BRIEFING DOCUMENT

for

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC) MEETING

of

June 9-10, 2009

GEODON® (ziprasidone hydrochloride)

Safety and Efficacy Supplement to NDA 20-825

Regarding the Treatment of Pediatric Patients with Bipolar I Disorder

NDA 20-825/S-032

ADVISORY COMMITTEE BRIEFING MATERIALS:

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

EXECUTIVE SUMMARY

This Briefing Document presents a critical analysis of the efficacy, safety, and pharmacokinetic (PK) data to support a new indication for the use of ziprasidone hydrochloride (referred to in this document as ziprasidone) in the treatment of acute manic or mixed episodes associated with bipolar disorder (BD), with or without psychotic features, in pediatric patients 10-17 years of age.

According to the Pediatric Research Equity Act (PREA) Pfizer was required to assess the safety and efficacy of ziprasidone in children with Bipolar I Disorder. FDA waived the requirement for data in children below the age of 10 years. Additionally, in the FDA Pediatric Written Request, the Division indicated that because of the continuity between adult and pediatric bipolar disorder, a pediatric indication for a drug already approved in adults may be supported by a single, independent, adequate and well-controlled clinical trial in pediatric Bipolar I Disorder. The efficacy results of one pivotal, double-blind, placebo-controlled study (A1281132) conducted at 36 centers in the US from 13 January 2006 to 26 July 2007 formed the basis of the efficacy section of the sNDA S-032 submission. Long-term open-label safety data from two additional studies are also provided. The supplemental NDA that is the subject of this document is focused on bipolar disorder in this population. It is noted that pursuant to the Written Request which also addresses schizophrenia in adolescent patients aged 13-17, a separate program of studies in this disorder is being analyzed. This program of studies is similar in scope to those presented in S-032, i.e., is comprised of a single short-term, placebo-controlled efficacy and safety study followed by a long-term open-label safety study. These studies were recently stopped per the Data Safety Monitoring Board as the efficacy study met predefined futility criteria.

Background:

Ziprasidone is an atypical antipsychotic with a high affinity as an antagonist for D_2 receptors and for the $5HT2_A$, $5HT2_C$ and $5HT1_D$ receptors, and as an agonist for the $5\text{-}HT1_A$ receptors. Ziprasidone demonstrates high $5\text{-}HT2_A/D_2$ ratio, which has been associated with a lower risk of extrapyramidal symptoms compared to typical antipsychotics. Ziprasidone has relatively low affinity for α1-adrenergic and histamine H1 receptors and muscarinic M1 receptors, which may be associated with modest orthostatic effects and sedation, and low incidence for weight gain and anticholinergic side effects, respectively. Because ziprasidone is metabolized predominantly by the aldehyde oxidase system, in addition to the cytochrome P4503A4 (CYP3A4) system, the likelihood of pharmacokinetic interactions between ziprasidone and other drugs is low.

Ziprasidone has been shown to be effective in adult patients in the treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features, based on short-term, double-blind, placebo-controlled, in-patient trials submitted under NDA 20-825, S-009 (approved 19 August 2004). Ziprasidone had also been approved earlier for the treatment of schizophrenia in the US (approval 5 February 2001).

Bipolar I Disorder is a lifelong severe psychiatric disorder characterized by recurrent periods of depression and elevated mood or mania, marked changes in sleep, energy level, activity,

thought content and processes and impulsivity. Bipolar I Disorder is estimated to affect up to 1.5% of the global population over the course of a lifetime, with no apparent difference in prevalence rates among men, women and racial groups. The prevalence of the BD in the prepubertal and adolescent population in US is estimated to range from 0.9% in community samples to 6% in outpatient settings, and up to 15% in inpatient samples.

Recognition and diagnosis of BD in children and adolescents could be challenging, as youth may have atypical presentation and symptoms overlapping with other, often comorbid disruptive behavioral and anxiety disorders. Despite these difficulties, the American Academy of Child and Adolescent Psychiatry (AACAP) guidelines advise that BD-I and BD-II can be reliably diagnosed in the pediatric population aged 10-17 years using the DSM-IV-TR criteria and the diagnosis can be supported by structured diagnostic interviews such as the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS). Diagnostic guidelines for children younger then 10 years are not well established.

Pediatric BD has become a major public health concern, now accounting for more then half of the clinical diagnoses of psychiatrically hospitalized youths. Children and adolescents with BD have significantly lower quality of life than youths with any other psychiatric or physical condition encountered in pediatric practice. Children diagnosed with BD may have a more chronic and severe form of the illness than adults. Pediatric bipolar disorder (PBD) is marked with rapid mood cycling, mixed dysphoric mood, intense irritability, and presence of psychosis, long episodes and minimal time in remission. Early onset of the disease is associated with greater rates of comorbid anxiety disorders and substance abuse, more recurrences, shorter periods of euthymia, greater likelihood of suicide attempts and violence, and poor outcome.

Weight gain is a serious concern in children and adolescents. The prevalence of overweight/obesity among youth in US continues to increase, and recent national data indicate that approximately 34% of youth are overweight/obese, with an even higher rate (42%) in youth diagnosed with BD. In patients with BD, overweight/obesity is associated with increased cardiovascular disease risk, diabetes mellitus, osteoarthritis, and the metabolic syndrome. These medical conditions and obesity have been associated with a worse disease course and likely contribute to the premature death observed in bipolar patients. Many of the commonly used pharmacological treatments for BD, including atypical antipsychotics, have been related to increased weight gain and metabolic effects in youth.

There is an unmet medical need in PBD. Despite the recognition of PBD as a serious, chronic disorder with severe burden of illness, there have been limited controlled pharmacotherapy trials in children and adolescents with BD. In US, there are only a few medications (lithium, risperidone and aripiprazole), that have been approved for the treatment of acute mania in youth. Furthermore, despite treatment with one of those pharmacotherapies, up to 40-60% of the youth continue to have inadequate response or fail to achieve remission. Because of the small number of currently approved pharmacotherapies for the treatment of mania in children and adolescents, more controlled clinical studies to evaluate the efficacy and safety of pharmacotherapies in the pediatric population are desirable.

Clinical Development Program:

The clinical development program for ziprasidone in pediatric Bipolar I Disorder consisted of three key studies completed in children and adolescents between the ages of 10 and 17 years:

- Study A1281132 was a pivotal 4-week, multicenter, double-blind, placebo-controlled safety and efficacy trial, in which subjects were randomized to ziprasidone 2:1 (n=149) and placebo (n=88). Subjects had a primary diagnosis of Bipolar I Disorder (single episode manic, most recent episode manic or most recent episode mixed) as defined by DSM-IV criteria and confirmed by the K-SADS. The inclusion criteria required that subjects have a Young Mania Rating Scale (YMRS) score of 17 or greater at screening and baseline and that current symptoms were present for at least 7 days prior to screening. Ziprasidone was titrated up to 120-160 mg/day (BID regimen) over the first 1-2 weeks depending on body weight (80-160 mg/day for subjects ≥45 kg; 60-80 mg/day for subjects <45 kg) and then flexibly dosed.

- Study A1281133 was an extension open-label 26-week safety and tolerability trial to study the long-term effects of flexible dose ziprasidone administration to subjects (n=162) who had enrolled in the short-term double-blind study A1281132.

- Study A1281123 was a safety and tolerability study that explored the range of tolerated doses of open-label ziprasidone during 3-weeks of low or high fixed dose administration, and also characterized the long-term safety and tolerability of open-label ziprasidone flexibly dosed for an additional 24 weeks. Subjects had a primary diagnosis of Bipolar I Disorder (manic or mixed), Schizophrenia or Schizoaffective Disorder.

This Briefing Document will focus primarily on the results of studies A1281132 and A1281133. The efficacy results are based on the pivotal A1281132 study.

- The primary efficacy measure in the A1281132 study was change from baseline to week 4 in YMRS total score. The YMRS is an 11-item instrument used to assess the severity of mania in subjects with a diagnosis of bipolar disorder.

- The secondary efficacy endpoints were change from baseline to week 4 in the Clinician Global Impression Severity Score (CGI-S, key secondary efficacy endpoint) and the raw CGI-I Improvement (CGI-I) score. The CGI is a standardized assessment tool used to rate the severity of a subject's illness.

- Additional exploratory assessments were collected; of these we will emphasize the Children's Global Assessment Scale (CGAS). The CGAS is a clinician-rated global assessment scale for children based on symptoms and social functioning at home, school, and community settings.

Results:

CLINICAL PHARMACOLOGY:

To establish the PK characteristics of ziprasidone in pediatric and adult population, data collected from 224 pediatric subjects and from 468 adult subjects were analyzed. PK behavior was consistent within the pediatric population and across both pediatric and adult studies.

- Body weight was the primary patient characteristic influencing exposure. Clearance increased with increasing weight. Age had a small positive impact on clearance.

- Exposure to ziprasidone was similar in children and adults, after correcting for body weight differences. The dosing regimen, specifying half the typical initial dose for children <45 kg, allowed for the appropriate adjustment.

- The change in QTcF (Fridericia-corrected)-exposure relationship for ziprasidone was characterized for pediatric subjects and compared to available data from adults. The slopes of the ΔQTcF-concentration relationship were different between populations. However, mean maximal changes from baseline QTcF for pediatric data from A1281132 (17.8 msec) and an adult study, 128-054, (15.9 msec) are similar.

EFFICACY:

In the A1281132 study, a total of 237 subjects were treated with ziprasidone (n=149, mean age 13.6 years, SD 2.0) or placebo (n=88, mean age 13.7 years, SD 2.0).

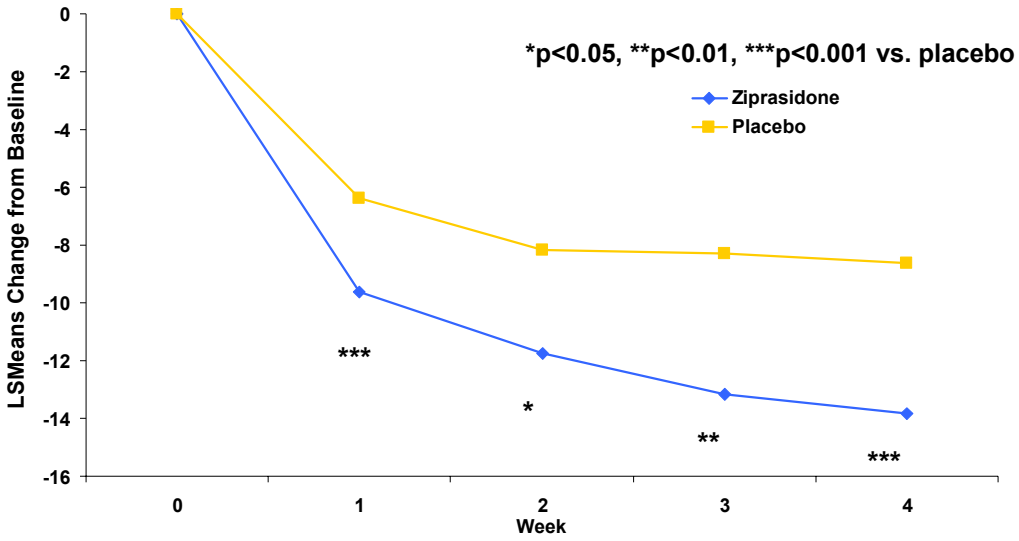
- Based on the primary efficacy endpoint, change from baseline in YMRS total score at week 4, subjects treated with ziprasidone improved significantly compared to the placebo-treated subjects (p=0.0005, see figure below). Furthermore, in a post-hoc analysis, the active and placebo groups separated as early as week 1. The baseline YMRS scores (26.2 mean ± 6.6 SD ziprasidone group and 27.0 ± 6.6 placebo group) indicated that subjects had a moderate to severe level of symptomatology. Ziprasidone was efficacious in both males (p<0.0001) and in females (p=0.0445), in both age groups (10 to <14, marginally p=0.0510 and 14 to <18, p<0.0001), and in subjects ≥45 kg (p=0.0001), but not for subjects <45 kg (p=0.5643). However, it should be noted the number of subjects in the <45 kg weight category was relatively small (n=31, ziprasidone and n=14, placebo).

- Ziprasidone also demonstrated significant improvement based on the key secondary efficacy endpoint, change from baseline to Week 4 in CGI-S (p=0.0001) and the secondary endpoint CGI-I scores (p=0.0004) at Week 4.

- Subjects treated with ziprasidone showed an overall improvement in their functioning, as indicated by the CGAS scale. At baseline, the percentage of the normal functioning subjects (i.e. having CGAS score ≥70) was only 2% of the ziprasidone group and 1.1% of the placebo group. At week 4, these percentages were 25.8% vs. 15.7%, respectively.

Furthermore, subjects reported to be at school had a better response with the active treatment (28.9% on ziprasidone vs. 4.2% on placebo were normal functioning).

YMRS Improvement from Baseline – Study A1281132



Placebo adjusted LS Means at week 4 (95%CI): -5.22 (-8.12; -2.31)

Mixed Model Repeated Measures analysis by week. Primary Analysis at week 4. Post-hoc analysis at weeks 1, 2, and 3.

SAFETY:

Short-term safety data was evaluated in 149 subjects in the pivotal 4-week, double-blind, placebo-controlled study. Long-term safety data was obtained from 3 studies total of 201 pediatric bipolar patients who received open-label ziprasidone.

Adverse Events (AEs): During both the short-term (4 weeks) and the long-term (mean duration 106.3 days) studies there were no new or unexpected findings in this pediatric population as compared to the safety profile in adults. The most commonly occurring AEs (i.e. sedation, dizziness and somnolence) were attributable to the known pharmacologic effects of ziprasidone in adults. The most frequent treatment-emergent AEs reported in ≥5% of all subjects treated with ziprasidone are listed in the table below. Most of the events did not result in discontinuation.

Treatment-emergent Adverse Events Reported in >=5% in Any Group – Study A1281132

System Organ Class Preferred Term (MedDRA)	**Ziprasidone (N=149)** N (%)	**Placebo (N=88)** N (%)
Any adverse event (%)	**136 (91.3)**	**58 (65.9)**
Eye disorders	**12 (8.1)**	**1 (1.1)**
Vision blurred	9(6.0)	1 (1.1)
Gastrointestinal disorders	**49 (32.9)**	**14 (15.9)**
Abdominal pain upper	8 (5.4)	3 (3.4)
Nausea	20 (13.4)	6 (6.8)
Vomiting	11 (7.4)	1 (1.1)
General disorders and administration site conditions	**28 (18.8)**	**14 (15.9)**
Fatigue	20 (13.4)	6 (6.8)
Injury, Poisoning, and procedural complications	**11 (7.4)**	**6 (6.8)**
Overdose	7 (4.7)	5 (5.7)
Infections and Infestations	**22 (14.8)**	**6 (6.8)**
Upper Respiratory Tract Infection	7 (4.7)	0 (0)
Musculoskeletal and connective tissue disorders	**22 (14.8)**	**10 (11.4)**
Musculoskeletal stiffness	8 (5.4)	0 (0)
Nervous system disorders	**115 (77.2)**	**31 (35.2)**
Dizziness	16 (10.7)	2 (2.3)
Headache	31 (20.8)	19 (21.6)
Sedation	49 (32.9)	4 (4.5)
Somnolence	37 (24.8)	7 (8.0)
Tremor	8 (5.4)	0 (0)
Psychiatric disorders	**34 (22.8)**	**21 (23.9)**
Insomnia	13 (8.7)	3 (3.4)
Restlessness	8 (5.4)	1 (1.1)

Incidence of 5% or greater based on the all causality events.
AEs=adverse events, MedDRA=Medical Dictionary for Regulatory Activities (Version 10.1)

- **Suicide Assessment:** Possibly suicide-related adverse events (PSRAEs) were reviewed by an independent panel of experts who categorized the events according to the Columbia classification system. There was no increase in suicidality in the subjects with Bipolar I Disorder treated with ziprasidone in the short- and in the long-term studies.

  In an ongoing pediatric schizophrenia development program, one 17 year-old subject with diagnosis of schizophrenia, disorganized type (160 mg/day ziprasidone) had a completed suicide.

- **Laboratory tests, Vital Signs, QT changes:** During both the short-term and the long-term studies, there were no new or unexpected safety findings in laboratory tests, vital signs, or ECGs. No subject had a QT interval, QT interval corrected using Bazett's formula (QTcB), or QTcF that was ≥500 msec.

In the short-term study, one subject in the ziprasidone group (60 mg) had an AE of prolonged (greater than 460 msec) QTcF that resulted in discontinuation. Mean change in QTcF at final visit was increased 8.7 msec in the ziprasidone group and decreased 3.7 msec in the placebo group. Maximum change from baseline in QTcF was increased 12.9 msec and decreased 4.9 msec in the ziprasidone and placebo groups, respectively. For QTcF intervals that were noted to be prolonged in the ziprasidone group compared to the placebo group, no differences for age, gender, race, or weight were evident.

QTcF - Mean Change at Final Visit and Maximum Change from Baseline – A1281132

	Ziprasidone	Placebo
	QTcF Changes at Final Visit (msec)	
N	101	69
Mean	8.7	-3.7
Standard Deviation	15.2	15.1
Range	(-43) – (51)	(-53) – (38)
	QTcF Maximum Change from Baseline (msec)	
N	132	83
Mean	12.9	-4.9
Standard Deviation	21.9	23.8
Range	(-57) – (69)	(-69) – (41)

QTcF =Fridericia-corrected QT interval

During long-term administration of ziprasidone, the mean change from baseline to last observation and mean maximum change from baseline for QTcF was 3.6 msec and 8.2 msec, respectively (see table below). There were no clinically meaningful differences in laboratory values, vital signs or ECGs by gender, age, or weight.

