mixed episodes associated with bipolar disorder in adult patients.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER LABORATORIES DIVISION OF PFIZER INC.	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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

/s/

GEORGE KORDZAKHIA
09/04/2009

PEILING YANG
09/05/2009

KOOROS MAHJOOB
09/06/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Ziprasidone
PRODUCT (Brand Name):	Geodon
DOSAGE FORM:	Oral Capsules
DOSAGE STRENGTHS:	20 mg, 40 mg , 60 mg and 80 mg capsules
NDA:	20825/S034
NDA TYPE:	Efficacy Supplement
SUBMISSION DATE:	April 10, 2009
SPONSOR:	Pfizer
REVIEWER	Andre Jackson

REVIEW OF FIRM'S RESPONSE TO QUESTIONS BASED UPON A SUBMITTED EFFICACY SUPPLEMENT

Background

A filing letter was sent to the firm on March 11, 2009 which contained the following comments from Clinical Pharmacology:

Clinical Pharmacology
Please provide a scientific rationale as to whether ziprasidone and valproic acid would or would not affect the in vivo steady state concentrations of each other, when ziprasidone and valproic acid are co-administered. Any relevant experimental data/references can be submitted to support the rationale.

You should submit the rationale and justification to the Agency no later than 30 days from the date of this letter.

Firm's RESPONSE

While no formal study has been conducted to examine the potential pharmacokinetic

interaction of ziprasidone and valproic acid, the fact that ziprasidone and valproate lack any common metabolic pathways suggests that pharmacokinetic interactions are unlikely. Specifically, the major pathways of valproate biotransformation include mitochondrial ß-oxidation and conjugation with glucuronic acid, while less than 15-20% of metabolism occurs by other oxidative mechanisms [1] such as CYP dependent oxidation. Among the CYP pathways involved in valproate disposition, the primary ones have been reported to be CYP2C9 and CYP2A6 [2].

In contrast, ziprasidone is metabolized by aldehyde oxidase (about two-thirds) and CYP3A4 (about one-third). Further, as an inhibitor, ziprasidone has been shown to have little effect on activities of CYP 1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human liver microsomes [3]. Consistent with this, in the Al281137 clinical trial, group mean lithium and valproic acid levels assessed at baseline and frequent post-baseline intervals throughout both the open label and the double-blind periods of the study were within the protocol specified therapeutic range (lithium (0.6 - 1.2 mEq/L); valproic acid (50-125 ug/ml)

References

[1]Depakene® approved US product label, Abbott Laboratories.

[2] Kiang TK, Ho PC, Anari MR, Tong V, Abbott FS, and Chang TK (2006) Contribution of CYP2C9, CYP2A6, and CYP2B6 to valproic acid metabolism in hepatic microsomes from individuals with the CYP2C9*1/*1 genotype. *Toxicol Sci* 94: 261–271.

[3] Geodon® approved US product label, Pfizer Inc

OCP Comments:

The firm's comments as a rationale related to the potential drug-drug interaction between ziprasidone and valproic acid as being unlikely is supported by the references (which have been reviewed by OCP) which the firm cited in their response to OCP. The firm's rationale is acceptable to OCP.

SIGNATURES

Andre Jackson_____
Reviewer, Psychiatric Drug Products, DCP I
Office of Clinical Pharmacology

RD/FTinitialized by Raman Baweja,
Ph.D._____
Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology

cc: NDA 20825/S-034, HFD-860(Mehta, Baweja, Jackson)
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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

/s/

ANDRE J JACKSON
10/20/2009

RAMAN K BAWEJA
10/20/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

OTHER REVIEW(S)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: October 27, 2009

TO: Doris Bates, Regulatory Project Manager
Francis Becker, Medical Officer
Division of Psychiatry Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA 20-825/SE1-034

APPLICANT: Pfizer, Inc.

DRUG: Geodon® (ziprasidone hydrochloride)

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Oral ziprasidone (Geodon®) for the maintenance treatment, adjunctive to lithium or valproate, of manic or mixed episodes associated with bipolar disorder. (b) (4)

CONSULTATION REQUEST DATE: 02/25/2009

DIVISION ACTION GOAL DATE: 11/21/2009

PDUFA DATE: 11/21/2009

I. BACKGROUND:

Pfizer submitted this Prior Approval Efficacy Supplement to provide data in support of a new indication in adults for oral ziprasidone (Geodon®) for the maintenance treatment, adjunctive to lithium or valproate, of manic or mixed episodes associated with bipolar disorder, (b) (4) Ziprasidone has previously been approved for the treatment of schizophrenia in adults in the United States (approval, February 2001) and for the treatment of bipolar disorder in adults with manic symptoms (approval, July 2004). The bipolar disorder approval letter included a Phase 4 commitment to submit the results of a clinical study or studies in adult patients, examining the short-term efficacy and safety of ziprasidone as add-on therapy in bipolar patients currently taking mood stabilizers (e.g., lithium, valproate) and long-term efficacy and safety of ziprasidone in bipolar disorder. This supplemental NDA, 20825/034, including Study A1281137, is intended to fulfill Pfizer's Postmarketing Commitment and support a new indication for oral ziprasidone as add-on therapy (to lithium or valproate) in the maintenance treatment of mania associated with Bipolar Disorder.

Study A1281137, entitled "A Phase 3, Randomized, 6-Month, Double-Blind Trial in Subjects with Bipolar I Disorder to Evaluate the Continued Safety and Maintenance Effect of Ziprasidone Plus a Mood Stabilizer (vs. Placebo Plus a Mood Stabilizer) Following a Minimum of 2 Months of Response to Open-Label Treatment with both Agents," data is presented as the basis for Pfizer's fulfillment of their post-marketing commitment as well as pivotal to a new indication.

Three clinical sites were inspected; that of Dr. Lydia Cohan, Site number 1027, that of Dr. Mariappa (Preeti) Srinivasa, Site number 1101, and that of Dr. Ranjive Mahajan, Site number 1104. These sites were selected for inspection because they are considered most important in demonstrating efficacy and safety claims made by the applicant.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	**Protocol #: and # of Subjects:**	**Inspection Date**	**Final Classification**
CI#1: Dr. Lydia Cohan (Site Number 1027) Meadowbrook Research, Inc. Suite 101 4383 North 75th Street Scottsdale, Arizona 85252	Protocol A1281137/11 subjects	June 9-26, 2009	Pending Interim classification: VAI
CI#2: Dr. Mariappa (Preeti) Srinivasa (Site Number 1101) Spandana Nursing Home No. 549/46, 6th Main Rajajinagar, Karnataka, 560 010 India	Protocol A1281137/12 subjects	September 7-11, 2009	Pending Interim classification: VAI
CI #3: Dr. Ranjive Mahajan (Site # 1104) Department of Psychiatry Dayanand Medical College and Hospital Ludhiana, 141001 India	Protocol A1281137/14 Subjects	September 14-18, 2009	Pending Interim classification: VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. **CI#1: Dr. Lydia Cohan**
   (Site Number 1027)
   Meadowbrook Research, Inc.
   Suite 101
   4383 North 75th Street
   Scottsdale, Arizona 85252

   a. **What was inspected**: The site screened 45 subjects, and 11 of those were randomized into the double-blind period of the trial. Four subjects completed the study. The study records of 24 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms for all 45 subjects.