QTcF - Mean Change at Final Visit and Maximum Change from Baseline – A1281123 and A1231133 (open-label)

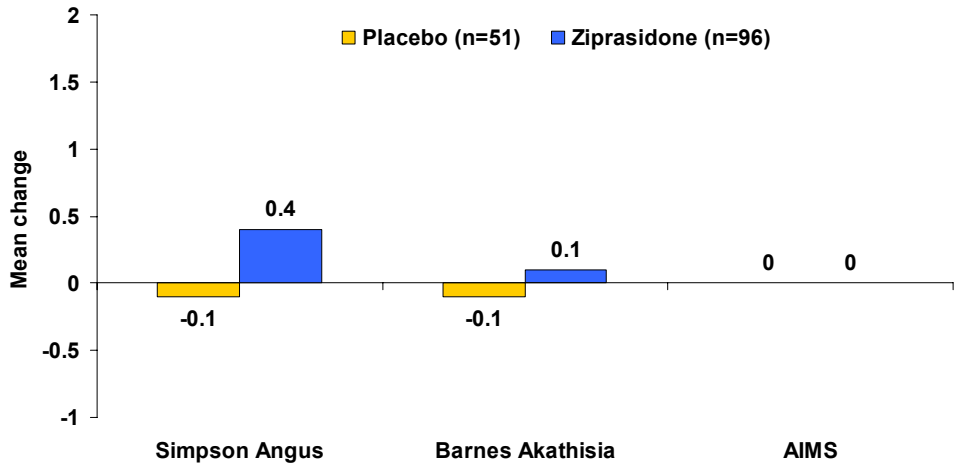
	Ziprasidone
	QTcF Changes at Final Visit (msec)
N	188
Mean	3.6
Standard Deviation	(16.8)
Range	(-45)-(51)
	QTcF Maximum Change from Baseline (msec)
N	188
Mean	8.2
Standard Deviation	(26.2)
Range	(-49)-(69)

QTcF =Fridericia-corrected QT interval

The effects on QTc observed in the pediatric subjects in both the short-term placebo-controlled study A1281132 and the long-term safety database were comparable to what was observed in adults treated with ziprasidone.

- **Movement Disorders** were assessed using the Simpson-Angus Rating Scale (SARS), Barnes Akathisia Rating Scale (BAS), and Abnormal Involuntary Movement Scale (AIMS). Mean total scores for these scales were generally similar between the ziprasidone and placebo treatment groups (see figure below).

Mean Change from Baseline in Movement Disorder Scales - A1281132

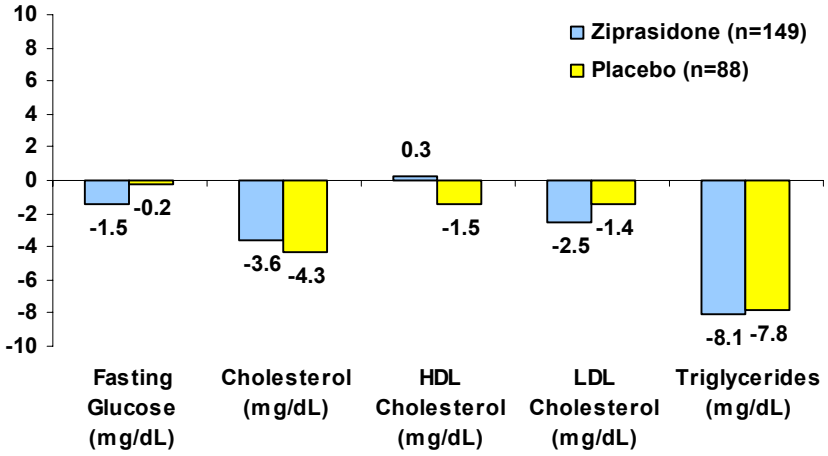


Endpoint: week 4

- **Body weight:** Ziprasidone was not associated with significant change in body weight, as assessed by the mean Body Mass Index (BMI)-Z score. The mean BMI-Z score change from baseline in the short-term placebo-controlled study for the ziprasidone and placebo was 0.0 (0.3 SD) vs. 0.0 (0.2 SD) respectively. The proportion of subjects meeting a weight gain criterion of ≥7% was 7% in the ziprasidone group vs. 4% in the placebo group. The change in BMI-Z score with long-term open-label ziprasidone administration was 0.0 (0.3 SD)

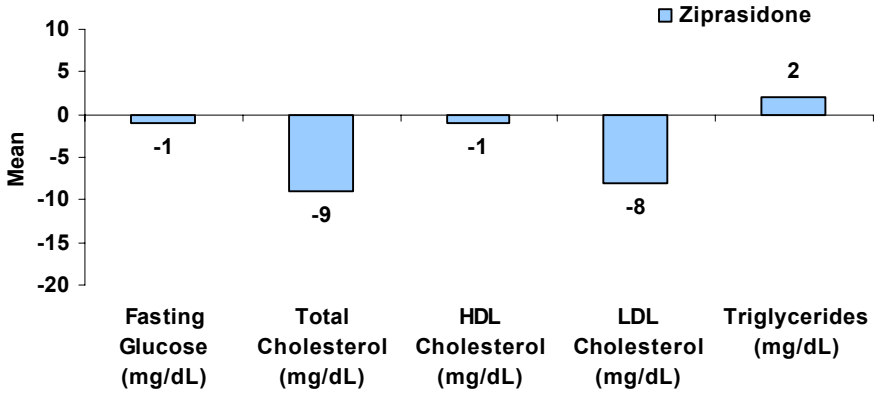
- **Metabolic parameters**: Ziprasidone administration was not associated with any adverse effects on the metabolic parameters in both short- and long-term administrations (see figures below).

Mean Change from Baseline for Lipids and Glucose - Study A1281132



Endpoint: Week 4/ET

Mean Change from Baseline to Last Observation for Lipids and Glucose - A1281123 and A128133 – Open Label



- A review of the post-marketing data revealed that the safety profile of ziprasidone in pediatric patents is comparable to that of the non-pediatric patients. No new or unanticipated safety issues were identified in the pediatric population with ziprasidone use.

- Overall, ziprasidone was generally well-tolerated. Data from children and adolescents aged 10-17 years in the double-blind, short-term, placebo-controlled study and from the two open-label, long-term safety and tolerance studies did not reveal any new or unexpected safety findings compared with the safety profile observed in adult patients with bipolar mania.

CONCLUSION:

- Ziprasidone was efficacious in the treatment of children and adolescents aged 10-17 with Bipolar I Disorder (manic or mixed) at doses from 40 – 160 mg/day. There was significant improvement in YMRS and CGI-S vs. placebo at 4 weeks.

- Ziprasidone was generally well tolerated in up to 30 weeks of treatment. The pediatric safety profile was similar to the adult profile, except for an increased incidence of sedation and somnolence. There were no clinically significant effects on weight. Ziprasidone was metabolically neutral.

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FIGURES

APPENDICES

List of Abbreviations

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
BAS	Barnes Akathisia Score
BD	Bipolar disorder
BID	Twice daily dosing
BL	Baseline
BMI	Body Mass Index
BMI-Z score	Calculated by subtracting the median reference value of the population from the observed value and dividing by the standard deviation of the reference population
BPRS-A	Brief Psychiatric Rating Scale-Anchored
CDRS-R	Child Depression Rating Scale-Revised
CGAS	Children's Global Assessment Scale
CGI-I	Children's Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CHQ	Child Health Questionnaire
CI	Confidence interval
CO	Clinical Overview
CPBAQ	Children's Problem Behavior and Aggression Questionnaire
CSR	Clinical study report
CTD	Common Technical Document
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition
ECG	Electrocardiogram
EOT	End of treatment
ET	Early termination
EPS	Extrapyramidal syndrome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Health Care Professional
IRB	Investigational Review Board
IIR	Investigator Initiated Research
ITT	Intent-to-treat
Kg	Kilogram
K-SADS	Schedule for Affective Disorders and Schizophrenia for School Age Children
LOCF	Last observation carried forward
LS	Least squares
MAA	Market Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MMRM	Mixed-effects model repeated measures
N	Number
NDA	New Drug Application
OC	Observed cases
PBD	Pediatric Bipolar Disorder
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
QT interval	Time from the beginning of the QRS complex to the end of the T wave. Represents both ventricular depolarization and repolarization.
QTcB	The QT interval corrected for heart rate using the Bazett formula
QTcF	The QT interval corrected for heart rate using the Fridericia formula
QTcI	The QT interval corrected by each individual's heart rate correction factor
SAE	Serious adverse event
SARS	Simpson-Angus Rating Scale
SD	Standard deviation
SE	Standard error

sNDA	Supplemental New Drug Application
Wk	Week
WR	Written Request
YMRS	Young Mania Rating Scale
Zip	Ziprasidone

1. BACKGROUND

This Briefing Document presents a critical analysis of the efficacy, safety, and pharmacokinetic (PK) data to support a new indication for the use of ziprasidone hydrochloride (referred to in this document as ziprasidone) in the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features, in pediatric patients 10-17 years of age.

1.1. Pharmacological Class and Scientific Background

Ziprasidone is an atypical antipsychotic with a high affinity as an antagonist for D_2 receptors and for the $5HT2_A$, $5HT2_C$ and $5HT1_D$ receptors, and as an agonist for the $5\text{-}HT1_A$ receptors (Schmidt et al., 2001; Patel and Keck, 2006). It has a high affinity for the dopamine D_2 receptor, potent in vivo activity in rat models of dopamine antagonism (blockade of d-amphetamine-induced locomotor activation and apomorphine-induced stereotypy), and potent activity in an antipsychotic model in rats that is potentially dopamine-independent (inhibition of conditioned avoidance). In addition, ziprasidone blocks re-uptake of serotonin and norepinephrine, similar to that of imipramine and amitriptyline. Ziprasidone demonstrates high $5\text{-}HT2_A/D_2$ ratio, which has been associated with a lower risk of extrapyramidal symptoms compared to typical antipsychotics. Its high affinity for $5HT2_A$, $5HT1_A$ and $5\text{-}HT1_D$ receptors, may also improve affective symptoms. Ziprasidone has relatively low affinity for α1-adrenergic and histamine H_1 receptors and muscarinic M_1 receptors, which may be associated with modest orthostatic effects and sedation, and low incidence for weight gain and anticholinergic side effects, respectively (Patel and Keck, 2006). Because ziprasidone is metabolized predominantly by the aldehyde oxidase system, in addition to the cytochrome P4503A4 (CYP3A4) system, the likelihood of pharmacokinetic interactions between ziprasidone and other drugs is low (Beedham et al., 2003).

Ziprasidone has been shown to be effective in adult patients in the treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features, based on short-term, double-blind, placebo-controlled, in-patient trials submitted under NDA 20-825, S-009 (approved 19 August 2004). These studies showed that ziprasidone was superior to placebo in the treatment of adult subjects with a manic or mixed bipolar episode, with clinically and statistically significant improvement. Ziprasidone had also been approved earlier for the treatment of Schizophrenia in the US (approval 5 February 2001). The overall profile of adverse events in the adult bipolar mania studies is comparable with that seen in schizophrenia studies, including QT prolongation. Ziprasidone demonstrated neutral effects on weight, glucose and lipid profiles in adult patients with mania (Patel and Keck, 2006).

1.2. Epidemiology and Diagnosis of Bipolar Disorder in Pediatric Patients

Bipolar I Disorder is a lifelong severe psychiatric disorder characterized by recurrent periods of depression and elevated mood or mania, marked changes in sleep, energy level, activity, thought content and processes and impulsivity. Bipolar I Disorder is estimated to affect up to 1.5% of the global population over the course of a lifetime (Weissman et al., 1996), with no

apparent difference in prevalence rates among men, women and racial groups (Keller, 1991; Kessler, 1994; Weissman, 1996; Suppes, 2001). This illness is associated with significant morbidity and mortality, and according to the World Health Association, it represents the sixth leading cause of disability worldwide (Pini et al., 2005).

Approximately 60% of adult bipolar patients report that their symptoms first emerged before age 19 or 20 (Lish et al., 1994; Hirshfeld et al., 2003). Unfortunately up to 69% of the bipolar patients are initially misdiagnosed, often as unipolar depression, resulting in 10 or more years of delay in appropriate treatment for many (Hirschfeld et al., 2003). The prevalence of Bipolar Disorder (BD) in the prepubertal and adolescent population in US is estimated to range from 0.9% in community samples (Lewinsohn et al., 1995) to 6% in outpatient settings (Youngstrom et al., 2005), and up to 15% in inpatient samples (Case et al., 2007). As in adults, there is no sex difference in the rate of BD in children and adolescents, although the disorder presents more often with manic mood in boys, and with depressed mood in girls (Duax et al., 2007).

Recognition and diagnosis of BD in children and adolescents could be challenging, as youth may have atypical presentation and symptoms overlapping with other, often comorbid conditions, such as attention-deficit disorder (ADHD), oppositional defiant disorder and conduct disorder (McClellan et al., 2007; Leibenluft and Rich, 2008). Comorbidity of these disorders in children diagnosed with Bipolar I Disorder can be very high, and contribute to the increased clinical severity of the illness (Joshi and Wilens, 2009). Although debate on the diagnosis of the wider spectrum of the disorder (e.g. severe mood dysregulation) and diagnosis in very young children (e.g. preschoolers) continues, it is now recognized that BD can manifest during childhood and adolescence, and that these children are in need for urgent recognition and treatment (McClellan et al., 2007; Leibenluft and Rich, 2008). According to the American Academy of Child and Adolescent Psychiatry (AACAP) guidelines, BD-I and BD-II can be reliably diagnosed in the pediatric population aged 10-17 years using the DSM-IV-TR criteria and the diagnosis can be supported by structured diagnostic interviews such as the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (McClellan et al., 2007). Diagnostic guidelines for children younger than 10 years are not well established. Misdiagnosis of the disorder can cause mis- or under-treatment and increased burden of illness (Birmaher, 2007; Freeman et al., 2009).

1.3. Burden of Disease

Children and adolescents with BD have significantly lower quality of life than youths with any other psychiatric or physical condition encountered in pediatric practice such as asthma, obesity, arthritis, oxygen dependency, heart surgery during infancy, depression and behavior disorders (Freeman et al., 2009). Pediatric BD has become a major public health concern (Moreno et al., 2007), now accounting for more then half of the clinical diagnoses of psychiatrically hospitalized youths (Blader and Carlson, 2007). Children and adolescents with BD have significant psychosocial morbidity both during and between episodes, which is marked with global and academic impairment, poor family and peer relationships and legal problems (Geller et al., 2000; Goldstein et al., 2009). The psychosocial morbidity in youth with BD is more severe than in youth with ADHD or with unipolar or subsyndromal BD (Lewinsohn et al., 1995; Geller et al., 2000), and is worse during adolescence, during manic

episodes, and in the presence of psychotic symptoms or comorbid conduct disorders (Goldstein et al., 2009). This functional impairment may be alleviated by early recognition and appropriate treatment (Birmaher, 2007; Rademacher et al., 2007; Jerrell and Prewette, 2008).

Children diagnosed with BD have a more chronic and severe form of the illness than adults (Carter et al., 2003; Geller et al., 2004; Perlis et al., 2004). Pediatric bipolar disorder is marked with rapid mood cycling, mixed dysphoric mood, intense irritability, presence of psychosis, long episodes and minimal time in remission (Findling et al., 2001; Geller et al., 2004). Onset of the disease before age 18 is associated with greater rates of comorbid anxiety disorders and substance abuse, more recurrences, shorter periods of euthymia, greater likelihood of suicide attempts and violence, and poor outcome (Findling et al., 2001; Carter et al., 2003; Geller et al., 2004; Geller et al., 2008). Furthermore, among the pediatric patients, those with younger age of onset have a more severe form of the illness, with higher familial aggregation for BD, and suboptimal responses to treatment (Strober et al., 1988; Faraone et al., 2003; Geller et al., 2004; Geller et al., 2008). Although most youths eventually recover from their index episode, up to 80% of those recovered experience recurrences in 2 to 8 year follow-up periods, indicating the continuity of illness into adulthood (Geller et al., 2004; Birmaher, 2007; Geller et al., 2008).

Weight gain is a serious concern in children and adolescents. The prevalence of overweight/obesity among youth in US continues to increase, and recent national data indicate that approximately 34% of youth are overweight/obese (Ogden et al., 2006). The prevalence of owerweight/obesity is even higher (42%) in youth diagnosed with BD (Goldstein et al., 2008). Overweight/obesity is associated with increased cardiovascular disease risk, diabetes mellitus, osteoarthritis, and the metabolic syndrome in patients with Bipolar Disorder (McElroy et al., 2002; Fagiolini et al., 2008). These medical conditions and obesity have been associated with a worse disease course and likely contribute to the premature death observed in bipolar patients (Fagiolini et al., 2008). Weight gain is also a major cause of treatment noncompliance, increased use of outpatient and inpatient services and consequently, higher healthcare costs (Fagiolini et al., 2008). Many of the commonly used pharmacological treatments for BD, including atypical antipsychotics, have been related to increased weight gain and metabolic effects in youth (Correll, 2007). Furthermore, youths may be more susceptible to antipsychotic-induced weight gain compared with adults (Safer, 2004).

1.4. Unmet Medical Need in Pediatric Bipolar Disorder

There is unmet medical need in PBD. Despite the recognition of PBD as a serious, chronic disorder with severe burden of illness, there have been limited controlled pharmacotherapy trials in children and adolescents with BD. Up until recently, lithium was the only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute mania in children aged 12 or older, and this approval was based on studies conducted in adults, rather than in youth. More recently, two atypical antipsychotics, risperidone and aripiprazole, have been approved for the treatment of mania in children aged 10 years or older. Many children and adolescents with BD remain inadequately treated. Despite treatment with one of those pharmacotherapies, 40-60% of the youth continue to have inadequate response, or fail

to achieve disease remission (Smarty and Findling, 2007; Nandagopal et al., 2009). Because of the small number of currently approved pharmacotherapies available for treatment of mania in children and adolescents, more controlled clinical studies to evaluate the efficacy and safety of pharmacotherapies in the pediatric population is desirable.

1.5. Regulatory History

Geodon® capsules (ziprasidone hydrochloride) NDA 20-825 was approved by FDA on 5 February 2001 for the treatment of schizophrenia. A supplemental new drug application under NDA 20-825 in support of the approval of Geodon® Capsules for the treatment of adults with manic or mixed episodes associated with bipolar disorder, with or without psychotic features, was approved on 19 August 2004.