      The general observations described below are based on a preliminary review of the final EIR and communication from the field investigator.

   b. **General observations/commentary**: The investigator was found to be reasonably adequate in the execution of the Protocol A1281137. The data for primary efficacy endpoint and key secondary efficacy endpoint data were verifiable; however, there were some data discrepancies between what was recorded on some of the source documents and what was recorded on the eCRF. The Form FDA 483, Inspectional Observations, was shared and discussed with the review division PMO, (b) (6), and Medical Officer, Frank Becker, on October 1, 2009. DSI reviewer, Lauren Iacono-Connors, proposed that while the list of inspectional observations was extensive with respect to protocol deviations and record keeping discrepancies, that each specific observation did not appear to be clinically significant. As such, the review division was informed that the data from the Cohan site may be considered reliable but that the review division medical officer may wish to consider each violation outlined in the Form FDA 483 and below, as it pertained to individual study subjects, and that the review division may wish to sensor subject-specific data as appropriate.

      i. Subject 1025 (b) (6) was consented with the wrong consent form. This subject was consented with an IRB-approved form for a different study.

ii. Subject 1047 (b) (6) was consented with an outdated consent form for this study.

iii. Subject 1035 (b) (6) did not sign or date the informed consent form prior to enrollment and screening into the study on 1/12/07.

iv. Subjects 1012 (b) (6), 1029 (b) (6) and 1035 (b) (6) did not meet inclusion criteria: *Be on a therapeutic level of a mood stabilizer, either lithium (0.6- 1.2 mEq/L) or divalproex sodium (50-125 ug/mL) for at least two weeks prior to the Baseline visit of the open label period.*

Subject	Mood Stabilizer	(Pre-Screening Visit) Date	Results	(Screening Visit) Date	Results	(Baseline Visit) Date	Results
1012 (b) (6)	Valporic Acid	4/25/06	46 ug/ml	5/2/06	46 ug/ml	5/10/06	22 ug/ml
1029 (b) (6)	Lithium	None		9/27/06	0.1 mEq/L	10/11/06	0.0 mEq/L
1035 (b) (6)	Valporic Acid	1/4/07	47 ug/ml	1/12/07	46 ug/ml	1/26/07	35 ug/ml

v. Triplicate baseline ECG's were not performed at approximately two minute intervals for the following subjects

Subject	Baseline Date	Time 1st ECG	Time 2nd ECG	Time 3rd ECG
1001 (b) (6)	3/3/06	17:43:57	18:00:28	18:04:05
1002 (b) (6)	3/8/06	17:14:41	17:19:39	17:23:49
1003 (b) (6)	3/7/06	13:13:28	13:21:57	13:25:15
1004 (b) (6)	3/10/06	13:14:03	13:20:27	13:31:07
1005 (b) (6)	3/13/06	17:31:53	17:36:08	17:40:01
1007 (b) (6)	3/14/06	16:54:40	17:04:03	17:08:28
1011 (b) (6)	5/3/06	12:27:10	12:35:55	12:46:11
1024 (b) (6)	9/6/09	11:45:38	11:59:59	12:02:04
1035 (b) (6)	1/26/07	11:22:41	11:26:29	11:41:44

vi. ECG's were not performed at every visit for the following subjects:
   a. Subject 1001 (b) (6) at week 1 visit dated 3/10/06.
   b. Subject 1008 (b) (6) at week 4 visit dated 4/12/06.

vii. Clinical rating scales source documents did not match information entered into the electronic case report forms for the following subjects:

Subject 1001 (b) (6)

a. SADS-CB Score Sheet dated 6/23/07 (Period 2/Week 1)
   Decreased Appetite recorded 1 on source and 0 on eCRF.
b. CGI dated 6/29/06 (Period 2/Week 2)
   Global Improvement recorded 4 (no change) on source and 2 (much improved) on eCRF.

c. CGI dated 7/14/06 (Period 2/Week 4)
   - Severity of Illness recorded 3 (mildly ill) on source and 2 (Borderline mentally ill) on eCRF.
   - Global Improvement recorded 4 (no change) on source and 2 (much improved) on eCRF.

d. PANSS Scale for Schizophrenia dated 7/14/06 (Period 2/Week 4)
   - G5. Mannerism and posturing recorded 1 on source and 3 on eCRF.
   - G6. Depression recorded 3 on source and 1 on eCRF.

e. SADS-CB Score Sheet dated 11/28/06 (Period 2/Week 24)
   - Overt Anger recorded 2 on source and 0 on eCRF.
   - Poor Judgment recorded 0 on source and 2 on eCRF.

Subject 1003 (b) (6)

a. SADS-CB Score Sheet dated 3/7/06 (Baseline)
   - Grandiosity recorded 2 on source and 1 on eCRF.
   - Overt Anger rated 1 on source and 2 on eCRF.

b. SADS-CB Score Sheet dated 6/2/06 (Period1/Week 12)
   - Elevated Mood recorded 1 on source and 0 on eCRF.

c. CGI dated 6/16/06 (Period 1/Week 14)
   - Severity of Illness recorded 2 (minimally ill) on source and 3 (mildly ill) on eCRF.

d. SADS-CB Score Sheet dated 10/25/06 (Period 2/Week 16)
   - Generalized Motor Hyperactivity recorded 1 on source and 0 on eCRF.
   - Pressured Speech recorded 0 on source and 1 on eCRF.
   - Poor Judgment recorded 2 on source and 0 on eCRF.
   - Lack of Insight recorded 0 on source and 2 on eCRF.

Subject 1004 (b) (6)

SADS-CB Score Sheet, dated 3/3/06 (Screening)
   - Delusions recorded 0 on source and 1 on eCRF.

Subject 1005 (b) (6)

MADRS Scale dated 3/3/06 (Screening)
   - Reported Sadness recorded 0 on source and 1 on eCRF.
   - Reduced Appetite recorded 0 on source and 1 on eCRF.

Subject 1008 ((b) (6)

CGI dated 3/30/06 (Period 1/Week 2)
   - Global Improvement recorded 3 (minimally improved) on source and 2 (much improved) on eCRF.

Subject 1011 ((b) (6)

a. SADS-CB Score Sheet dated 4/26/06 (Screening)
   - Racing Thoughts recorded 1 on source and 2 on eCRF.

b. SADS-CB Score Sheet dated 5/3/06 (Baseline)
   - Overt Anger recorded 2 on source and 0 on eCRF.
   - Impairment in Functioning recorded 2 on source 3 on eCRF.

- Appearance recorded 0 on source 2 on eCRF.
- Apparent Sadness recorded as 0 on source and 2 on eCRF.

c. SADS-CB Score Sheet dated 5/17/06 (Period 1/Week 2)
- Racing Thoughts recorded 0 on source and 1 on eCRF.
- Grandiosity recorded 1 on source 0 on eCRF.
- Overt Anger recorded 2 on source 1 on eCRF.
- Poor Judgment recorded as 1 on source and 2 on eCRF.
- Lack of Insight recorded 0 on source and 1 on eCRF.

d. PANSS Scale for Schizophrenia dated 5/23/06 (Period 1/Week 4)
- G6. Depression recorded 3 on source and 1 on eCRF.

e. SADS-CB Score Sheet dated 6/6/06 (Period 1/Week 8)
- Agitation (not associated with mania) recorded 1 on source and 0 eCRF.

f. SADS-CB Score Sheet dated 7/5/06 (Period 1/Week 12)
- Grandiosity recorded 1 on source and 0 eCRF.

g. PANSS Scale for Schizophrenia dated 7/28/06 (Period 2/Week 24)
- G6. Depression recorded 3 on source and 1 on eCRF.

Subject 1016 ((b) (6)

a. SADS-CB Score Sheet dated 5/10/06 (Screening)
- Self-reproach recorded 1 on source and 0 on eCRF.
- Negative Evaluation of Self recorded as 1 on source and 0 on eCRF.

b. SADS-CB Score Sheet dated 6/9/06 (Period 1/Week 2)
- Overt Anger recorded 1 on source and 2 on eCRF.
- Poor Judgment recorded 0 on source and 1 on eCRF.

c. SADS-CB Score Sheet dated 6/21/06 (Period 1/Week 4)
- More Energetic recorded 3 on source and 4 on eCRF.
- Grandiosity recorded 1 on source and 2 on eCRF.

d. SADS-CB Score Sheet dated 9/15/06 (Period 1/Week 16)
- Elevated Mood recorded 1 on source and 0 on eCRF
- Less Need for Sleep recorded 1 on source and 0 on eCRF.

e. SADS-CB Score Sheet dated 9/22/06 (Period 2/Week 1)
- Bodily Concern recorded 0 on source and 1 on eCRF.
- Loss of Interest recorded 1 on source and 2 on eCRF.
- Subjective Anger recorded 2 on source and 1 on eCRF.
- Overt Irritability recorded 1 on source and 2 on eCRF.
- Agitation (not associated with mania) recorded 2 on source and 0 on eCRF.

Subject 1027 ((b) (6)

a. SADS-CB Score Sheet dated 12/18/06 (Period 2/Week 2)
- Overt Anger recorded 1 on source and 0 on eCRF.

b. SADS-CB Score Sheet dated 1/3/07 (Period 2/Week 4)
- Overt Anger recorded 2 on source and 0 on eCRF.
- Poor Judgment recorded 0 on source and 2 on eCRF.

Subject 1032 ((b) (6)

SADS-CB Score Sheet dated 12/13/06 (Period 1/Week 2)
- Concentration Difficulties recorded 2 on source and 0 on eCRF.

Subject 1033 ((b) (6)

a. SADS-CB Score Sheet dated 2/16/07 (Period 1/Week 8)
   - Dysphoric Mood recorded 1 on source and 0 on eCRF.
   - Worry recorded 1 on source and 0 on eCRF.

b. SADS-CB Score Sheet dated 3/30/07 (Period 2/Week 24)
   - Concentration Difficulties recorded 3 on source and 0 on eCRF.

Subject 1035 ((b) (6)

a. PANSS Scale for Schizophrenia dated 1/26/07 (Baseline)
   - P2. Conceptual disorganization recorded 1 on source and 2 on eCRF.
   - P3. Hallucinatory behavior recorded 1 on source and 4 on eCRF.
   - P4. Excitement recorded 2 on source and 1 on eCRF.
   - P5 Grandiosity recorded 4 on source and 1 on eCRF.

b. SADS-CB Score Sheet dated 2/1/07 (Period 1/Week)
   - Concentration Difficulties recorded 2 on source and 0 on eCRF.

c. SADS-CB Score Sheet dated 2/8/07 (Period 1/Week 2)
   - Lack of Insight recorded 0 on source and 1 on eCRF.

Subject 1039 (b) (6)

a. CGI dated 2/23/07 (Screening)
   - Global Improvement recorded 4 (Moderately ill) on source and 3 (Mildly ill) on eCRF.

b. SADS-CB Score Sheet dated 3/1/07 (Baseline)
   - Language Thought Disorder recorded 2 on source and 0 on eCRF.

c. SADS-CB Score Sheet dated 3/9/07 (Period 1/Week 1)
   - Language Thought Disorder recorded 2 on source and 0 on eCRF.

d. CGI dated 3/9/07 (Period 1/Week 1)
   - Global Improvement recorded 2 (Much improved) on source and 3 (Minimally improved) on eCRF.

e. SADS-CB Score Sheet dated 3/28/07 (Period 1/Week 4)
   - Subjective Anger recorded 1 on source and 0 on eCRF.

Subject 1046 ((b) (6)

SADS-CB Score Sheet dated 6/22/07 (Screening)
- Poor Judgment recorded 1 on source and 2 on eCRF.

Subject 1048 (b) (6)

SADS-CB Score Sheet dated 10/23/07 (Period 2/Week 4)
- Worry recorded 2 on source and 3 on eCRF.

viii. Drug assignment unit numbers 91513 and 128317 were assigned by the (b) (4) interactive voice response system to two different subjects on two different days.

- **Subject 1002 ((b) (6)** was dispensed units 91513 and 128317 on 3/13/06.
- **Subject 1008 ((b) (6)** was dispensed units 91513 and 128317 on 3/21/06.