According to the Pediatric Research Equity Act (PREA) Pfizer was required to assess the safety and efficacy of ziprasidone in children with Bipolar I Disorder. FDA waived the requirement for data in children below the age of 10 years. Additionally, in the FDA Pediatric Written Request, the Division indicated that because of the continuity between adult and pediatric bipolar disorder, a pediatric indication for a drug already approved in adults may be supported by a single, independent, adequate and well-controlled clinical trial in pediatric Bipolar I Disorder. The efficacy results of one pivotal, double-blind, placebo-controlled study (A1281132) conducted at 36 centers in the US from 13 January 2006 to 26 July 2007 formed the basis of the efficacy section of the sNDA S-032 submission. Long-term open-label safety data from two additional studies are also provided. The supplemental NDA (S-032) that is the subject of this document is focused on bipolar disorder in this population.

It is noted that pursuant to the Written Request which also addresses schizophrenia in adolescent patients aged 13-17, a separate program of studies in this disorder is being analyzed. This program of studies is similar in scope to those presented in S-032, i.e., is comprised of a single short-term, placebo-controlled efficacy and safety study (A1281134) followed by a long-term open-label safety study (A1281135). These studies that followed the safety/tolerability study A1281123 discussed herein were recently stopped per the Data Safety Monitoring Board as the efficacy study met predefined futility criteria.

Pre-submission Regulatory Activity Highlights

11 Feb 2003	Pediatric Written Request (WR) for pediatric studies in schizophrenia and bipolar mania was issued to Pfizer.
27 Aug 2003	Pfizer met with FDA to discuss the pediatric program.
24 Nov 2003	New protocol for Study A1281123 (open-label safety/tolerability) was submitted to FDA.
08 Nov 2004	FDA/Pfizer teleconference regarding interim results from Study A1281123 and plans to initiate Phase 3 studies

6 Apr 2005	New protocols for the safety and efficacy study (A1281132) and the long-term open-label extension follow up study (A1281133) were submitted to FDA.
18 Apr 2008	Pfizer and FDA met to review the proposed sNDA, which is comprised of the efficacy study (A1281132), the long-term open-label safety study A1281133 and the safety/tolerability Study A1281123.
21 Oct 2008	Pfizer submitted S-032 with the intent that following FDA review, the sponsor will be considered to have fulfilled the post-marketing commitment under PREA. In addition, proposals to the US prescribing information were provided to include the appropriate data for bipolar disorder in this population.

2. CLINICAL DEVELOPMENT PROGRAM

This Briefing Document presents the results of clinical trials designed to assess the efficacy, safety, and tolerability of oral ziprasidone in the treatment of Bipolar I Disorder with manic or mixed episodes in children and adolescents aged 10-17 years (Table 1 below). Supplementary studies that provide additional pharmacokinetic data in the pediatric population are provided in Table 2 below.

Table 1. Key Studies Supporting the Pediatric Bipolar I Disorder Clinical Development Program

			Treatment Groups			
Study	**Design**	**Duration**	**Ziprasidone doses**	**N**	**Comparator**	**N**
Short-term (4-week), Pivotal, Double-blind, Placebo-Controlled Study						
A1281132	Randomized, double-blind, placebo-controlled, flexible dose, subjects with Bipolar I Disorder	4 weeks	120-160 mg/day for subjects >45 kg; 60-80 mg/day for subjects <45 kg/day; BID dose regimen	149	Placebo	88
Open-label Extension Study (26 weeks) to study A1281132						
A1281133	Open-label, flexible dose, subjects with Bipolar I Disorder	26 weeks	80-160 mg/day for subjects >45 kg; maximum dose of 80 mg/day for subjects <45 kg; BID dose regimen	162	Not applicable	---
Open-label Safety and Tolerability Study (27 weeks), including a 3-week dose finding period						
A1281123	Open-label, 3-week fixed dose titration period followed by a 24-week flexible dosing period; subjects with Schizo-phrenia, Schizo-affective disorder, Bipolar I Disorder	27 weeks	3-week, fixed dose titration: Low dose=10 mg BID titrated up sequentially by 10 mg BID increments to 40 mg BID; High dose=20 mg BID titrated up sequentially by 20 mg BID increments to 80 mg BID; 24-week, flexible dose titration: 10-80 mg BID	46 (Period 1); 39 (Period 2)	Not applicable	—
N=number of subjects who received at least one dose of study medication and considered evaluable for safety						

The clinical development program for ziprasidone consisted of three key studies completed in children and adolescents between the ages of 10 and 17 years: (1) Study A1281132 was a pivotal 4-week, double-blind, placebo-controlled safety and efficacy trial that supports the efficacy and safety of flexibly dosed ziprasidone in the treatment of Bipolar I Disorder in pediatric patients. (2) Study A1281123 was a safety and tolerability study that explored the range of tolerated doses of open-label ziprasidone during 3-weeks of low or high fixed dose administration, and also characterized the long-term safety and tolerability of open-label ziprasidone flexibly dosed for an additional 24 weeks. (3) Study A1281133 was a safety and

tolerability study that assessed the safety and tolerability of open-label ziprasidone during long-term administration to subjects who had enrolled in the short-term double-blind study. Studies A1281123 and A1281133 also provided supportive uncontrolled efficacy data, although no inferential statistical analyses were performed. This Briefing Document will focus primarily on the results of the A1281132 and A1281133 studies.

Table 2. Supplementary Studies with Ziprasidone in the Pediatric Population

Open-label, Single-dose Study in Subjects with Tourette's Syndrome						
			Treatment Groups			
Study	**Design**	**Duration**	**Ziprasidone doses**	**N**	**Comparator**	**N**
Tourettes: 128-044	Phase 1, open-label, single dose, oral study, to evaluate the PK of ziprasidone in children and adolescents in Tourette's syndrome	Single-dose study	Ziprasidone (oral), 20 mg, 10 mg, 5 mg based on body weight	24	Not applicable	Not applicable
Phase 2, Tolerability, Safety, Pharmacokinetics and Efficacy Study with Subjects with Tourette's Syndrome						
Tourettes: 128-122	Phase 2, randomized, DB, PC, pilot, to evaluate the toleration, safety, pharmacokinetics and efficacy of oral ziprasidone in children and adolescents with Tourette's syndrome or chronic motor or vocal tic disorder	8-week study	Ziprasidone (oral, 5 mg once per day escalating dose to a maximum of 20 mg BID, flexible dosing)	16	Placebo	9
N=number of subjects who received at least one dose of study medication and considered evaluable for safety.						

3. CLINICAL PHARMACOLOGY

3.1. Pediatric Pharmacokinetics Background and Overview

Ziprasidone concentration data from pediatric and adult patients were obtained from multiple studies to establish the characteristics and test the similarity of adult and pediatric pharmacokinetics. The concentration data collected in these studies were summarized and assessed using model based, population pharmacokinetic methods employing NONMEM. The consistency of pediatric pharmacokinetics from four separate studies as well as the

comparison of adult and pediatric pharmacokinetic behavior indicate that after correcting for body weight differences, exposure to ziprasidone is similar in children and adults.

The data analyses and summaries below indicate that the following characteristics for ziprasidone pharmacokinetics are apparent:

- Body weight is the primary subject characteristic which determines exposure to ziprasidone. It is associated with increasing clearance across the pediatric and adult age ranges in a continuous way. After correction for body weight differences, exposure to ziprasidone was similar in both children and adults.

- Age has only a small effect on clearance.

- Absorption is somewhat faster in pediatric patients compared to adults.

Consistent with the identification of the subject weight influence on ziprasidone clearance from the results of the population pharmacokinetic modeling, observed concentration data obtained from adult and pediatric studies indicates that weight based dosing adjusts exposure appropriately across pediatric subjects.

3.1.1. Ziprasidone Pharmacokinetic Data from Pediatric Subjects

Pediatric data available for the assessment of pharmacokinetics are derived from four clinical studies with studies A1281132 and A1281123 providing the primary sources of information. A total of 224 pediatric subjects contributed 839 ziprasidone concentration samples for pharmacokinetic assessment. Subjects were 7 to 18 years of age with an average weight of 56.0 kg (SD 16.5; [21.8 – 109.9]), (Table 3).

Table 3. Summary of Subjects Contributing Pediatric Pharmacokinetic Data

		Mean (SD) [Range]		
Study	**Treatment Design**	**Age (yr)**	**WT (kg)**	**# Subjects (Samples)**
A1281132	4 weeks 120-160 mg/day ≥45kg 60-80 mg/day <45 kg	13.5 (2.2) [10-18]	56.6 (14.0) [28.0 – 86.6]	128 (413)
A1281123	Period 1 (3 weeks): Group 1: Titrate to 40 mg BID over 10 days (20 mg BID if <45kg) Group 2: Titrate to 80 mg BID over 10 days (40 mg BID if <45 kg) Period 2 (24 weeks): 10 – 80 mg BID	13.8 (2.2) [10 – 17]	61.9 (17.4) [31.8 – 109.9]	57 (210)
128-044	Single Dose Group 1 (>60 kg): 20 mg Group 2 (31 – 60 kg): 10 mg Group 3 (16 – 30 kg): 5 mg	10.8 (3.2) [7 – 16]	43.4 (17.2) [21.8 – 69.4]	23 (171)
128-122	8 weeks Begin with 5 mg to maximum total daily dose of 20 mg BID	11.3 (2.6) [7 - 14]	47.6 (18.9) [26.8 – 95.9]	16 (45)
Total		13.1 (2.5) [7 – 18]	56.0 (16.5) [21.8 – 109.9]	224 (839)

3.1.2. Ziprasidone Pharmacokinetic Data from Adult Subjects

Ziprasidone concentration data collected from five studies (A1281037, 128-109, 128-114, 128-115, 128-303) of adult healthy volunteers and patients were incorporated into the comparison of ziprasidone pharmacokinetics between adult and pediatric subjects. Four hundred sixty eight (468) adult subjects contributed 2057 ziprasidone concentration samples which were used in comparisons of pharmacokinetic characteristics between adult and pediatric subjects. Subjects were 18 to 82 years of age with an average weight of 75.3 kg (SD 15.7; [43.5 – 155.0]), Table 4.

Table 4. Summary of Subjects Contributing Adult Pharmacokinetic Data

		Mean (SD) [Range]		
Study	**Treatment Design**	**Age (yr)**	**WT (kg)**	**# Subjects (Samples)**
A1281037	3 Day treatment period 20 mg capsule 20 mg suspension	26.4 (3.8) [19 – 37]	69.9 (10.7) [45 – 82]	16 (639)
128-109	6 weeks Group 1: 20 mg QID Group 2: 80 mg BID	38.0 (8.8) [20 – 55]	75.0 (14.4) [57.2 – 108.9]	21 (107)
128-114	6 weeks 40 or 80 mg BID	36.6 (10.5) [18 – 67]	75.5 (14.8) [44.5 – 137.0]	132 (334)
128-115	6 weeks 20, 60, 100 mg BID	40.3 (10.8) [21 – 72]	79.0 (16.6) [45.8 – 125.2]	154 (550)
128-303	52 weeks 20, 40, 80 mg BID	50.3 (13.4) [18 – 82]	71.9 (15.3) [43.5 – 155.0]	145 (427)
Total		41.8 (13.0) [18 - 82]	75.3 (15.7) [43.5 – 155.0]	468 (2057)

3.2. Assessment of Pediatric Pharmacokinetics and Comparison to Pharmacokinetic Characteristics in Adult Subjects

The similarity of the pharmacokinetics between pediatric and adult patient populations has been established primarily through population pharmacokinetic methods. The primary objectives of these analyses were to characterize the primary pharmacokinetic parameters of ziprasidone in adults and pediatric subjects and to identify and quantify subject characteristics that are determinants of ziprasidone exposure. Descriptions of the primary analyses and results are highlighted as follows.

3.2.1. Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone

A Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone (Appendix 1.3) incorporated the pharmacokinetic data from 2 pediatric (128-044, 128-122) plus 5 adult (128-109, 128-114, 128-115, 128-303, A1281037) clinical studies. This analysis was conducted prior to the availability of the data from studies A1281123 and A1281132. The PK model incorporated the effects of weight, identified as the most important covariate influencing clearance (CL/F), and age and demonstrated that once these subject characteristics are taken into account, pediatric patients exhibit similar PK to adults. Furthermore, although the effect of age was identified on clearance and absorption, the analysis demonstrates that pharmacokinetic behavior is continuous across the range of ages in the adult and pediatric populations studied.

- Over the range of weights in the subjects evaluated (22 – 160 kg), typical values of clearance ranged from 26.8 to 76.1 L/h. For adults aged 35 years over a weight range of 50 to 160 kg, clearance of ziprasidone ranged from 44.6 to 72.0 L/h. Age impacts ziprasidone to a lesser extent with estimated values of clearance ranging from 51.2 to 58.1 L/h for subjects weighting 70 kg with ages ranging from 35 to 80 years old.

3.2.2. Population Pharmacokinetic Analysis for Ziprasidone Study A1281132

A separate population pharmacokinetic analysis of the child and adolescent data from protocol A1281132, (Appendix 1.4), was performed and compared with the results of the adult and pediatric retrospective pooled analysis of pharmacokinetic data. Consistent with the pooled analysis cited above, the analysis of the data from study A1281132 identified weight as a covariate affecting clearance (CL/F). Weight was also identified as a covariate influencing volume of distribution.

- Over the range of weights in this study (28.0 – 86.6 kg), typical values of clearance were estimated to range from 28.6 to 74.7 L/h, similar to the range estimated for the pooled adult and pediatric analysis (Sections 3.2.1 and Appendix 1.3).

3.2.3. Population Pharmacokinetic Analysis for Ziprasidone Study A1281123

A population pharmacokinetic assessment, (Appendix 1.5), was conducted utilizing the data from protocol A1281123 and a preliminary version of the model identified in the Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone. The model was

used to assess whether the data obtained from A1281123 were consistent with previously obtained adult and pediatric data. Weight and age were again identified as covariates influencing ziprasidone clearance with age included in the PK model as a covariate on absorption coefficient (Ka).

- For this assessment, subject weight was also identified as being important for predicting ziprasidone exposure. Higher weight results in faster clearance and corresponding lower exposure. Estimates of clearance for subjects in this study ranged from approximately 37 to 80 L/h over the subject weight range of 32 to 110 kg.

3.2.4. Pharmacokinetic Assessments of Data from Studies 128-044 and 128-122

In addition to being incorporated in the subsequent Retrospective Pooled Population Pharmacokinetic analyses (Section 3.2.1 and Appendix 1.3), early PK assessments done using the ziprasidone concentration data from pediatric studies 128-044 (Appendix 1.6) and 128-122 (Appendix 1.7) demonstrated that these data were consistent with both prior adult data as well as pediatric data from studies A1281132 and A1281123.

- Predictions of concentration using a preliminary PK model were consistent with the observed data for study 128-122. Consistent with the assessments outlined above, predictions of clearance for these data appeared to be related to both subject age and weight.

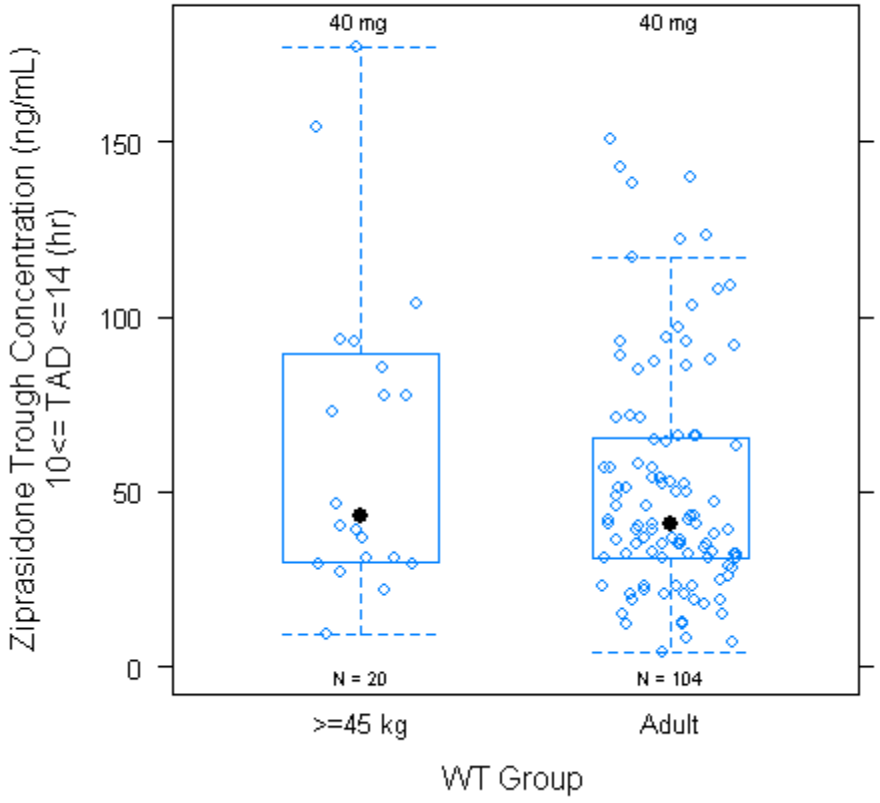
- After correction for subject weight, estimates of mean clearance values from the data in study 128-044 were similar across the dose groups which varied by weight and were consistent with the results from the population PK evaluations discussed above. Clearance values were 43.7, 30.4 and 20.3 L/h for the 20 (58 - 69kg), 10 (31 – 56 kg) and 5 (22 – 29 kg) mg dose groups, respectively.

3.3. Comparison of Observed Trough Ziprasidone Concentrations Between Pediatric and Adult Subjects

The target dose range of ziprasidone in adult schizophrenia or bipolar mania patients is 120 – 160 mg/day divided in two daily doses. Pediatric patients have been generally studied (Studies A1281132 and A1281123) over a target dose range of 120 - 160 mg/day for individuals with body weights ≥45 kg and 60 – 80 mg/day for subjects with weights <45 kg.