The study coordinator at the site recorded the units as being dispensed to each subject on their drug medication logs on the respective dates. The drug shipment records indicate that units 91513 and 128317 arrived in shipment ID 127526 on 3/14/06 and there was only one unit assigned to each of these numbers. The study coordinator did not have any records or documentation to show when the other two units with the same numbers arrived to the site. A determination could not be made whether or not the site received drug unit numbers 91513 and 128317 twice.

ix. The site failed to report promptly, within 3 days, to the IRB all unanticipated problems involving risk to human subjects or others, in accordance with local IRB policy. Specifically, on (b) (6) the site became aware of a Serious Adverse Event (Exposure in Utero) that occurred with Subject 1029 ((b) (6) The site notified the IRB within 4 days of becoming aware of the event.

It should be noted that Dr. Lydia Cohan was not the primary clinical investigator responsible for the conduct of this study until the near the end where only 2 subjects remained on study; from July 2007 to present. The majority of conduct of study A1281137 was under the control of the previous clinical investigator, Dr. Thomas Gazda; from December 2005 until July 2007. A draft Warning Letter is under development for Dr. Gazda (b) (4)

Consistent with the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A Form FDA 483 was issued citing 6 Observations.

Observation 1: Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration and conducting study-related tests. [21 CFR 312.60]

Observation 2: Informed consent was not properly documented in that the written informed consent used in the study was not signed by the subject or the subject's legally authorized representative at the time of consent and was not dated by the subject or the subject's legally authorized representative at the time of consent. [21 CFR 50.27(a)]

Observation 3: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. [21 CFR 312.60]

Observation 4: Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. [21 CFR 312.62(b)]

Observation 5: Investigational drug disposition records are not adequate with respect to dates and quantity. [21 CFR 312.62(a)]

Observation 6: Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others. [21 CFR 312.66]

c. **Assessment of data integrity**: Although several regulatory violations were noted, and based on discussions with the Review Division MO, the findings are unlikely to significantly impact data integrity. The data for Dr. Cohan' site, associated with study A1281137 submitted to the Agency in support of NDA 20-825/034, appear reliable based on available information. The general observations and actions on inspection are based on preliminary review of the final EIR.

2. **CI#2: Dr. Mariappa (Preeti) Srinivasa**
(Site Number 1101)
Spandana Nursing Home
No. 549/46, 6th Main
Rajajinagar, Karnataka, 560 010
India

a. **What was inspected**: The site screened 19 subjects, and 12 of those were randomized into the double-blind period of the trial. Seven subjects completed the study. The study records of 18 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol.

The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**: The investigator was found to be adequate in the execution of Protocol A1281137. The study was found to be well controlled and well documented. Several minor GCP deviations were observed.

i. There were 2 unreported AEs noted involving subject 1008 (b) (6)
   a. Period 1 Week 4 (11/22/06) clinic notes reported blurred vision in sunlight, but no eCFR report was made.
   b. Period 2 Week 16 (4/20/07) clinic notes reported loose stools and abdominal pain, but no eCRF report was made.

ii. There were minor data discrepancies involving incorrect entry of scores for either MADRS or CGI evaluations or visit dates.

Subject 1001 ((b) (4)

a. Period 1 Week 8 MADRS source document dated 11/13/06 shows a total score of 7, but the MADRS Open Label data listing reported by Pfizer shows all individual values entered as 0 with a total score of 0.
b. Period 1 Week 6 (9/29/06) CGI source documents show scores of 3/3, but the data listing shows scores of 3/0

Subject 1004 ((b) (4)

Period 1 Week 1 CGI source document dated 9/21/06 indicates a severity score of 3 (mildly ill) with an improvement score of 4 (no change), but the CGI Open Label data listing reported by Pfizer shows a severity score of 1 (Normal, not at all ill) with an improvement score of 4 (no change).

Subject 1011 ((b) (4)

Incorrect dates were entered in the data listings for Period 2 Week 2 MADRS and CGI data (1/16/07 was incorrectly entered for the 1/19/07 visit)

Subject 1012 ((b) (4)

a. Period 1 Week 4 (11/28/06 was incorrectly entered for the 11/25/06 visit)
b. Data listings for an unscheduled screening visit on 10/18/06 shows scores for MADRS and CGI evaluations that were not done; no hard copy CRF documents could be found in the study files.

iii. There was inadequate documentation in clinic notes and CRF documents to justify enrollment of 2 subjects (1008(b) (6) and 1010/(b) (6) who failed to have at least 2 weeks of documented mood stabilizer levels within the limits specified in the protocol.

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A Form FDA 483 was issued for the following issues:

Observation 1: Failure to report [promptly] to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, the investigational drug [21 CFR 312.64(b)].

Observation 2: Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. [21 CFR 312.62(b)]

Observation 3: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. [21 CFR 312.60]

c. **Assessment of data integrity:** The data for Dr. Srinivasa's site, associated with study A1281137 submitted to the Agency in support of NDA 20-825/034, appear reliable based on available information; the noted deficiencies are unlikely to impact data reliability. The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. **CI#3: Dr. Ranjive Mahajan**
(Site # 1104)
Department of Psychiatry
Dayanand Medical College and Hospital
Ludhiana, 141001
India

a. **What was inspected**:

The site screened 22 subjects, and 14 of those were randomized into the double-blind period of the trial. Ten subjects completed the study. The study records of 22 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, and reporting of AEs in accordance with the protocol.

The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary**:

The investigator was found to be adequate in the execution of Protocol A1281137. The study was found to be well controlled and well documented. Several minor GCP deviations were observed.

i. There was inadequate reporting of adverse events.

   a. Site failed to report to the sponsor that Subject 1020 (b) (6) developed elevated TSH levels at the period 2 week 24 study closure visit (8/21/07).
   b. There was inadequate reporting of an AE for subject 1016 (b) (6) The subject reported loose stools at the 10/9/06 study visit. No subject number or date was included on the AE CRF form and the AE was not included in the data listing provided in the NDA.
   c. An AE CRF form reporting a UTI for Subject 1022 (b) (6) did not include the subject number and was not included in the data listing provided in the NDA. However, the norfloxacin used to treat the infection was reported in the concomitant medications data listing provided in the NDA.

ii. The site failed to perform protocol-required pregnancy tests for the following study visits by female subjects.
   a. Subject 1017 ((b) (6) at the baseline study visit on 10/16/06.
   b. Subject 1022 (b) (6) at the period 1 week 8 study visit on 9/15/06 and the period 2 week 8 study visit on 12/12/07.

iii. Source documents and CRF documents prepared by sub-investigator . (b) (6) routinely failed to include pertinent information, such as complete dates, subject numbers and data. These documents were also hastily completed and signed with illegible signature or initials. For example,
   a. Two versions of the SADS-CB dated 1/6/07 for Subject 1014 were found in the subject study file, each with different rating scores.
   b. The SADS-CB CRF evaluation form for Subject 1015 ((b) (6) dated 10/11/06 was incomplete in that no score was marked for Item 24, Agitation (not associated with mania).
   c. The CRF source document Cognitive Testing Form for Subject 1013 ((b) (6) at the 9/28/06 study visit was neither completed, signed nor dated by (b) (6) who prepared other CRF documents at that time.

iv. There were minor data discrepancies noted between source documents and the data listings provided in the NDA.
   a. The MADRS source document score of 5 for Subject 1018 ((b) (6) at the period 2 week 1 visit (2/14/07) was incorrectly reported as 0.
   b. The MADRS source document score of 0 for Subject 1021 ((b) (6) at the period 1 week 8 visit (1/11/07) was incorrectly reported as 1.
   c. The CGI-S source document score of 3 for Subject 1021 ((b) (6) at the period 2 week 8 visit (4/19/07) was incorrectly reported as 2.
   d. Clinic notes and CRF forms for the period 1 week 1 study visit for Subject 1007 ((b) (6) on 10/31/06 were incorrectly reported as 10/30/06 in the data listing provided in the NDA.

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A Form FDA 483 was issued for the following issues:

Observation 1: Failure to report [promptly] to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, the investigational drug [21 CFR 312.64(b)].

Observation 2: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. [21 CFR 312.60]

Observation 3: Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. [21 CFR 312.62(b)]

c. **Assessment of data integrity**: Although regulatory violations were noted at Dr. Mahajan's site, these are unlikely to importantly impact study outcome. The data for Dr. Mahajan's site, associated with Study A1281137 submitted to the Agency in support of NDA 20-825/034, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on preliminary review of inspectional findings, the study data collected by Dr. Cohan, Dr. Srinivas and Dr. Mahajan appear reliable. All 3 sites were issued Form FDA 483s, Inspectional Observations; however, only the Cohan site raised concerns and required a more detailed assessment of the clinical impact of the inspectional observations on study outcome. There were numerous counts of protocol violations and record keeping errors. A copy of the Cohan Form FDA 483 was provided to the review division medical officer, Dr. Becker, on October 1, 2009. At that time DSI reviewer Lauren Iacono-Connors, proposed that while the list of inspectional observations was extensive with respect to protocol deviations and record keeping discrepancies, that each specific observation did not appear to be clinically significant. The review division may consider the overall data from the Cohan site reliable. However, the review division may wish to consider each violation pertaining to protocol adherence and record keeping by subject, outlined in the Form FDA 483, and described in detail above. The review division may wish to sensor subject-specific data from study analyses as appropriate.

The final reports (EIRs) have not been completed to date for 2 inspections; that of Dr. Srinivas and Dr. Mahajan.

Observations noted above are, in part, based on the preliminary communications provided by the field investigators and copies of the Form FDA 483, inspectional observations, issued to each clinical investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

LAUREN C IACONO-CONNORS
10/28/2009

TEJASHRI S PUROHIT-SHETH
10/28/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-825/S034

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patent and Exclusivity Search Results from query on Appl No 020825 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020825	001	4831031	Mar 2, 2012	Y	Y	U-720	
020825	001	5312925	Sep 1, 2012	Y	Y		
020825	001	6150366	May 27, 2019		Y		
020825	001	6245766	Dec 18, 2018			U-601	

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

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Office of Generic Drugs
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Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through October, 2009
Patent and Generic Drug Product Data Last Updated: November 17, 2009

Patent and Exclusivity Search Results from query on Appl No 020825 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020825	002	4831031	Mar 2, 2012	Y	Y	U-720	
020825	002	5312925	Sep 1, 2012	Y	Y		
020825	002	6150366	May 27, 2019		Y		
020825	002	6245766	Dec 18, 2018			U-601	

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

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Orange Book Data - **Monthly**
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Orange Book Data Updated Through October, 2009
Patent and Generic Drug Product Data Last Updated: November 17, 2009

EXCLUSIVITY SUMMARY

NDA # 20-825 SUPPL # 034 HFD # 130

Trade Name Geodon capsules

Generic Name ziprasidone HCl

Applicant Name Pfizer, Inc.

Approval Date, If Known 11/19/09

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

SE1

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

three

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 20825 Geodon capsules

NDA# 20919 Geodon injectable; intramuscular

NDA# 21483 Geodon oral suspension

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Trial A1281137 was a multicenter, randomized, double-blind, placebo-controlled maintenance study of ziprasidone (as adjunctive therapy to lithium or valproate) in 239 subjects with Bipolar I Disorder, recent manic or mixed or mixed episode.

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

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

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

Trial A1281137 was a multicenter, randomized, double-blind, placebo-controlled maintenance study of ziprasidone (as adjunctive therapy to lithium or valproate) in
239 subjects with Bipolar I Disorder, recent manic or mixed or mixed episode.

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

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

Investigation #1		!
		!
IND # 54,297	YES ☒	! NO ☐
		! Explain:

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

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

Investigation #1 !

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

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Terry Harrison, Pharm.D.
Title: Regulatory Project Manager
Date: 11/18/09

Name of Office/Division Director signing form: Thomas Laughren, M.D.
Title: Director, Division of Pyschiatry Products

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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/s/

TERRY HARRISON
11/19/2009
This Exclusivity Summary was reviewed by CPMS, Paul David on 11/19/09.

THOMAS P LAUGHREN
11/19/2009

FDA Certification Source Review as of 21 NOVEMBER 2008

The following FDA and NIH listings were reviewed for postings regarding investigators and subinvestigators from the attached Master Investigator List who were involved in the conduct of clinical studies using Geodon (A1281137).