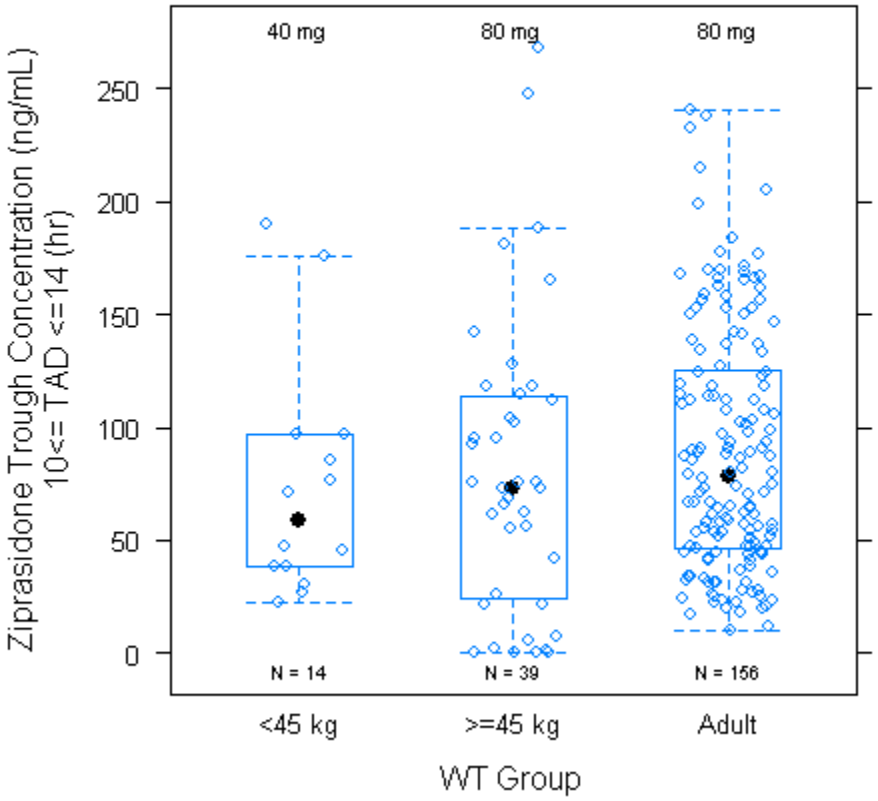
Observed ziprasidone concentrations collected at approximately trough (10 to 14 hours post previous dose) for pediatric subjects weighing ≥45 kg and adult subjects administered 40 mg BID were similar, Figure 1.

ric (>=45kg) and



In order to take into account the dependence of ziprasidone pharmacokinetics on body weight, target doses for subjects <45 kg in studies A1281123 and A1281132 were halved from the maximum, 40 mg BID rather than 80 mg BID. Although the data are limited, ziprasidone concentration samples taken approximately at trough, 10 to 14 hours post previous dose, indicate that, consistent with the results obtained from the population pharmacokinetic modeling, the weight based dose regimen appropriately adjusts exposure, (Figure 2) to concentration ranges similar to those observed for adult subjects.

Figure 2. Observed Trough Ziprasidone Concentrations from Pediatric Subjects (<45 k) Ad i i d 40 BID P di i (45 k) S bj Administered 80



Furthermore, comparison of ziprasidone concentrations collected at the estimated time of Cmax, approximately 5 to 7 hours post previous dose, suggests that incorporation of the pediatric subject weight in the dosing regimen results in exposures that are similar to those obtained at target doses for adults. Pediatric subjects weighing ≥45 kg and dosed 40 mg BID had a similar concentration range to adults administered the same dose regimen (Figure 3). Pediatric subjects weighing less than 45 kg and dosed 40 mg BID as well as pediatric subjects ≥45 kg and dosed 80 mg BID had similar observed approximately maximal concentration ranges as adults dosed 80 mg BID (Figure 4). Although the data are limited, consistent with the results obtained from the population pharmacokinetic modeling, the weight based dose regimen appropriately adjusts exposure to concentration ranges similar to those observed for adult subjects.

Fi 3 Ob d Zi id C i C ll d 5 7 H Post Dose from g BID

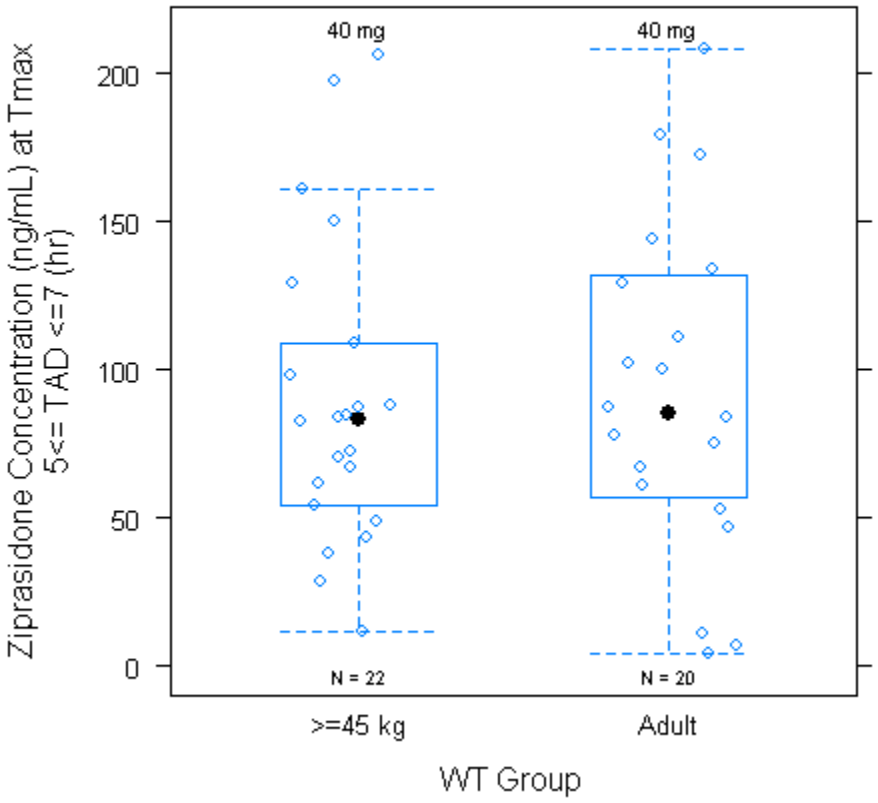
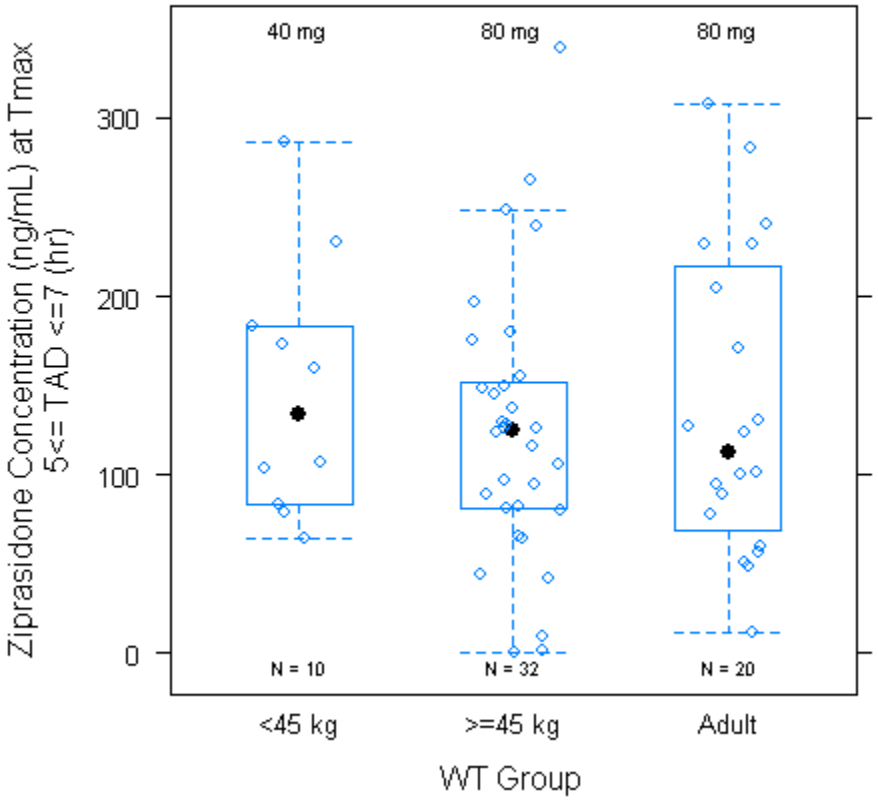


Figure 4. Observed Ziprasidone Concentrations Collected 5-7 Hours Post Dose from P di i S bj (45 k) Ad i i d 40 BID d Pediatric Subjects



3.4. Pharmacokinetic Characteristics of Ziprasidone in Pediatric and Adult Subjects

Taking into account body weight differences, age having only a small effect, the pharmacokinetic characteristics of ziprasidone are similar in children and adults. This is supported by the observed concentration data of ziprasidone which indicates that the weight based dosing regimen appropriately adjusts exposure for pediatric subjects.

- Within the pediatric populations in different studies, a similar range of clearance values was identified, showing a similar increase with increasing body weight.
- Body weight was identified as the most important covariate. It is associated with increasing clearance across the pediatric and adult age ranges in a continuous way. After correction for body weight differences, exposure to ziprasidone was similar in both children and adults.
- Age had only a small effect on clearance.
- Absorption was somewhat faster in pediatric patients compared to adults.

4. CLINICAL EFFICACY

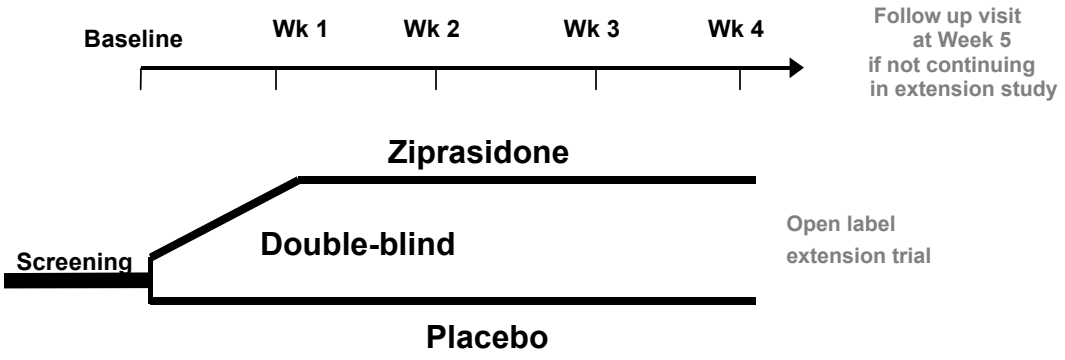
4.1. Overview of Efficacy

The efficacy of ziprasidone in the treatment of Bipolar I Disorder (with manic or mixed episodes) in children and adolescents between the ages of 10 and 17 years is summarized below. In the written request, the Division indicated that because of the continuity between adult and pediatric bipolar disorder, a pediatric indication for a drug already approved in adults may be supported by a single, independent, adequate and well-controlled clinical trial in pediatric Bipolar I Disorder. The efficacy results of one pivotal, double-blind, placebo-controlled study (A1281132) conducted at 36 centers in the US from 13 January 2006 to 26 July 2007 formed the basis of efficacy for this sNDA submission.

4.1.1. Study Design

Study A1281132 was a 4-week, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy, safety, and tolerability of flexibly dosed ziprasidone compared with placebo for the treatment of Bipolar I Disorder in children and adolescents aged 10-17 years (Figure 5 below).

Figure 5. Study Diagram



4.1.2. Subject Eligibility

Subjects enrolled in pivotal study A1281132 were male and female subjects between the ages of 10 and 17 years, who had a primary diagnosis of Bipolar I Disorder (single episode manic, or most recent episode manic, or most recent episode mixed) as defined by DSM-IV criteria and confirmed by the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS). The inclusion criteria required that subjects have an YMRS score of 17 or greater at screening and baseline and that current symptoms were present for at least 7 days prior to screening.

Additional salient exclusion criteria include the following: Pregnant or breast-feeding females, or females not using a medically acceptable form of contraception (including abstinence during the period of the study) were excluded from the study. Subjects with

significant cardiovascular disease history or abnormal ECGs at screening or baseline were excluded. Subjects were also excluded if they had a substance-induced psychotic disorder or a behavioral disturbance thought to be due to substance abuse, significant mental retardation (ie, IQ less than 70) that would interfere with study conduct or with the interpretation of the study assessments, or if they had autism or pervasive developmental disorder. Subjects who were clinically stable on treatment regimens that were well tolerated were excluded.

All current medications that were not allowed by the protocol (including psychotropics) were discontinued during the wash-out period between the Screening and Baseline visits. Use of psychotropic medication (except prn lorazepam ≤2 mg/day for anxiety or agitation) was prohibited throughout the study. For treatment of insomnia, lorazepam could be used as specified, or alternatively diphenhydramine or zolpidem were permitted.

4.1.3. Dose Selection and Dosing Regimen

The maximum tolerated doses and the maximum tolerable dose range used for the titration regimen for study A1281132 were determined during the low and high dose fixed dose titration period in study A1281123. In study A1281132, ziprasidone was titrated over the first 1-2 weeks of treatment and flexibly dosed through weeks 3 and 4. Ziprasidone was titrated from a starting dose of 20 mg/day with dose increases of 20 mg/day every 2nd day up to a target dose of 120-160 mg/day for subjects weighing ≥45 kg. The target dose was to be obtained by day 14. The dose was to increase above 120 mg/day only in subjects who tolerated 120 mg/day. For children weighing <45 kg, the target dose was 60-80 mg/day and a more gradual dose escalation could be employed.

Asymmetric dosing, with morning doses 20 mg or 40 mg less than evening doses, was permitted. In children requiring a more rapid onset of action based on their clinical history and symptoms, the dose could be titrated more rapidly with daily dose increases of 20 mg/day every day from the same starting dose to the same target dose.

4.1.4. Median and Mean Modal Doses

A total of 149 subjects received flexible doses of ziprasidone in the double-blind, placebo-controlled study for a mean duration of 22.9 days. During weeks 3, 4, including early termination from the study, the median modal dose and mean modal dose of ziprasidone for all subjects weighing <45 kg was 80 mg/day and 69.2 mg/day, respectively, and the median modal dose and mean modal dose for all subjects weighing ≥45 kg was 120 mg/day and 118.8 mg/day, respectively.

A total of 188 subjects diagnosed with Bipolar I Disorder received ziprasidone at flexible doses up to 160 mg/day in the two long-term safety and tolerability studies, A1281123 and A1281133. The majority of subjects in these studies received ziprasidone 120-160 mg/day for a mean duration of 116.5 days.

4.1.5. Primary and Secondary Efficacy Parameters

The protocol-specified primary efficacy endpoint in study A1281132 was change from baseline to week 4 in YMRS total score. The YMRS is an 11-item instrument used to assess the severity of mania in subjects with a diagnosis of bipolar disorder. The YMRS was developed for the assessment of mania severity in hospitalized adults, but its validity in pre-pubertal subjects has been demonstrated, and it is now widely accepted and used as a primary measure of mania severity in outpatient studies of children and adolescents with bipolar disorder.

The CGI scale, a standardized assessment tool used to rate the severity of a subject's illness and improvement over time, was specified as a secondary efficacy endpoint in study A1281132. The CGI scale consists of two subscales: the CGI-S score and the CGI-I score. The CGI-S assesses the investigator's impression of the subject's current illness state. The CGI-I rates the subject's improvement or worsening from baseline. The CGI-S was administered at every study visit beginning at the screening visit, and the CGI-I was administered at every study visit beginning at week 1.

A variety of exploratory outcomes assessments were obtained, including the Children's Global Assessment Scale (CGAS), the Children's Health Questionnaire and the School Placement Questionnaire. However, for the sake of brevity, only data from the CGAS are presented in this document. The CGAS is a clinician-rated global assessment scale for children based on symptoms and social functioning at home, school, and community settings (CGAS; Shaffer et al, 1983). Scores on this single item range from 1-100 (higher levels indicate greater health), with descriptive anchors for every 10-point interval. Scores above 70 on this scale are considered within the "normal" range.

Table 5. Schedule of Efficacy and Outcome Ratings

	Screening	Baseline	Treatment			EOT
Study Day	-10 to –1	0	7	14	21	28
YMRS	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X
CGI-I			X	X	X	X
CGAS	X	X		X		X
CGAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impression of Improvement, CGI-S = Clinical Global Impression of Severity, EOT = end-of-treatment, FU = follow up, K-SADS = Schedule for Affective Disorders and Schizophrenia for School Age Children, YMRS = Young Mania Rating Scale						

4.1.6. Analysis of Efficacy

Definition of study population

In this study, an Intent-to-Treat (ITT) analysis set was defined as the set of all subjects who were randomized, had baseline measurements, took at least one dose of study medication (ziprasidone or placebo), and had at least one post-baseline visit.

Statistical model, primary efficacy endpoint

The primary efficacy endpoint was the change from baseline in YMRS score. The primary time point was Week 4. All other collection time points were considered to be secondary.

The analysis of change from baseline in the YMRS score was performed using SAS PROC MIXED to fit a mixed model repeated measures analysis of covariance (ANCOVA) with center and subject within center as random effects, treatment, visit and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

Supplemental analyses of the primary variable (including ANCOVA at week 4, both observed case and LOCF) were performed to support the robustness of the conclusions drawn from the primary mixed models repeated measures analysis described above. Although specific results are not presented here, again, for the sake of brevity, the results were supportive of the primary analysis findings.

The percentage of subjects showing at least a 30% and at least a 50% reduction in YMRS scores from baseline to Week 4 were presented for each treatment group. This was done using both the LOCF and OC (observed cases).

Subgroup analyses on the primary endpoint

Post-hoc subgroup analyses by gender, age group, weight category, and race were performed. Results were obtained from a mixed model repeated measures analysis of covariance with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects and baseline score as covariate.

Statistical model, secondary efficacy endpoints

The secondary efficacy endpoints included the change from baseline in the CGI-S score (key secondary efficacy endpoint), and the raw CGI-I score. The primary time point was Week 4, all other time points were considered secondary.