FDA Disqualified / Restricted listing:
Clinical investigators who have at one time been disqualified, restricted, or have agreed to certain restrictions on their conduct in future studies. If an investigator has been reinstated or restrictions have expired, it is so noted
http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

FDA Debarment list:
Individuals or firms barred from participating in the drug industry because they have been convicted of crimes related to FDA's regulation of drugs.
http://www.fda.gov/ora/compliance_ref/debar/default.htm

Public Health System Administrative Actions Listing:
Researchers who have had administrative actions imposed against them by the Office of Research Integrity (ORI).
http://silk.nih.gov/public/CBZ1BJE.@WWW.ORIDTLS.HTML#TOP

Health & Human Services: Warning Letters
Sent from FDA about regulatory issues.

http://www.fda.gov/foi/warning.htm

Notification of Initiation of Disqualification Proceedings and Opportunity to Explain listing (NIDPOE) :
Letters issued by FDA when it believes that a clinical investigator repeatedly or deliberately violated FDA's regulations governing the proper conduct of clinical studies involving investigational products or submitted false information to the sponsor.
http://www.fda.gov/foi/nidpoe/default.html

Randall Kaja

Director of Clinical Research
Manager, Site Selection Specialists
US Pfizer Country Office
Clinical Study Operations, PGRD
Phone: (b) (6)
RightFax: 860-686-5944
randall.w.kaja@pfizer.com

NDA 20-825

GEODON®

BIPOLAR MANIA MAINTENANCE

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(l)]

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signature of Company Representative

24 Nov 2008
Date

Bates, Doris J

From: Bates, Doris J
Sent: Wednesday, January 21, 2009 1:48 PM
To: 'McCawley, Chris'
Cc: Kordzakhia, George; Bates, Doris J
Subject: NDA 20-825 S-034: Geodon, Adult Maintenance Bipolar Disorder

Importance: High

Good afternoon Dr. McCawley,

We are conducting our filing review of your submission:

NDA 20-825 S-034, indication bipolar adult maintenance, submitted and received December 19, 2008; this supplemental NDA provides for the use of oral ziprasidone as (b) (4) of manic or mixed episodes associated with bipolar disorder, (b) (4).

Our statistical review team has the following question:

"Please provide the primary analysis data set containing the primary efficacy variable, Time to Intervention for Mood Episode During Double-Blind Period ("TIME"), and the SAS program used to produce Table 13.4.2.1.1 of the Clinical Study report A1281137.

If the data set was already submitted please provide its location in the S-034 submission folder."

Please 'reply to all' when responding, in order to avoid the need for internal rerouting of messages. We understand that the data file[s] may be too large for email, and therefore are likely to be submitted only to the supplement directly. If the supplement is amended electronically, please email us when the amendment is submitted.

If you have any questions, please feel free to contact me.

Thank you and best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
1/21/2009 01:55:40 PM
CSO
question sent to applicant on 21JAN09 at time shown on email.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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/s/

NIKOO N MANOCHEHRI-KALANTARI
11/25/2009

Bates, Doris J

From: Bates, Doris J
Sent: Friday, January 30, 2009 11:35 AM
To: 'McCawley, Chris'
Cc: Bates, Doris J; Becker, Francis E; Levin, Robert
Subject: NDA 20-825, S-034: Geodon, Adult Bipolar Maintenance: Information Request

Importance: High

Dear Dr. McCawley:

We are reviewing your supplemental NDA, referenced above, and have the following request for information:

Please provide a table of investigators and sites that lists all investigators and subinvestigators for each site, provides the site address, and indicates the total number of patients screened, randomized, deaths, dropouts, and completers, as well as n for drug and placebo.

If this information is already available in the existing submission, please indicate its location.

Please feel free to reply initially via e-mail, using 'reply to all' to avoid the need for internal rerouting. Formal amendments to the electronic file will be needed, but these may be bundled and submitted together if they have been previously provided by e-mail to assist timely review.

Thank you for your help --

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
1/30/2009 05:16:24 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**SUPPLEMENTAL NDA ACKNOWLEDGED/FILED:
FILING REVIEW ISSUES IDENTIFIED**

NDA 20-825 / S-034

Pfizer Global Research & Development
Attn: Christopher L. McCawley, MS, VMD
Director, Worldwide Regulatory Strategy
Worldwide Regulatory Affairs and Quality Assurance
50 Pequot Avenue
New London, CT 06320

Dear Dr. McCawley:

Please refer to your supplemental new drug application (sNDA), referenced above, which was submitted and received on January 21, 2009 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Geodon (ziprasidone hydrochloride) capsules.

The supplemental application provides for the use of ziprasidone, adjunctive to lithium or valproic acid, as maintenance treatment of bipolar disorder in adult patients.

We have completed our filing review for the supplemental application and have determined that your application is sufficiently complete to permit a substantive review. The application is filed as of March 22, 2009 under section 505(b) of the Act and in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following review issues:

Clinical Pharmacology
Please provide a scientific rationale as to whether ziprasidone and valproic acid would or would not affect the in vivo steady state concentrations of each other, when ziprasidone and valproic acid are coadministered. Any relevant experimental data/references can be submitted to support the rationale.

You should submit the rationale and justification to the Agency no later than 30 days from the date of this letter.

Statistics
According to the study protocol, following open-label treatment, stable subjects (240 patients) were randomized into Period 2 in a 1:1 ratio to one of the two blinded treatment groups; ie, ziprasidone plus mood stabilizer (127 patients) or placebo plus mood stabilizer (113 patients). It

appears that the numbers of patients randomized to the two treatment groups are unbalanced. Please provide more details on the randomization method used. What was the reason for this lack of balance in randomization?

Clinical

Please provide:

1. Total exposures to ziprasidone in person-years (separately for the controlled phase and the open-label phase).
2. Mean dose for the controlled phase and the open-label phase separately.
3. Mean doses by study visit (or week) for the controlled phase and the open-label phase separately.

At this time, we request that you please respond only to the above comments and questions. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Please also note that our filing review is only a preliminary evaluation of the application, and is not indicative of all deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, please contact Doris J. Bates, Senior Regulatory Project Manager, by phone at (301) 796-2260 or via secure electronic mail at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
3/11/2009 05:03:37 PM

Harrison, Terry

From: Harrison, Terry
Sent: Wednesday, August 12, 2009 1:40 PM
To: 'chris.mccawley@pfizer.com.'
Subject: NDA 20825/ S-034 Primary analysis data set variables "country" or "region"

Hi Dr. McCauley,

The review team has requested that you submit the Primary Analysis Data Set with the variable "country or region" included. If this data is already included within the submission, please provide us with the location of that information.

Thank you,
Terry

Terry Harrison, Pharm.D., CDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Building 22, Room 4111
Phone: 301-796-2770
Fax: 301-796-9839
terry.harrison@fda.hhs.gov

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/s/

TERRY HARRISON
08/12/2009

Harrison, Terry

From: Harrison, Terry
Sent: Monday, August 31, 2009 3:20 PM
To: 'McCawley, Chris'
Subject: NDA 20825 S-034 Geodon (Ziprasidone) Bipolar Maintenance Clinical Information Request

Hi Mr. McCawley,

Please respond to the requested clinical information below by 5:00 pm on Wednesday, September 2, 2009. You should email me your response, but also submit a copy to the document room to be placed in your official file.