For the change from baseline in the CGI-S score, analyses were conducted using SAS PROC MIXED to fit a mixed model repeated measures ANCOVA with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate.

For the raw CGI-I score, analyses were 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.

4.1.7. Subject Characteristics

Subject demographics of A1281132 are presented in Table 6.

Table 6. Subject Demographics – Study A1281132

	Ziprasidone				Placebo		
	Male N=84	**Female N=65**	**Total N=149**		**Male N=47**	**Female N=41**	**Total N=88**
Age (years)							
10-13	47 (56.0)	27 (41.5)	74 (49.7)		19 (40.4)	16 (39.0)	35 (39.8)
14-17	36 (42.9)	38 (58.5)	74 (49.7)		28 (59.6)	25 (61.0)	53 (60.2)
18*	1 (1.2)	0 (0)	1 (0.7)		0 (0)	0 (0)	0 (0)
Mean	13.2	14.1	13.6		13.5	14.0	13.7
SD	2.4	2.0	2.2		2.0	1.9	2.0
Range	10-18	10-17	10-18		10-17	10-17	10-17
Race							
White	66 (78.6)	55 (84.6)	121 (81.2)		38 (80.9)	34 (82.9)	72 (81.8)
Black	15 (17.9)	6 (9.2)	21 (14.1)		8 (17.0)	6 (14.6)	14 (15.9)
Asian	0 (0)	1 (1.5)	1 (0.7)		0 (0)	0 (0)	0 (0)
Other	3 (3.6)	3 (4.6)	6 (4.0)		1 (2.1)	1 (2.4)	2 (2.3)
Ethnicity							
Hispanic/Latino	5 (6.0)	6 (9.2)	11 (7.4)		2 (4.3)	5 (12.2)	7 (8.0)
Not Hispanic/Latino	79 (94.0)	59 (90.8)	138 (92.6)		45 (95.7)	36 (87.8)	81 (92.0)
Weight (kg)							
Mean	55.9	58.8	57.2		61.3	58.5	60.0
SD	16.3	11.5	14.4		17.9	13.4	16.0
Range	28.0-88.0	34.1-94.4	28.0-94.4		29.0-109.4	32.1-87.1	29.0-109.4
Height (cm)							
Mean	160.3	158.1	159.3		163.4	157.1	160.5
SD	14.1	8.0	11.9		13.8	8.1	11.9
Range	128-188	134-174	128-188		137-193	133-170	133-193

SD = standard deviation
*One subject turned 18 after the screening visit and was allowed to participate in the study.

The mean age of subjects who received ziprasidone (13.6 years) and placebo (13.7 years) in the double-blind study was comparable. The subjects in the ziprasidone group were equally distributed across the younger (10-13 years, 49.7%) and older (14-17 years, 49.7%) age categories, while a greater proportion of subjects in the placebo group fell into the older age category (60.2%) than the younger age category (39.8%).

The primary diagnoses and duration of disease at screening are shown in Table 7.

Table 7. Primary Diagnoses and Duration of Disease at Screening – Study A1281132

	Ziprasidone N=149	Placebo N=88
Primary Diagnosis (MedDRA, Version 10.1)		
Bipolar I Disorder		
Number of subjects	149	88
Duration since first diagnosis (months)		
Mean	11.6	9.1
Range	0.0-111.9	0.0-103.1
Unspecified	1	0
Primary Diagnosis Characteristics		
Bipolar I Disorder, single manic episode	14	8
Bipolar I Disorder, most recent episode manic	45	23
Bipolar I Disorder, most recent episode mixed	90	57
Duration from first diagnosis to Screening Visit; MedDRA = Medical dictionary for Regulatory Activities (Version 10.1)		

All subjects met diagnostic criteria for Bipolar I Disorder, manic or mixed episode, as defined by DSM-IV criteria and confirmed by a semi-structured diagnostic interview (K-SADS). At the Screening visit, the mean duration since first diagnosis of disease was 11.6 months (range = 0-112 months) in the ziprasidone group and 9.1 months (range = 0-103 months) in the placebo group.

The mean baseline CGAS scores and the proportion of subjects who had a baseline score ≥70 (ie, indicating normal functioning) are shown in Table 8.

Table 8. Baseline CGAS Scores & % >=70 – Study A1281132

Baseline CGAS Score	Ziprasidone (N=149)	Placebo (N=88)
Mean (SD)	45.1 (10.6)	43.6 (11.8)
Range	10 -75	10 – 80
% ≥70	2.0% (3/149)	1.1% (1/88)

The CGAS scores of the subjects enrolled into study A1281132 were consistent with scores reported in previous studies of children with bipolar disorder (Geller et al, 2008) and indicative of "a moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area" (Shaffer et al, 1983).

Current psychiatric comorbid diagnoses, prior treatment with stimulants, and parental and family history of bipolar disorder, and are described in Table 9 below.

Table 9. Comorbidities, Prior Stimulant Treatment, & Parental and Family History – Study A1281132

	Ziprasidone (N=149)	Placebo (N=88)	All Treatments (N=237)
	n (%)	n (%)	n (%)
Current Comorbid Psychiatric Diagnoses			
ADHD	66 (44.3)	36 (40.9)	102 (43.0)
Conduct Disorder	13 (8.7)	6 (6.8)	19 (8.0)
OCD	4 (2.7)	2 (2.3)	6 (2.5)
ODD	41 (27.5)	25 (28.4)	66 (27.8)
Prior Stimulant Treatment	30 (20.1)	22 (25.0)	52 (21.9)
Parental History of BD	61 (40.9)	35 (39.8)	96 (40.5)
Family History of BD	96 (64.4)	57 (64.8)	153 (64.6)

Overall, 43% of the subjects enrolled in A1281132 were diagnosed with ADHD at screening using the K-SADS; 8% with Conduct Disorder; and approximately 28%, with Oppositional Defiant Disorder (ODD). The rates of disruptive behavior disorders diagnosed in this sample are consistent with rates reported in previous studies of childhood and adolescent bipolar disorder (Singh et al, 2006; Castilla-Puentes, 2008; Geller et al, 2008). Our data indicate that approximately 22% of the subjects in the A1281132 study had been previously treated with stimulants. For comparison, stimulants were used in 24% to 35% of adolescents diagnosed with bipolar disorder in other clinical samples (Soutullo et al., 2002; Castilla-Puentes, 2008).

In our sample 40.5% of the children had a parental history for bipolar disorder and 64.6% had some family history for bipolar disorder. The high parental history for bipolar disorder in the A1281132 subjects is comparable to the 33.3% rate of parental bipolar disorder reported for children with narrow phenotype pediatric bipolar disorder, compared to the only 2.7% rate reported for children with severe mood dysregulation, i.e. the "broad phenotype" of pediatric bipolar disorder (Brotman et al., 2007).

4.1.8. Study Results

4.1.8.1. Subject Disposition

Subject disposition is summarized in Table 10 below. A total of 327 subjects were screened and 238 were randomized to treatment. Of these subjects, 237 took study medication (1 subject was assigned but did not receive treatment). The percentage of subjects who completed the study was 65% in the ziprasidone group and 58% in the placebo group.

The most common reasons for discontinuation were categorized as “Other” and occurred more frequently in the placebo group (24% vs 11% in the ziprasidone group). Among the discontinuations categorized as “Other”, a total of 7 subjects in the ziprasidone group and 17 subjects in the placebo group discontinued for lack of efficacy. A higher percentage of subjects from the ziprasidone group discontinued due to treatment-related adverse events than placebo subjects (9% vs 3%, respectively). Discontinuations due to AEs are discussed in Section 5.2.1 of this Briefing Document.

Table 10. Subject Disposition – Study A1281132

	Ziprasidone	Placebo
Number (%) of subjects:		
Screened: N=327		
Assigned to study treatment: N=238		
Treated	149	88
Completed	97 (65.1)	51 (58.0)
Discontinued	52 (34.9)	37 (42.0)
Reason for discontinuation:		
Related to study drug:	14 (9.4)	3 (3.4)
Adverse event	13 (8.7)	3 (3.4)
Laboratory abnormality	1 (0.7)	0 (0)
Not related to study drug:	38 (25.5)	34 (38.6)
Adverse event	5 (3.4)	10 (11.4)
Lost to follow-up	8 (5.4)	1 (1.1)
Other	16 (10.7)	21 (23.9)
Subject no longer willing to participate	9 (6.0)	2 (2.3)
Analyzed for efficacy:		
Intent-to-treat	143 (96.0)	86 (97.7)
Per protocol	103 (69.1)	66 (75.0)
Analyzed for safety:		
Adverse events	149 (100)	88 (100)
Laboratory data	134 (89.9)	84 (95.5)

4.1.8.2. Results from Primary Efficacy Variable

Table 11 below provides a summary of the primary statistical analysis in the ITT population from baseline to week 4 in the YMRS total score. The difference in treatment effect was statistically significant (p=0.0005).

Table 11. Summary of Primary Statistical Analysis for Change from Baseline in YMRS at Week 4, ITT Population - A1281132

	Ziprasidone N=133	Placebo N=85
LS Mean (SE)	-13.83 (0.96)	-8.61 (1.10)
Difference from placebo LS Mean (SE)	-5.22 (1.48)	--
95% CI for the difference from placebo	[-8.12, -2.31]	--
p-value	0.0005	--
CI=confidence interval; LS Mean=least square mean; SE=standard error; N=number of subjects with a YMRS score at baseline and with at least 1 post-baseline measurement windowed to a study visit. Results obtained from a mixed model repeated measures analysis of covariance model with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate.		

The baseline group mean YMRS scores (± SD) were comparable between the ziprasidone (26.2 ± 6.6) and placebo (27.0 ± 6.6) treatment groups and indicated subjects had a moderate to severe level of baseline symptomatology (Table 12).

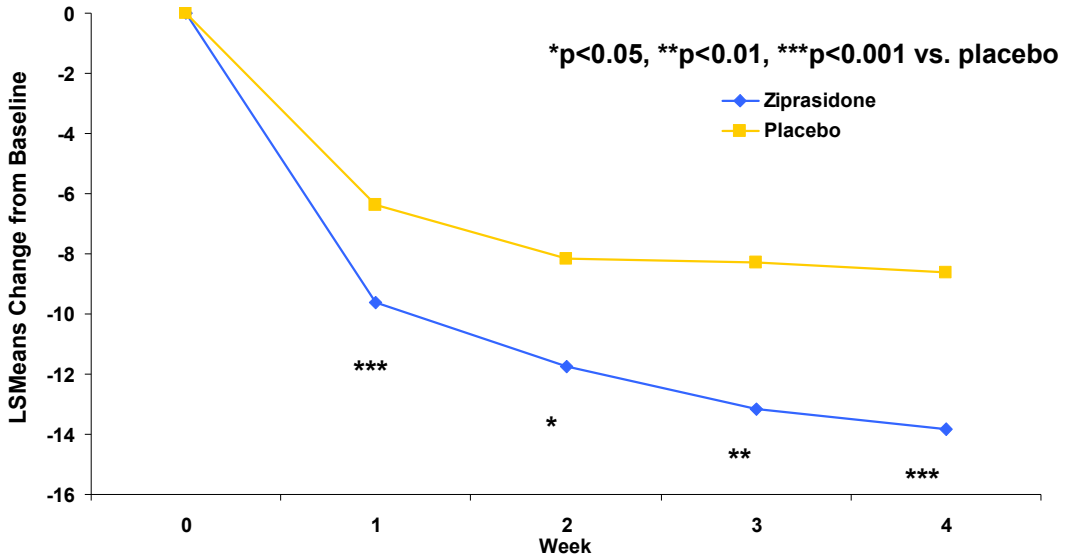
In patients with Bipolar I Disorder, achieving early control of symptoms is important, as well as ensuring an early sustained response. Table 12 below provides descriptive statistics for YMRS total score at baseline and change from baseline by visit for the ITT population. These data support the conclusions in the primary statistical analysis and show the active and placebo groups separating as early as week 1 for the change from baseline in YMRS total score. Figure 6 provides a graphical representation of YMRS improvement from baseline by week.

Table 12. Descriptive Statistics for YMRS Total Score at Baseline and Change from Baseline by Treatment Group and Visit, ITT Population – A1281132

	Ziprasidone					Placebo				
Visit	**N**	**Mean (SD)**	**Median**	**Min/ Max**	**(95% CI)**	**N**	**Mean (SD)**	**Median**	**Min/ Max**	**(95% CI)**
BL	143	26.2 (6.6)	26	9/49	(25.08, 27.26)	86	27.0 (6.6)	26	8/43	(25.59, 28.43)
Wk 1	131	-9.3 (7.5)	-8	-34/7	(-10.63, -8.04)	85	-6.3 (7.1)	-6	-20/10	(-7.86, -4.80)
Wk 2	120	-11.5 (8.7)	-11	-33/15	(-13.07, -9.92)	81	-8.1 (7.9)	-8	-32/8	(-9.88, -6.40)
Wk 3	108	-13.0 (8.1)	-13	-35/5	(-14.51, -11.42)	65	-9.0 (7.3)	-9	-25/9	(-10.82, -7.21)
Wk 4	97	-13.8 (7.8)	-14	-31/7	(-15.32, -12.18)	51	-9.9 (7.7)	-10	-22/9	(-12.03, -7.70)
ET	20	-5.1 (5.6)	-5	-14/6	(-7.68, -2.42)	7	-2.3 (5.5)	-2	-8/9	(-7.37, 2.80)
Wk 4-LOCF	133	-12.8 (8.4)	-13	-35/15	(-14.27, -11.37)	85	-7.1 (7.8)	-7	-22/9	(-8.74, -5.40)

BL=baseline, and is day 1; Wk=week; CI=Confidence Interval; ET=early termination, and includes observations that did not meet windowing criteria; LOCF=last observation carried forward.

Figure 6. YMRS Improvement from Baseline – Study A1281132



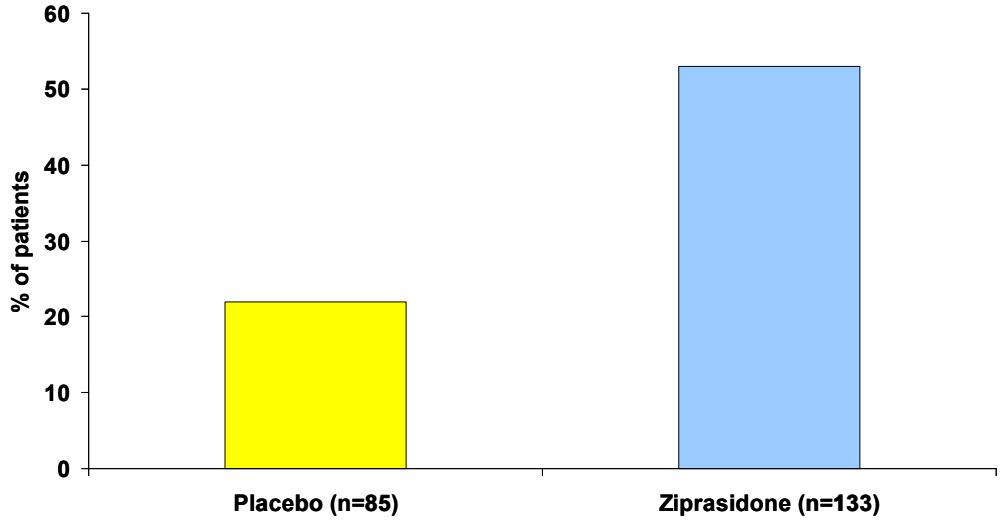
Placebo adjusted LS Means at week 4 (95%CI): -5.22 (-8.12; -2.31)

Mixed Model Repeated Measures analysis by week. Primary Analysis at week 4. Post-hoc analysis at weeks 1, 2, and 3.

Note: Test results shown at weeks 1, 2, and 3 are from post-hoc exploratory analyses with no adjustment for multiplicity.

A ≥50% reduction in YMRS was achieved in 62% of the subjects in the ziprasidone group compared to 35% of the subjects in the placebo group (OC). A ≥30% reduction in YMRS was achieved in 77% of the subjects in the ziprasidone group compared with 65% of the subjects in the placebo group (OC). Figure 7 below presents the frequency of subjects with at least a 50% reduction in YMRS from baseline to week 4 (LOCF). These data further support the conclusions in the primary statistical analysis.

Figure 7. YMRS ≥50% Responder Rate (LOCF) - Week 4 – Study A1281132



Patients with ≥50% reduction from baseline at week 4 (LOCF)
Baseline YMRS: placebo =27, ziprasidone = 26.2

4.1.8.2.1. Analyses of Subgroups

Post hoc subgroup analyses by gender, age group, weight, and race were performed. Results were obtained from a mixed model repeated measures analysis of covariance with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects and baseline score as covariate (Table 13).

Table 13. Subgroup Efficacy Summary Table – Study A1281132

	Zip[1]	Pbo[1]	Diff from Pbo[1]	P-value[2]
YMRS Change from Baseline at Wk 4 By Gender				
Male	-13.41 (1.12) (N=74)	-6.50 (1.48) (N=44)	-6.91 (1.72)	<0.0001
Female	-14.44 (1.15) (N=59)	-10.70 (1.45) (N=41)	-3.74 (1.85)	0.0445
YMRS Change from Baseline at Wk 4 By Age				
10 - <14	-12.44 (1.12) (N=66)	-8.57 (1.71) (N=35)	-3.88 (1.98)	0.0510
14 - <18	-15.36 (1.15) (N=67)	-8.33 (1.31) (N=50)	-7.03 (1.62)	<0.0001
YMRS Change from Baseline at Wk 4 By Weight				
<45 kg	-12.83 (1.86) (N=31)	-10.97(2.92) (N=14)	-1.86 (3.22)	0.5643
≥45 kg	-14.15 (0.90) (N=102)	-8.21 (1.11) (N=71)	-5.93 (1.36)	<0.0001
YMRS Change from Baseline at Wk 4 By Race[3]				
White	-13.98 (0.95) (N=112)	-7.68 (1.21) (N=69)	-6.29 (1.37)	<0.0001
Black	-12.44 (2.30) (N=15)	-11.38 (2.51) (N=14)	-1.06 (3.26)	0.7461
Other	-11.96 (2.62) (N=5)	-17.54 (4.01) (N=2)	5.59 (4.80)	0.2640

[1]LSMeans (SD)
[2]MMRM analysis of covariance with center and subject within center as random; treatment, visit, and visit by treatment interaction as fixed, and baseline as covariate.
[3]No analysis performed on the single Asian ziprasidone subject.

The treatment effect was statistically significant in favor of ziprasidone for both males (p<0.0001) and females (p=0.0445) and for both age groups: 10-<14 (marginally p=0.0510) and 14-<18 years (p<0.0001). A statistically significant treatment effect was also documented for subjects ≥45 kg (p=0.0001) but not for subjects <45 kg (p=0.5643). However, it should be noted the number of subjects in the <45 kg weight category was relatively small. No meaningful conclusions could be drawn with respect to the effect of ziprasidone on the YMRS based on race due to the small numbers of subjects in the Black (ziprasidone N=15; placebo N=14), Asian (ziprasidone N=1; placebo N=0), and Other (ziprasidone N=5; placebo N=2) racial groups.

4.1.8.3. Results of Key Secondary Efficacy Variable for Pivotal Efficacy Study A1281132

Table 14 below summarizes the statistical analysis for the key secondary endpoint, change from baseline to Week 4 in CGI-S total score. The difference in treatment effect was statistically significant (p=0.0001) in favor of ziprasidone.

Table 14. Summary of Statistical Analysis for Change from Baseline in CGI-S Total Score at Week 4 Repeated Measures, ITT Population - A1281132

	Ziprasidone N=133	Placebo N=85
LS Mean (SE)	-1.43 (0.13)	-0.74 (0.13)
Difference from placebo LS Mean (SE)	-0.69 (0.18)	--
95% CI for the difference from placebo	[-1.03, -0.34]	--
p-value	0.0001	--
CI=confidence interval; LS Mean=least square mean; SE=standard error; Results obtained from a mixed-effect repeated measures analysis of covariance model with center and subjects within center as random effects, treatment visit, and visit-by-treatment interaction as fixed effects and baseline score as a covariate.		

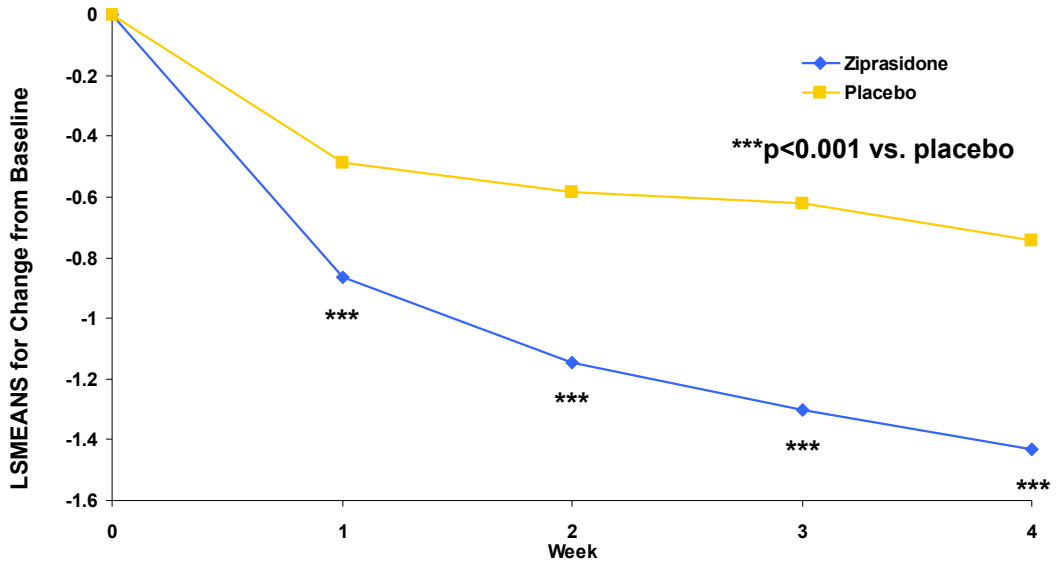
The baseline group mean CGI-S scores (± SD) were comparable between the ziprasidone (4.5 ± 0.7) and placebo (4.5 ± 0.7) treatment groups and indicated that subjects were moderately to markedly ill at baseline (Table 15 below).

Table 15. Descriptive Statistics for CGI-S Score at Baseline and Change from Baseline by Treatment Group and Visit, ITT Population – A1281132

	Ziprasidone					Placebo				
	N	Mean (SD)	Median	Min/Max	(95% CI)	N	Mean (SD)	Median	Min/Max	(95% CI)
BL	143	4.5 (0.7)	4	3/7	(4.41, 4.46)	86	4.5 (0.7)	4	3/6	(4.39, 4.79)
Wk 1	131	-0.9 (0.8)	-1	-3/1	(-1.00, -0.71)	85	-0.5 (0.9)	0	-4/2	(-0.69, -0.30)
Wk 2	120	-1.1 (1.0)	-1	-4/1	(-1.31, -0.94)	82	-0.6 (0.9)	0	-3/1	(-0.79, -0.38)
Wk 3	108	-1.3 (1.0)	-1	-4/0	(-1.49, -1.12)	65	-0.7 (1.0)	-1	-3/2	(-0.94, -0.44)
Wk 4	96	-1.4 (1.1)	-1	-5/2	(-1.68, -1.22)	51	-0.9 (0.9)	-1	-3/1	(-1.11, -0.61)
ET	20	-0.4 (0.5)	0	-1/0	(-0.58, -0.12)	7	-0.6 (1.0)	-1	-2.1	(-1.47, 0.33)
Wk 4-LOCF	133	-1.3 (1.1)	-1	-5/2	(-1.51, -1.12)	85	-0.6 (0.9)	0	-3/2	(-0.75, -0.35)
BL=baseline; Wk=week; ET=early termination, and includes observations from visits that did not meet windowing criteria; LOCF=last observation carried forward.										

Figure 8 provides a graphical representation of CGI-S improvement from baseline by week. These data support the conclusions in the key secondary statistical analysis and show the active and placebo groups separating as early as Week 1 for the change from baseline in CGI-S score.

Figure 8. CGI-S Improvement from Baseline – Study A1281132



Mixed Model Repeated Measures analysis by week. Key-Secondary Analysis at week 4. Post-hoc analysis at weeks 1, 2, and 3.

Note: Test results shown at weeks 1, 2, and 3 are from post-hoc exploratory analyses with no adjustment for multiplicity.

Another secondary endpoint was CGI-I score. The CGI-I rates the subject's improvement or worsening from baseline. Table 16 below summarizes the statistical analysis of GCI-I score at Week 4. The difference in treatment effect was statistically significant (p=0.0004) in favor of ziprasidone.

Table 16. Summary of Statistical Analysis of CGI-I Score at Week 4 ITT Population – Study A1281132

	Ziprasidone N=132	Placebo N=85
LS Mean (SE)	2.30 (0.13)	3.06 (0.16)
Difference from placebo LS Mean (SE)	-0.76 (0.21)	--
95% CI for the difference from placebo	[-1.18, -0.34]	--
p value	0.0004	--
CI=confidence interval; LS Mean=least squares mean; SE=standard error; N=the number of subjects with a CGI-I score at baseline and with at least 1 post-baseline measurement windowed to a study visit. Results obtained from a mixed-effect repeated measures analysis of covariance model with center and subject within center as random effects, treatment, visit, and visit-by-treatment interaction as fixed effects.		

Table 17 presents descriptive statistics for CGI-I score by visit for the ITT population. CGI-I scores were consistently lower in the ziprasidone group relative to the placebo group at each visit, further supporting the efficacy of ziprasidone.

Table 17. Descriptive Statistics for CGI-I Score by Treatment Group and Visit, ITT Population – A1281132

	Ziprasidone					Placebo				
	N	Mean (SD)	Median	Min/Max	(95% CI)	N	Mean (SD)	Median	Min/Max	(95% CI)
Wk 1	132	2.8 (0.9)	3	0/4	(2.60, - 2.90)	85	3.4 (0.9)	3	1/6	(3.17, - 3.56)
Wk 2	120	2.5 (1.1)	2	0/6	(2.34, - 2.74)	82	3.2 (1.1)	3	1/7	(2.95, - 3.45)
Wk 3	108	2.4 (1.0)	2	0/5	(2.22, - 2.61)	65	3.1 (1.3)	3	0/6	(2.74, - 3.38)
Wk 4	96	2.3 (1.0)	2	1/7	(2.08, - 2.50)	51	2.8 (1.1)	3	1/5	(2.54, - 3.15)
ET	20	3.6 (1.3)	4	0/7	(2.93, 4.17)	7	3.7 (1.6)	4	1/6	(2.23 – 5.20)
Wk 4-LOCF	132	2.4 (1.1)	2	0/7	(2.19, - 2.57)	85	3.4 (1.2)	3	1/7	(3.10, - 3.63)

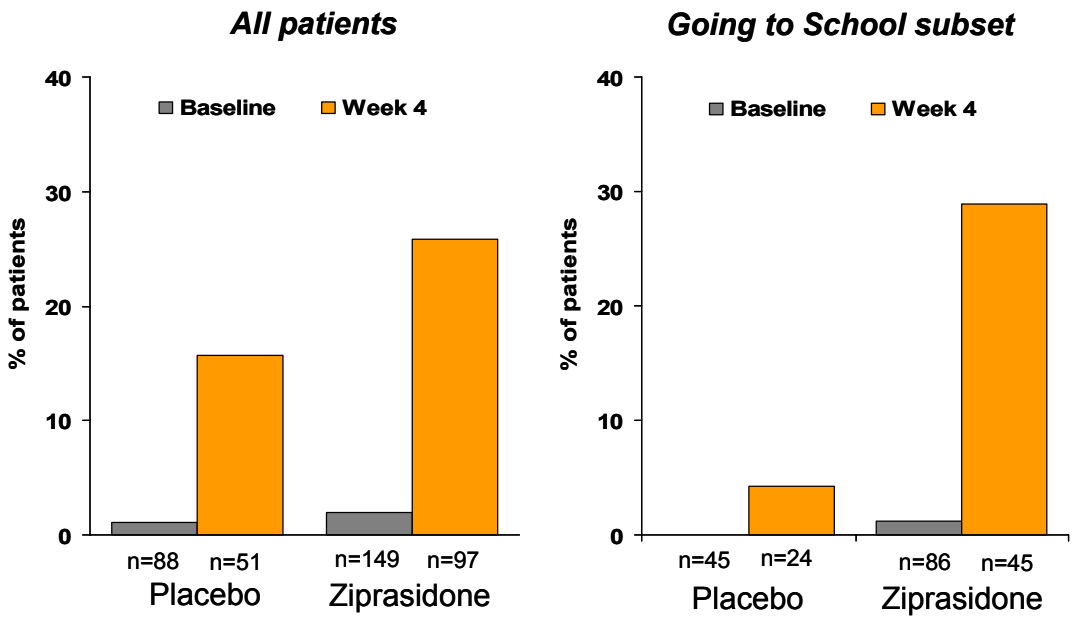
BL=baseline; Wk=week; ET=early termination, and includes observations from visits that did not meet windowing criteria; LOCF=last observation carried forward.

4.1.8.4. Results of CGAS Assessments

Overall, CGAS data showed a trend toward improved scores for subjects receiving ziprasidone compared with placebo. Moreover, those subjects who were reported to be in

school showed better responses with active treatment. The mean change from baseline to Week 4 showed an increase in the CGAS score of 14.9 vs 11.2 in the active vs placebo groups, respectively. Subjects reported to be in school had a greater spread in mean scores between the active and placebo groups (change from baseline to Week 4 was 14.8 vs 9.0 for active vs placebo, respectively). In the active vs placebo groups, the percentage of subjects having a CGAS score of 70 or greater (ie, normal functioning) was 2% vs 1.1% at baseline and 25.8% vs 15.7% at Week 4 (Figure 9). For subjects reported to be in school, the percentages were 1.2% vs 0% at baseline and 28.9% vs 4.2% at Week 4. Thus, subjects reported to be in school had a better response with the active treatment.

Figure 9. Percent of Subjects with CGAS Score ≥70 - Study A1281132



CGAS: Children's Global Assessment Scale ≥70 represents normal functioning

4.1.8.5. Efficacy Conclusions

- Based on the primary efficacy endpoint (change from baseline to Week 4 in YMRS total score), there was a statistically significant treatment effect (p=0.0005) for ziprasidone over placebo.

- Results from the analysis of the key secondary efficacy endpoint, the change from baseline in CGI-S score at Week 4, were consistent with the findings in YMRS total score. Ziprasidone demonstrated a statistically significant (favorable) difference from placebo (p=0.0001).

- Results from the secondary efficacy endpoint, CGI-I score at Week 4, were consistent with the findings for YMRS total score. Ziprasidone demonstrated a statistically significant (favorable) difference from placebo (p=0.0004).

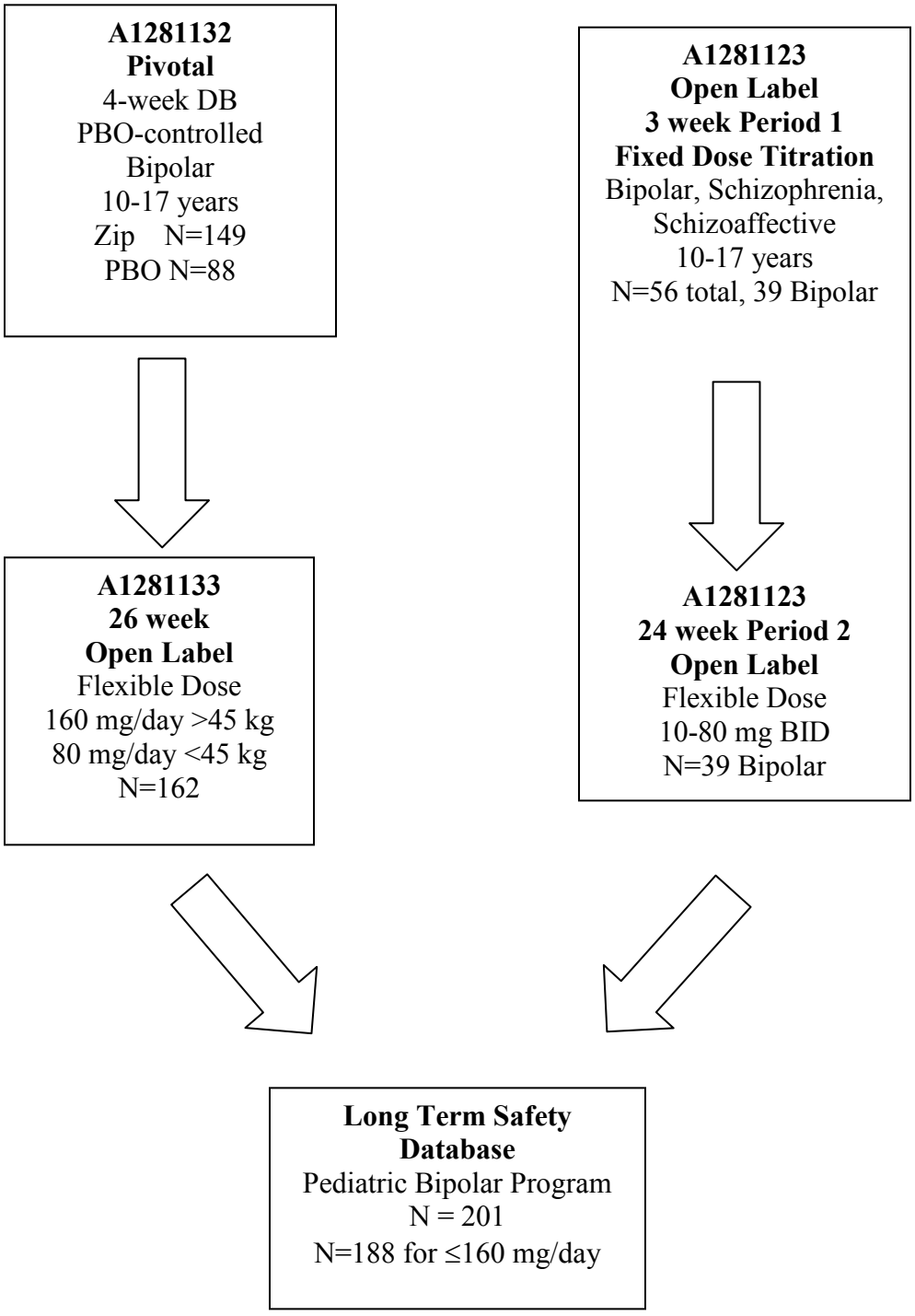
- Overall, oral ziprasidone was shown to be effective in the treatment of children and adolescents with Bipolar I Disorder (manic or mixed).

5. CLINICAL SAFETY

Oral ziprasidone is approved for the treatment of Bipolar I Disorder, as well as for schizophrenia, in the adult patient population. The general safety and adverse reaction profile of ziprasidone is known in that population and represented in the current approved labeling. This section of the Briefing Document addresses the safety profile of the use of ziprasidone as treatment for Bipolar I Disorder in children and adolescents between the ages of 10-17 years. Safety data from the completed 4-week, double-blind, placebo-controlled, pediatric Bipolar I Disorder study A1281132 form the basis of this summary of safety.

Integrated long-term safety data from two open-label studies (A1281123 and A1281133) are also discussed (Figure 10). The first open-label study, A1281123, enrolled subjects with Bipolar I Disorder, schizophrenia, and schizoaffective disorder and was comprised of two active periods of up to 3 weeks and 24 weeks of treatment. The second open-label study, A1281133, was a 26-week extension study for subjects who completed the short-term study, A1281132. Subjects with Bipolar I Disorder only are discussed in the context of the open-label, long-term safety studies. All subjects who received ziprasidone ≤160 mg/d will be discussed. Thirteen subjects (of 201 total) in the open-label studies inadvertently received >160 mg/d ziprasidone and relevant safety information is discussed separately.