NDA 20825 S-034 Relapse Mood Events

Reference is made to NDA 20825 S-34, Protocol A1281137, "A Phase 3 Randomized, Double-Blind Trial in Subjects with Bipolar I Disorder to Evaluate the Continued Safety and Maintenance Effect of Ziprasidone Plus a Mood Stabilizer (vs. Placebo Plus a Mood Stabilizer) Following a Minimum of 2 months of Response to Open-Label Treatment with Both Agents."

In **Section 7.2.1 (Time to Intervention for Mood Episode During Double-Blind Period)**, it is stated that the ITT analysis revealed that, "19.7% (25/127) of the ziprasidone subjects required intervention for a mood episode compared with 32.4% (36/111) of the placebo subjects." Review of data files (data set pidflg.xpt; ITT population) appears consistent with this statement as shown in the table below:

Discontinuations Due to Mood Episode (Double Blind Period)- JMP Data

Episode Type	Manic n (%)	Mixed n (%)	Depressed n (%)	Not Specified n (%)	Total N
Ziprasidone Group	6 (24.0)	2 (8.0)	14 (56.0)	3 (12)	25
Placebo Group	14 (38.9)	6 (16.7)	14 (38.9)	2 (5.6)	36

However, **Table B1.2.3** titled "**Discontinuations Due to Mood Episodes (Double Blind Period)**" lists 126 subjects in the ziprasidone group, 22 of whom were discontinued from the study due to mood episode (17.5%), and 113 subjects in the placebo group, 36 of whom were discontinued from the study due to mood episode (31.9%), as shown in the table below:

Discontinuations Due to Mood Episode (Double Blind Period) - from TableB1.2.3

Episode Type	Manic n (%)	Mixed n (%)	Depressed n (%)	Not Specified n (%)	Total N
Ziprasidone Group	6 (27.3)	2 (9.1)	14 (63.6)	0 (0)	22
Placebo Group	16 (44.4)	6 (16.7)	14 (38.9)	0 (0)	36

In another table, **Table B12** titled "**Components of the Primary Analysis- Time to Intervention to Mood Episode (Double-Blind Period),**" 22 of 127 patients (17.3%) in the ziprasidone group are listed as having a discontinuation due to mood episode compared to 35 of 112 (31.25%) in the placebo group as follows:

Discontinuations Due to Mood Episode (Double Blind Period) - from Table B12

Episode Type	Manic n (%)	Mixed n (%)	Depressed n (%)	Not Specified n (%)	Total N
Ziprasidone Group	6 (27.3)	2 (9.1)	14 (63.6)	0 (0)	22
Placebo Group	15 (42.9)	6 (17.1)	14 (40.0)	0 (0)	35

By cross-referencing the subject identification numbers in the three tables, the following discrepancies were identified:

Ziprasidone Group

Subject 10621007: In the pidfflg.xpt file, this subject is listed as having a discontinuation due to mood episode of unspecified type. In Table B1.2.3, this subject is listed as not being discontinued due to mood episode. In Table B12, the subject is listed as having a TIME outcome of "event," but reason for discontinuation from the study is reported as "subject no longer willing to participate in study" and not as mood episode.

Subject 11391010: This subject is also listed in the pidflg.xpt data as having a discontinuation due to mood episode of unspecified type. In Table B1.2.3, this subject is listed as not having a discontinuation due to mood episode, and in Table B12, the subject is listed as having a TIME outcome "event" but was discontinued from the study for a protocol violation and not for a mood episode.

Subject 11461041: This subject is also listed as having a discontinuation due to mood episode of unspecified type in the pidflg.xpt data and as not having a discontinuation due to mood episode in Table B1.2.3. In Table B12, this subject is reported as having a TIME outcome of "event" and as being discontinued from the study for "adverse event" and not for mood episode.

Placebo Group

Subject 11351004: This subject is listed in the pidflg.xpt data as having a discontinuation due to mood episode of unspecified type and is listed in Table1.2.3 as not being discontinued due to mood episode. In Table B12, this subject is reported as having a TIME outcome "event" but as having "completed" the study.

Subject 11421015: This subject is also listed as having a discontinuation due to mood episode of unspecified type in the pidflg.xpt data and as not having a discontinuation due to mood episode in Table B1.2.3. In Table B12, this subject is reported as having a TIME outcome of "event" but is listed as having "completed" the study.

Subject 11531017: In Table B1.2.3, this subject is listed as having a discontinuation due to mood episode, and the type of episode is reported as "manic." This subject is not listed in Table B12.

Subject 11681009: In Table B1.2.3, this subject is listed as having a discontinuation due to mood episode, and the type of episode is reported as "manic." In Table B12, this subject is listed as having a discontinuation due to mood episode, and the type of episode is described as "manic." However, the reason for discontinuation is listed as "lost to follow-up."

Relapse Mood Events related questions. The Division requests the following:

1. Please identify which subjects had relapse events and which were counted as relapses in the primary analysis.
2. Please identify the type of mood event for each subject who relapsed.
3. Clarify what happened to the five subjects who were listed in the ITT Analysis set (pidflg.xpt data) as having an intervention for mood episode but for whom the type of mood episode is not specified.
4. Explain why Subjects 11681009 and 11531017 were listed in Table B1.2.3 as having a discontinuation due to mood episode of manic type but were not included in the ITT Analysis.
5. Is it possible that some relapse events were psychotic events and not captured as depressive or manic? If so, please provide details and/or narratives for these cases.

Additional Clinical Information Request questions. Please provide the following:

1. Total ziprasidone exposures in person-years for the controlled and open-label phases separately.
2. Mean daily ziprasidone dose for the controlled and open-label phases separately.
3. Mean daily ziprasidone doses by study visit (or week) for the controlled phase and the open-label phase separately.
4. Identify subjects who had an increase in daily study drug dose during the controlled phase, compared to their stabilization dose in the open-label phase.

Thank you,
Terry

Terry Harrison, Pharm.D., CDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Building 22, Room 4111
Phone: 301-796-2770
Fax: 301-796-9839
terry.harrison@fda.hhs.gov

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/s/

TERRY HARRISON
08/31/2009

Harrison, Terry

From: Harrison, Terry
Sent: Monday, November 02, 2009 12:13 PM
To: 'McCawley, Chris'
Subject: NDA 20-825/S-034 Geodon - Clinical Information Request

Follow Up Flag: Follow up
Due By: Tuesday, November 03, 2009 2:00 PM
Flag Status: Red

Hi Chris,

Please provide the requested information by COB Tuesday, November 3, 2009.