Figure 10. Studies Contributing to the Safety Database



5.1. Extent of Exposure

5.1.1. Mean Duration of Exposure

Ziprasidone was administered to a total of 149 pediatric subjects with Bipolar I Disorder in the double-blind, placebo-controlled efficacy and safety study A1281132; 88 subjects received placebo. Two hundred one pediatric subjects with Bipolar I Disorder received ziprasidone in open-label long-term safety and tolerability trials.

The mean duration of exposure for subjects who received ziprasidone in the double-blind, placebo-controlled study was 22.9 days (placebo mean duration of exposure was 23.7 days) (Table 18).

Table 18. Duration of Exposure - A1281132

	Ziprasidone N=149	Placebo N=88
Duration Category (Days)		
<7	16	2
7-<14	12	7
14-<21	16	17
21-<28	17	15
28-<35	86	45
≥35	2	2
Mean duration, days	22.9	23.7
Median duration, days	28	28
Range, days	1-37	1-35
Duration is the total number of dosing days from first to last (inclusive) day of each study treatment.		

The mean duration of exposure for subjects diagnosed with Bipolar I Disorder who received ziprasidone in the open-label, long-term safety and tolerability studies was 106.3 days. The cumulative mean duration exposure for subjects who completed the 4-week double-blind, placebo-controlled study who received ziprasidone and who continued in the long term extension study A1281133 was 132.5 days. The total duration of exposure across the three studies was approximately 70.32 patient years.

5.2. Discontinuations of Therapy

Table 19 presents a summary of reasons for discontinuation in the double-blind placebo-controlled study. Fifty-two subjects receiving ziprasidone and 37 subjects receiving placebo discontinued from the study. Of the ziprasidone-treated subjects, 9.4% (14/149) discontinued due to reasons related to the study drug (13 subjects due to an adverse event; 1 subject due to laboratory abnormality), and of the placebo-treated subjects, 3.4% (3/88) discontinued due to reasons related to the study drug (3 subjects due to an adverse event).

Table 19. Reasons for Discontinuation from Study A1281132

Number (%) of Subjects	Ziprasidone (N = 149)	Placebo (N = 88)
Related to Study Drug	**14 (9.4)**	**3 (3.4)**
Adverse event	13 (8.7)	3 (3.4)
Laboratory abnormality	1 (0.7)	0
Not Related to Study Drug	**38 (25.5)**	**34 (38.6)**
Adverse event	5 (3.4)	10 (11.4)
Lost to follow-up	8 (5.4)	1 (1.1)
Other	16 (10.7)	21 (23.9)
Unwilling to participate further	9 (6.0)	2 (2.3)

During long-term treatment with ziprasidone for subjects with Bipolar I Disorder, 38 (20.2%) subjects discontinued from treatment due to treatment-emergent, all causality adverse events. None of the subjects discontinued due to a laboratory test abnormality.

5.2.1. Adverse Events Associated with Discontinuation

In the double-blind placebo-controlled study, 18 (12.1%) of the 149 ziprasidone-treated subjects discontinued due to adverse events. The most frequent treatment-emergent adverse event associated with discontinuation (≥1% incidence) among ziprasidone-treated subjects were dystonia (2/149), headache (2/149), and sedation (4/149). In placebo-treated subjects, 13 (14.8%) of 88 subjects discontinued due to an adverse event. Bipolar disorder (3/88) and suicidal ideation (3/88) were the most frequent treatment-emergent adverse events associated with discontinuation in placebo-treated subjects.

During long-term treatment with ziprasidone, 107 (57%) of the 188 subjects discontinued; 38/188 (20.2%) discontinued due to a treatment-emergent adverse event. Discontinuations due to treatment-emergent adverse events were most frequently associated with Psychiatric disorders (20/188, 10.6%) and Nervous system disorders (14/188, 7.4%). Of the adverse events (>1 subject) that led to discontinuation, 7 subjects experienced sedation, 4 subjects each experienced somnolence or bipolar disorder, 3 subjects reported suicidal ideation, and 2 subjects each reported depression, mania, fatigue or aggression. The majority of subjects that discontinued did so during their first month of treatment.

5.3. Incidence of AEs

5.3.1. General Summary of Common AEs

The percentage of subjects reporting at least one treatment-emergent adverse event in the double-blind placebo-controlled study was 91% (136/149) for ziprasidone and 66% (58/88) for placebo (Table 20)

Table 20. Overview of Treatment-Emergent Adverse Events - A1281132

Number (%) of Subjects	Ziprasidone	Placebo
Subjects evaluable for adverse events	**149**	**88**
Number of adverse events	468	160
Subjects with adverse events	136 (91.3)	58 (65.9)
Subjects with serious adverse events	6 (4.0)	5 (5.7)
Subjects with severe adverse events	18 (12.1)	6 (6.8)
Subjects discontinued due to adverse events*	18 (12.1)	11 (12.5)
Subjects with dose reduced or temporary discontinuation due to adverse events	60 (40.3)	2 (2.3)

*Does not include two subjects in the placebo group who discontinued due to AEs that were not treatment-emergent

Treatment-emergent adverse events occurring with the incidence of ≥5% in ziprasidone-treated subjects and at a higher incidence rate than placebo are presented in Table 21.

Table 21. Treatment-Emergent, All Causality Adverse Events Occurring at an Incidence of >= 5% in Any Group - Study A1281132

System Organ Class Preferred Term (MedDRA)	Ziprasidone (N=149) n (%)	Placebo (N=88) N (%)
Any adverse event, n (%)	136 (91.3)	58 (65.9)
Eye disorders	**12 (8.1)**	**1 (1.1)**
Vision blurred	9 (6.0)	1 (1.1)
Gastrointestinal disorders	**49 (32.9)**	**14 (15.9)**
Abdominal pain upper	8 (5.4)	3 (3.4)
Nausea	20 (13.4)	6 (6.8)
Vomiting	11 (7.4)	1 (1.1)
General disorders and administration site conditions	**28 (18.8)**	**14 (15.9)**
Fatigue	20 (13.4)	6 (6.8)
Injury, poisoning, and procedural complications	11 (7.4)	6 (6.8)
Overdose	7 (4.7)	5 (5.7)
Infections and Infestations	**22 (14.8)**	**6 (6.8)**
Upper Respiratory Tract Infection	**7 (4.7)**	**0 (0)**
Musculoskeletal and connective tissue disorders	**22 (14.8)**	**10 (11.4)**
Musculoskeletal stiffness	8 (5.4)	0 (0)
Nervous system disorders	**115 (77.2)**	**31 (35.2)**
Dizziness	16 (10.7)	2 (2.3)
Headache	31 (20.8)	19 (21.6)
Sedation	49 (32.9)	4 (4.5)
Somnolence	37 (24.8)	7 (8.0)
Tremor	8 (5.4)	0 (0)
Psychiatric disorders	**34 (22.8)**	**21 (23.9)**
Insomnia	13 (8.7)	3 (3.4)
Restlessness	8 (5.4)	1 (1.1)

Incidence of 5% or greater based on the all causality events.
AEs = adverse events, MedDRA = Medical Dictionary for Regulatory Activities (Version 10.1).

During long-term administration of ziprasidone for subjects with Bipolar I Disorder, the number of subjects with adverse events on ziprasidone was 163 (86.7%) of 188 subjects and 38 (20.2%) subjects discontinued early due to a treatment-emergent adverse event. In those

subjects that inadvertently received ziprasidone >160 mg/d, 13 (100%) of the 13 subjects had an adverse event and all were considered related to treatment. An overview of treatment-emergent adverse events is provided in Table 22.

Table 22. Overview of Treatment-Emergent Adverse Events - Studies A1281123 and A1281133 – Open Label

	Ziprasidone Dosage Group (mg/d) All subjects n=188
	No. of Subjects (%)
Subjects with AEs	163 (86.7)
Treatment-related AEs	140 (74.5)
SAEs	19 (10.1)
Severe AEs	29 (15.4)
Discontinuations due to AEs	38 (20.2)
Dose reduction/temporary discontinuation	42 (22.3)

All-causality adverse events are described except where treatment related is indicated
AEs=adverse events, SAEs=serious adverse events

During long-term administration of ziprasidone for subjects, sedation and somnolence occurred at an incidence of >20% and nearly all events were considered treatment-related. Headache occurred at an incidence of >10%. All-causality treatment emergent adverse events reported in ≥5% of subjects that received ziprasidone are summarized in Table 23. In those 13 subjects that inadvertently received ziprasidone >160 mg/d, the most common (≥10%) adverse events were somnolence (7/13, 53.8%), headache (7/13, 58.3%), insomnia (5/13, 38.5%), overdose (5/13, 38.5%), Bipolar disorder (4/13, 30.8%), sedation (3/13, 23.1%) and abdominal pain upper (2/13, 15.4%). Overall, the most frequently reported all causality adverse events were consistent with what was observed in the short-term double-blind study. The initial onset of these events was in most cases within the first week of treatment.

Table 23. Treatment-Emergent, All Causality Adverse Events Reported in >=5% of All Ziprasidone Subjects in Decreasing Order by System Organ Class – A1281123 and A1281133 – Open-Label

Body System and Preferred Terms MedDRA v. 11	Ziprasidone n=188
Nervous system	**123 (65.4)**
Sedation	54 (28.7)
Somnolence	40 (21.3)
Headache	34 (18.1)
Dizziness	14 (7.4)
Psychiatric	**61 (32.4)**
Insomnia	18 (9.6)
Gastrointestinal	**53 (28.2)**
Nausea	17 (9.0)
Stomach discomfort	10 (5.3)
Abdominal pain upper	13 (6.9)
Vomiting	12 (6.4)
General/Administrative Site Conditions	**34 (18.1)**
Fatigue	16 (8.5)
Respiratory, thoracic and mediastinal	**25 (13.3)**
Nasal congestion	12 (6.4)
Investigations	**25 (13.3)**
Weight increased	10 (5.3)

MedDRA= medical dictionary for regulatory activities

5.4. Serious Adverse Events

5.4.1. Deaths

There were no deaths reported in any of the three studies in children and adolescents aged 10-17 years with Bipolar I Disorder. In a long-term schizophrenia study (A1281135) in pediatric subjects, one death occurred. A brief narrative follows:

A 17 year-old subject with a diagnosis of schizophrenia, disorganized type, had a history of paranoid delusions, auditory hallucinations, schizophrenic psychosis with depressive symptoms, biochemical hyperthyroidism, and thyrotoxicosis. The subject entered extension study A1281135 from short-term double-blind study A1281134 and reached the maximum daily dose of ziprasidone (160 mg/day). The patient continued to have hallucinations and delusions, but did not verbalize any suicidal ideations and no self-harm behavior was observed during her hospitalization. During a home leave, the patient killed herself by jumping from a window; no suicide note was left behind. The patient was not taking any concomitant medication at the time of the event, but had most recently received lorazepam. According to the investigator, there is a reasonable possibility that the event, Completed suicide, was related to the study medication and was the result of poor control of the symptoms of schizophrenia by the study drug.

5.4.2. Other Serious Adverse Events

Fourteen subjects reported 18 total serious adverse events (SAEs) in the double-blind placebo-controlled study. Six subjects reported eight SAEs while receiving ziprasidone and

seven subjects reported nine SAEs while receiving placebo. A single subject reported one SAE (agitation) prior to randomization. One ziprasidone-treated subject (10261001) was administered an overdose of study medication and had an acute dystonic reaction due to study treatment. A listing of all causality SAEs is presented in Table 24.

Table 24. All-Causality Serious Adverse Events - A1281132

System Organ Class	Preferred Term	Ziprasidone (N=149) Number of Events	Placebo (N=88) Number of Events
Infections and Infestations	Viral Infection	1	0
Injury, poisoning and procedural complications	Overdose	1[a]	0
Investigations	Liver function test abnormal	1	0
Nervous system disorders	Dystonia	1[a]	0
Psychiatric disorders	Aggression – physical, verbal, or violence	1	2
	Bipolar I disorder/Bipolar disorder	0	2
	Hallucination	0	1
	Hypersexuality	1	0
	Mania	1	0
	Paranoia	0	1
	Suicidal ideation	1	3

[a] Treatment-related

During long-term administration of ziprasidone for subjects with Bipolar I Disorder, 35 subjects experienced a total of 45 serious all causality adverse events, which are summarized in Table 25. Psychiatric disorders (either alone or combined with other events) comprised the majority (39 serious adverse events). All subjects recovered. In 3 subjects, the serious adverse event was considered related to treatment (one event each of constipation, electrocardiogram QT prolonged, and sedation). In one subject (11171004), constipation was considered to be non-treatment emergent because it began in the previous double-blind study. Another subject (10131002), a 16-year-old male, was hospitalized due to a lack of efficacy and the worsening adverse event of sedation. The subject discontinued the study but subsequently recovered a few days later. It was determined that this subject did not take his assigned medication, therefore the serious adverse event was not considered treatment-emergent. The third subject was not considered serious by the investigator but was considered serious by Pfizer. This subject (10121004), a 12-year-old female, self-administered an overdose of 960 mg ziprasidone, 2 mg lorazepam, and 6 tablets of naproxen in an attempt to harm herself. Prior to enrollment in the study, the subject had been hospitalized twice for previous self-harm concerns. The subject experienced an elevated corrected QT interval (QTc) associated with the overdose of ziprasidone and was discontinued from the study due to non-compliance. The investigator attributed the self-harm attempt to the disease under study and the elevated QTc to the study drug. Additional details for this subject are provided in Section 5.5.1.4.

Table 25. All Causality Serious Adverse Events – Studies A1281123 and A1281133 – Open-label

System Organ Class	Preferred Term	Ziprasidone Number of Events
Gastrointestinal	Constipation	1[a,b]
Injury, poisoning and procedural complications	Overdose	1
Investigations	Drug ineffective	2
	Electrocardiogram QT prolonged	1[a]
Nervous system disorders	Sedation	1[a]
Psychiatric disorders	Aggression - physical, verbal, or violence	3
	Agitation	1
	Bipolar I disorder/Bipolar disorder	13
	Conversion disorder	1
	Delusion	1
	Depressive symptom	1
	Hallucination – auditory, mixed, or visual	3
	Homicidal behavior	1
	Homicidal ideation	1
	Intentional self harm	1
	Mania	1
	Negative thoughts	1
	Oppositional defiant disorder	2
	Self-injurious behavior	1
	Suicidal ideation	8

[a]Treatment-related; [b]SAE was not treatment emergent

5.5. Adverse Events of Special Interest

5.5.1.1. QT/Cardiac

There were four adverse events (right bundle branch block [1 subject], palpitations [1 subject], and tachycardia [2 subjects]) associated with the Cardiovascular system in ziprasidone-treated subjects in the short-term, double-blind, placebo-controlled study. These events were considered related to treatment and were mild in severity. One subject (10401007) experienced a severe adverse event of electrocardiogram QT prolonged, which was considered related to treatment and is described in more detail in Section 6.7.1.

In the open-label, long-term administration of ziprasidone in subjects with Bipolar I Disorder, five subjects reported adverse events associated with the Cardiovascular system (atrial fibrillation [1 subject], tachycardia [2 subjects], and palpitations [2 subjects]). One subject (10121004) who had overdosed on 960 mg of ziprasidone experienced an adverse event of ECG QT prolonged. This adverse event was considered related to treatment and is described in Section 5.5.1.4.

5.5.1.2. Movement Disorders and Extrapyramidal Symptoms

In the short-term, double-blind, placebo controlled study, the incidence of treatment-emergent all causality adverse events related to extrapyramidal symptoms (excluding akathisia) was 24% (36/149) for ziprasidone-treated subjects vs 7.9% (7/88) for placebo. Seven (4.7%) subjects receiving ziprasidone and 1 (1.1%) subject receiving placebo experienced akathisia during the study (Table 26).

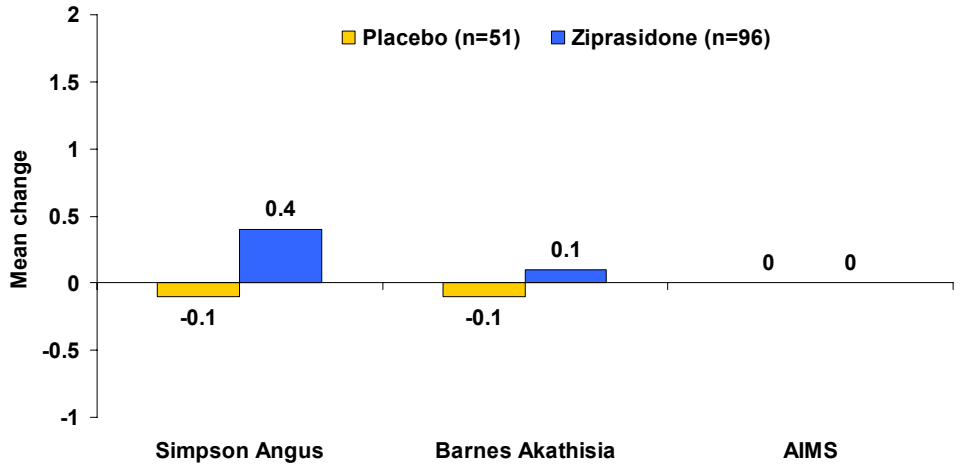
Table 26. Incidence of Treatment-emergent Adverse Events Related to Extrapyramidal Symptoms - Study A1281132

Adverse event (MedDRA v. 11.0)	Ziprasidone (N=149) n (%)	Placebo (N=88) n (%)
Extrapyramidal Symptoms	**36 (24.1)**	**7 (7.9)**
Musculoskeletal stiffness	8 (5.4)	0
Tremor	8 (5.4)	0
Extrapyramidal disorder	7 (4.7)	1 (1.1)
Dystonia	6 (4.0)	1 (1.1)
Drooling	4 (2.7)	0
Dyskinesia	3 (2.0)	1 (1.1)
Muscle Twitching	2 (1.3)	0
Tic	1 (0.7)	0
Muscle spasms	1 (0.7)	3 (3.4)
Cogwheel rigidity	1 (0.7)	0
Gait disturbance	1 (0.7)	0
Torticollis	0	1 (1.1)
Other EPS-related events		
Akathisia	7 (4.7)	1 (1.1)

AEs = adverse events, MedDRA = Medical Dictionary for Regulatory Activities

Movement disorders and extrapyramidal symptoms were assessed using the Simpson-Angus Rating Scale (SARS), Barnes Akathisia Rating Scale (BAS), and Abnormal Involuntary Movement Scale (AIMS). Mean total scores for these scales were generally similar between the ziprasidone and placebo treatment groups (Figure 11).