Clarify the 5 subjects included in the primary analysis as relapses based on mood rating scale scores >=18, please specify for each whether this was based on MRS, MADRS, or both.

Subjects: PID10621007, PID11391010, PID11461041, PID11351004, PID11421015

In order to expedite this process, please send the response to me via email. Also, you will need to send an amendment to this NDA to the document room in triplicate (one original and two copies) to be included in your official file. If you have any questions, please contact me.

Thanks,
Terry

Terry Harrison, Pharm.D., CDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Building 22, Room 4111
Phone: 301-796-2770
Fax: 301-796-9839
terry.harrison@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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/s/

TERRY HARRISON
11/02/2009

Harrison, Terry

From: Greeley, George
ent: Wednesday, November 04, 2009 1:24 PM
To: Harrison, Terry
Cc: Stowe, Ginneh D.
Subject: NDA 20-825/034 Geodon

Importance: High

Hi Terry,

The Geodon (Ziprasidone HCL) partial waiver/deferral and plan was reviewed by the PeRC PREA Subcommittee on October 28, 2009.

The Division recommended a partial waiver for pediatric patients 0-9 years because studies are impossible or highly impractical (the number of patients is so small or is geographically dispersed) and a deferral from 10 to 17 years of age because the product is ready for approval in adults.

The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

Harrison, Terry

From: Levin, Robert
Sent: Monday, November 16, 2009 10:15 AM
To: Laughren, Thomas P; Harrison, Terry; Mathis, Mitchell
Subject: RE: Geodon/Bipolar Maint

Yes, the sponsor requested a categorical exclusion, and CMC reviewers granted it.
Thanks.

Bob

From: Laughren, Thomas P
Sent: Sunday, November 15, 2009 12:19 PM
To: Levin, Robert; Harrison, Terry
Cc: Mathis, Mitchell; Laughren, Thomas P
Subject: Geodon/Bipolar Maint

Just one minor question about this application. I assume there was a request for categorical exclusion, and if so, was this granted?

Terry, is there a package for this application, and I need it ASAP. We should have both AP and CR letters to go, since it is quite possible we will reach an impasse on labeling.

Regarding labeling, there are some problems with their proposed changes beyond the obvious problems in Highlights, Indications and D&A. We can talk.

Tom

Harrison, Terry

From: Harrison, Terry
Sent: Wednesday, November 18, 2009 6:45 PM
To: 'DeMicco, Eileen'
Cc: McCawley, Chris
Subject: RE: NDA 20-825/S-034 Geodon Labeling

Hello Ms. DeMicco,

We acknowledge your acceptance (b) (4) We are in agreement on the labeling changes for NDA 20-825/S-034 Geodon.

Thank you,
Terry

Terry Harrison, Pharm.D., CDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Phone: 301-796-2770
Fax: 301-796-9839
terry.harrison@fda.hhs.gov

From: DeMicco, Eileen [mailto:Eileen.DeMicco@pfizer.com]
Sent: Wednesday, November 18, 2009 6:28 PM
To: Harrison, Terry
Cc: McCawley, Chris
Subject: Re: NDA 20-825/S-034 Geodon Labeling

Dear Terry,

That is great news. We agree with (b) (4)

Thank you,
Eileen

From: Harrison, Terry <Terry.Harrison@fda.hhs.gov>
To: DeMicco, Eileen
Cc: McCawley, Chris
Sent: Wed Nov 18 18:11:35 2009
Subject: RE: NDA 20-825/S-034 Geodon Labeling

Hello Ms. Demicco,

The Division accepts the labeling changes you have proposed, except one point.

(b) (4)

Please respond by noon tomorrow. If you have any questions, please email or call me.

Thank you,
Terry

T , Harrison, Pharm.D., CDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Phone: 301-796-2770
Fax: 301-796-9839
terry.harrison@fda.hhs.gov

From: DeMicco, Eileen [mailto:Eileen.DeMicco@pfizer.com]
Sent: Wednesday, November 18, 2009 2:34 PM
To: DeMicco, Eileen; Harrison, Terry
Cc: McCawley, Chris
Subject: RE: NDA 20-825/S-034 Geodon Labeling

Terry,

One minor thing that Chris just caught is that the cross-reference at the end of the Carcinogenesis paragraph in Section 13.1 should probably be to 5.11 instead of 5.10.

Sorry for the last minute change.

Thanks,
Eileen

From: DeMicco, Eileen
Sent: Wednesday, November 18, 2009 1:59 PM
To: Harrison, Terry
Cc: McCawley, Chris; DeMicco, Eileen
Subject: RE: NDA 20-825/S-034 Geodon Labeling

Dear Terry,

Thank you for these comments and for having the teleconference yesterday.

We agree with almost all of your comments and would only like to request two minor changes:

1) In Section 1, we would like to re-propose the addition of two sentences that are similar to what we proposed on 11/12/09. Since this is the Indications and Usage section, we feel strongly that it is important to start the section with our indications. Also, this would align our PI with current PI and with Fanapt's PI. We do, however, agree with keeping the QT language following the first two indication sentences.
2) In Section 6.1, we appreciate that you reconsidered the bipolar maintenance weight gain data and that you agreed to leave it in the label. However, we slightly modified your proposed language.

I also made a few very minor editorial changes (I made the "z" in ziprasidone lowercase in one instance, I changed the line spacing in a few places, and I changed the version number at the end of the document).

Please let me know if you have any questions.

Thank you,
Eileen

From: Harrison, Terry [mailto:Terry.Harrison@fda.hhs.gov]
Sent: Wednesday, November 18, 2009 9:15 AM

To: DeMicco, Eileen
Cc: McCawley, Chris
Subject: NDA 20-825/S-034 Geodon Labeling
Importance: High

Hello Ms. DeMicco,

See the attached revised labeling for Geodon NDA 20-825/S-034. The changes that we discussed yesterday have been incorporated and noted with track changes. Review and reply that you accept the revised labeling by COB today. If you make any changes, please indicate with track changes. If you have any questions, please email or call me.

<<Laughren Edits_111709_Levin_111709_20-825 Geodon PLR bipolar maintenance 11-17-09.doc>>
Thank you,
Terry

Terry Harrison, Pharm.D., CDR USPHS
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Building 22, Room 4111
Phone: 301-796-2770
Fax: 301-796-9839
terry.harrison@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20825	SUPPL-34	PFIZER INC	GEODON (ZIPRASIDONE HCL)20/40/60/80MG CA

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/s/

TERRY HARRISON
11/19/2009
The date of communication is the date indicated on the email.