Figure 11. Mean Change from Baseline in Movement Disorder Scales - A1281132



Endpoint: week 4

During long-term administration, the incidence of treatment-emergent adverse events related to extrapyramidal symptoms (excluding akathisia) was 13.2% (25/188) for ziprasidone-treated subjects. Five (2.7%) subjects receiving ziprasidone experienced akathisia during the studies (Table 27).

Table 27. Incidence of Treatment-emergent Adverse Events Related to Extrapyramidal Symptoms - A1281123 and A1281133 – Open Label

Adverse event (MedDRA v. 11.0)	**Ziprasidone (N=188) n (%)**
Extrapyramidal Symptoms	**25 (13.2)**
Tremor	8 (4.3)
Extrapyramidal disorder	8 (4.3)
Muscle spasms	4 (2.1)
Drooling	4 (2.1)
Dystonia	2 (1.1)
Dyskinesia	2 (1.1)
Muscle Twitching	2 (1.1)
Musculoskeletal stiffness	2 (1.1)
Muscle tightness	2 (1.1)
Bradykinesia	2 (1.1)
Cogwheel rigidity	1 (0.5)
Gait disturbance	1 (0.5)
Other EPS-related events	
Akathisia	5 (2.7)

5.5.1.3. Suicidality

In the short-term double-blind study, suicidality-related adverse events were reported in 2 ziprasidone-treated subjects (overdose, suicidal ideation) and in 3 placebo-treated subjects (all Suicidal ideation). In addition, periodic searches of the AE database were conducted to identify all possibly suicide-related adverse events (PSRAEs). These events were reviewed by an independent panel of experts, led by Dr. Kelly Posner of Columbia University, who categorized the events according to the Columbia classification system of PSRAEs. Based on this assessment, there was no increase in suicidality in the ziprasidone-treated group; 1 subject in each group attempted suicide (self injurious behavior and skin laceration), and 3 subjects in each group had thoughts of suicide (suicide ideation or self-injurious ideation). One subject from the ziprasidone group engaged in self mutilation.

In the long-term study, A1281133, a similar assessment for suicidality was conducted as described above for the short-term, double blind study. Two subjects (11081001 and 11261012) attempted suicide (adverse events of skin laceration and drug overdose, respectively) during the study. Subject 11261012, who reported a drug overdose, is further described in Section 5.5.1.4. One subject displayed preparatory acts towards imminent suicidal behavior; 5 had suicidal ideation; 2 had self-injurious behavior with unknown intent; 3 had self-injurious behavior with no suicide attempt; and 7 had Columbia classifications of "Other" (ie, accident, psychiatric, or medical).

In the second long-term study, A1281123, 6 subjects reported adverse events associated with suicidal ideation (5 subjects with Bipolar I disorder, 1 subject with schizophrenia), including suicidal ideation, suicidal thoughts, would rather die than go to safety officer, and auditory hallucination to self-harm. Of the subjects that experienced suicidal ideation, the presence of suicidal ideation before entering the study, psychosocial stressors, and the underlying disorder, were considered relevant information for each of these events. Two subjects (10021013 and 10121004) overdosed on ziprasidone (880 mg and 960 mg, respectively) and are described in Section 5.5.1.4.

In a long-term schizophrenia study in pediatric subjects, one suicide occurred (see Section 5.4.1).

5.5.1.4. Overdose

In double-blind, placebo-controlled study A1281132 and its long-term extension study A1281133, a total of 17 subjects (12 ziprasidone and 5 placebo) experienced an overdose or accidental overdose. Twelve (8 ziprasidone and 4 placebo) subjects had overdoses due to dosing errors (total daily dosage exceeded the maximum dose allowed in the study protocol) and reported an adverse event associated with the dosing error. There were no cardiac adverse events in any of the subjects and none of the subjects had prolongation of the QT interval (ie, QTcF interval of 460 msec or longer). There were three serious adverse events reported in these 17 subjects. One subject (10261001) in study A1281132, an 11 year-old female receiving ziprasidone, experienced an adverse event of Overdose and Dystonia, which the investigator considered to be of moderate severity and related to treatment (both events), and the subject was subsequently discontinued from the study due to the adverse events. The

second subject (10131001) in study A1281133, a 13 year-old male, had a serious adverse event reported of exacerbation of bipolar symptoms during the post treatment phase. This subject was discontinued from the study due to the serious adverse event, and the investigator considered the event to be related to the disease under study. The third subject (11261012) in study A1281133, a 13 year-old female, took 320 mg of ziprasidone, 100 mg of methacycline, 500 mg Tylenol and 1200 mg of ibuprofen and was taken to the emergency room. Additional history included frequent suicidal ideation without shared thoughts and planned means of overdose on pills. There was a previous suicide attempt (overdose on pills) and thoughts of self-harm with multiple superficial cuts on her arm 5 months prior to this event.

In study A1281123, two subjects intentionally overdosed on ziprasidone. One subject (10121004), a 12 year-old female, took 960 mg of ziprasidone in a self-harm attempt and experienced a serious adverse event of QT prolongation (unconfirmed). The subject was hospitalized and two ECGs obtained the same day revealed QTc intervals of 446 and 500 msec. The subject was admitted to a telemetry unit for observation and the QTcF intervals the following day were 469 msec and 427 msec. The subject was discharged from the hospital. This subject's QTcF values at screening/baseline were 426 msec and 374 msec, respectively. The highest QTcF values observed during the study were 434 msec (Week 2) and 424 msec (Week 3). The second subject (10021013), a 16 year-old female, ingested 880 mg of ziprasidone on study day 56, and was hospitalized the next day due to exacerbation of bipolar disorder. An ECG was performed on day 58, and the subject experience a 6 msec increase over baseline in QTcB (380 msec) and a 3 msec decrease from baseline in QTcF (383 msec). No other adverse events were reported with this event. The subject withdrew from the study and recovered from the event.

5.6. Laboratory Parameters

5.6.1. Discontinuations due to Laboratory Abnormalities

In the short-term, double-blind, placebo-controlled study, one subject each in the ziprasidone group discontinued due to increased hepatic enzymes and abnormal liver function test. A 17 year-old female (1040122; 40 mg) had an AE of abnormal liver function test on Day 10 and was discontinued from the study due to the AE. Her aspartate aminotransferase (AST) was 202 U/L and alanine aminotransferase (ALT) was 242 U/L on Day 11. This event was considered an SAE and attributed to mononucleosis. A 16-year-old male (11221002; 100 mg) had an AE of elevated liver enzymes. On Day 16, his AST was 89 U/L (normal range = 0-41 U/L). On Day 23, his AST returned to within normal range (33 U/L). His ALT levels were 50, 147, and 56 U/L on Days -5, 16, and 23, respectively (normal range = 5-30 U/L). The AE report for these subjects had not resolved at the time of termination.

During long-term administration of ziprasidone for subjects with Bipolar I Disorder, one subject (10151009), a 16 year-old male, experienced an adverse event of elevated AST (268 IU/L on Day 21 with normal baseline of 16 IU/L) and was discontinued from the study.

5.6.2. Laboratory Abnormalities Exceeding Threshold Criteria

In the short-term, double-blind, placebo-controlled study, a comparable proportion of subjects in each treatment group experienced laboratory abnormalities (54% ziprasidone vs. 57% placebo). When laboratory tests were examined without regard to baseline abnormality, the incidences of laboratory test abnormalities were slightly decreased in the ziprasidone-treated subjects (66%) compared to placebo-treated subjects (75%).

Laboratory abnormalities observed at an incidence of greater than or equal to 5% in either treatment group measured for subjects without regard to baseline are shown in Table 28. The most frequently occurring abnormal laboratory tests (10% occurrence or greater in any group) were increased presence of urine blood/hemoglobin (≥1), decreased serum bicarbonate, presence of urine ketones (≥1+), elevated blood prolactin, and elevated eosinophils and monocytes. Elevated blood prolactin occurred more frequently in the ziprasidone group (12%) compared to the placebo group (3%) while the incidence of all other frequently occurring abnormal laboratory findings (10% occurrence or greater in any group) was either similar in both groups or higher in the placebo group. None of the subjects having elevated blood prolactin had an AE of hyperprolactinemia and none had AEs in the reproductive organ system class. The types of AEs reported in these subjects were similar to AEs reported in the ziprasidone group (ie, AEs commonly related to stomach upset/nausea, sedation, and somnolence). One subject (11241010) in the ziprasidone group had an AE of elevated blood prolactin that was clinically significant (see Section 5.9.1.3).

There were no clinically relevant changes in lipid profiles in either group.

Table 28. Incidence of Laboratory Test Abnormalities without Regard to Baseline (5% or Greater in Any Group) - Study A1281132

Parameter	Criteria	Ziprasidone n/N	Ziprasidone %	Placebo n/N	Placebo %
Hematology					
Total neutrophils (abs) (10^3/mm^3)	>0.8 × LLN	6/129	5	4/81	5
Basophils (%)	>1.2 × ULN	3/129	2	4/81	5
Eosinophils (%)	>1.2 × ULN	4/86	5	8/60	13
Monocytes (%)	>1.2 × ULN	4/129	3	8/81	10
Lipids					
Triglycerides	>1.3 × ULN	4/123	3	5/78	6
Electrolytes					
Phosphate (mg/dL)	>1.2 × ULN	7/90	8	2/62	3
Bicarbonate (mEq/L)	<0.9 × LLN	25/132	19	16/84	19
Hormones					
Prolactin (ng/mL)	>1.1 ULN	14/120	12	2/75	3
Testosterone (ng/dL)	>1.2 × ULN	8/91	9	4/59	7
Urinalysis (Dipstick)					
Urine specific gravity	>1.030	7/133	5	8/84	10
Urine ketones	≥1	21/133	16	20/84	24
Urine blood/Hgb (Qual)	≥1	35/133	26	20/84	24
Urinalysis (Microscopy)					
Urine red blood cells (/hpf)	≥6	8/133	6	5/84	6
Urine white blood cells (/hpf)	≥6	7/133	5	4/84	5

n = number of subjects with an abnormal lab value
N = total number of subjects with at least 1 observation of the given laboratory test
Abs = absolute, hpf = high power field, LLN = lower limit of normal, ULN = upper limit of normal

During long-term administration of ziprasidone for subjects with Bipolar I Disorder, 100 (63%) of 160 evaluable subjects with normal baseline values had a subsequent laboratory test abnormality. In subjects with a laboratory value that is without regard to baseline, 119 (74%) of 160 evaluable subjects had a laboratory abnormality. The most frequently reported laboratory test abnormality without regard to baseline were decreased HDL cholesterol (8/160, 5%) and bicarbonate (40/127, 31%), and increased monocytes (10/158, 6%), triglycerides (12/160, 8%), insulin (6/100, 6%), prolactin (16/158, 10%), testosterone (26/151, 17%), and urine ketones, blood RBCs and WBCs. Elevated insulin was reported at an incidence of 7% (7/106).

5.6.3. Change from Baseline for Laboratory Parameters

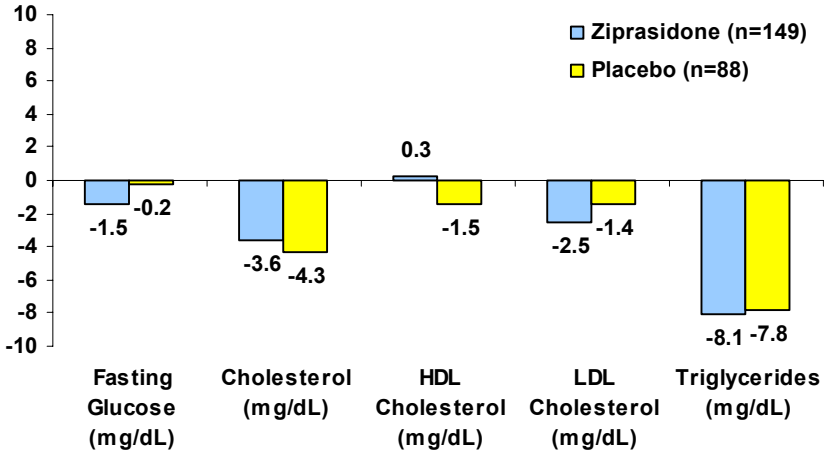
Mean and median changes from baseline to last observation in laboratory test data were evaluated in the short-term, double-blind, placebo controlled study. In general, the mean values of laboratory parameters in the two treatment groups were comparable at baseline and mean/median changes from baseline in both treatment groups were small and not clinically meaningful.

During long-term administration of ziprasidone for subjects with Bipolar I Disorder, median change from baseline to last observation in laboratory test data was evaluated. In general, the median values of laboratory parameters were comparable at baseline and the median changes from baseline within the dosage groups were small and not clinically meaningful.

5.6.4. Metabolic Effect/Body Weight

In the short-term, double-blind, placebo-controlled study, there was no difference in the mean change from baseline in fasting glucose between ziprasidone and placebo subjects (-1.5±14.4 mg/dL and -0.2±13.1 mg/dL, respectively). The ziprasidone and placebo patients showed no difference in the mean change from baseline in fasting levels of total cholesterol (-3.6±22.0 vs -4.3±19.7 mg/dL), HDL (0.3±9.0 vs -1.5 ±7.3 mg/dL), LDL (-2.5±17.6 vs -1.4±16.6 mg/dL), and triglycerides (-8.1±51.7 vs 7.8±53.2 mg/dL) (Figure 12).

Figure 12. Mean Change in Baseline for Lipids and Glucose - Study A1281132



As summarized in Table 29 there was no difference in mean weight gain between ziprasidone and placebo subjects (0.5±2.2 vs 0.6±2.3 kg, respectively). The proportion of subjects meeting a weight gain criterion of ≥7% between ziprasidone and placebo subjects was 7% vs 4%, respectively.

Table 29. Mean Baseline and Mean Change from Baseline in Body Weight and BMI Z-Score - Study A1281132

	Ziprasidone		Placebo	
	N	Mean (SD)	N	Mean (SD)
Weight, kg				
Mean baseline	149	57.2 (14.4)	88	60.0 (16.0)
Change from baseline				
Week 4/ET	131	0.5 (2.2)	81	0.6 (2.3)
BMI Z-Score				
Mean Baseline	149	0.7 (0.9)	88	0.8 (0.9)
Change from Baseline				
Week 4/ET	131	0.0 (0.3)	81	0.0 (0.2)
	N	**%**	**N**	**%**
% ≥7% Weight gain	9	7	3	3.7

Baseline was measurement taken immediately prior to randomization.
BMI = body mass index, ET = end of treatment, SD = standard deviation

During long-term administration of ziprasidone for subjects with Bipolar I Disorder, there were no clinically meaningful changes from baseline in mean glucose or lipid parameters (Figure 13) or in mean change in body weight (Table 30).

Figure 13. Mean Change from Baseline to Last Observation in Lipids and Glucose - A1281123 and A1281133 – Open Label

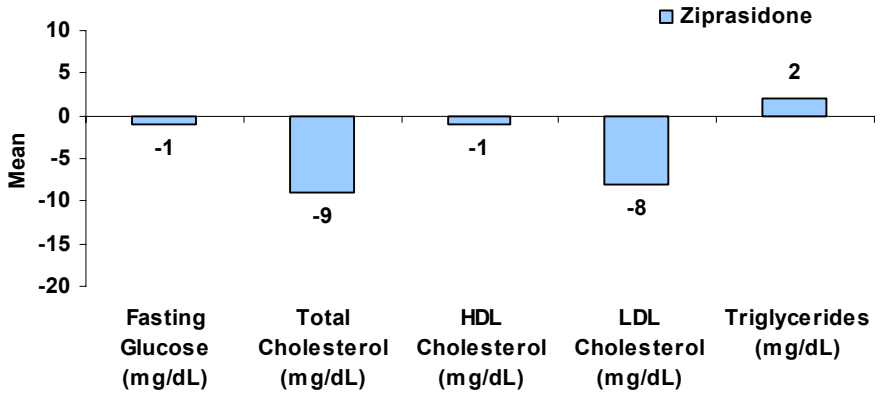


Table 30. Mean Baseline and Mean Change from Baseline in Body Weight and BMI Z-Score - A1281123 and A1281133 – Open Label

	Ziprasidone	
	N	Mean (SD)
Weight, kg		
Mean baseline[a]	186	57.4 (15.4)
Change at last visit	175	1.4 (3.9)
BMI Z-score, derived		
Mean baseline[a]	150	0.7 (0.9)
Change at last visit	139	0.0 (0.3)

[a]Baseline is defined as the pre-dose observations at the baseline visit.
BMI = body mass index, ET = end of treatment, SD = standard deviation

5.7. ECG and Vital Signs

5.7.1. ECG Changes

In the short-term, double-blind, placebo controlled study, mean baseline and mean change from baseline to last observation for ECG data were evaluated. ECG mean change at final visit and mean maximum change from baseline for QTcF are summarized below in Table 31. Mean change in QTcF at final visit was increased 8.7 msec in the ziprasidone group and decreased 3.7 msec in the placebo group. Maximum change from baseline in QTcF was increased 12.9 msec and decreased 4.9 msec in the ziprasidone and placebo groups, respectively.

Table 31. QTcF - Mean Change at Final Visit and Maximum Change from Baseline - A1281132

	Ziprasidone	Placebo
	QTcF Changes at Final Visit (msec)	
N	101	69
Mean	8.7	-3.7
Standard Deviation	15.2	15.1
Range	(-43) – (51)	(-53) – (38)
	QTcF Maximum Change from Baseline (msec)	
N	132	83
Mean	12.9	-4.9
Standard Deviation	21.9	23.8
Range	(-57) – (69)	(-69) – (41)

QTcF =Fridericia-corrected QT interval
From baseline where baseline is defined as the mean of the pre-dose triplicate at the baseline visit

The incidence of clinically significant changes in ECG reading is summarized below in Table 32. No subject had a QTcF >480 msec.

Table 32. Incidence of Categorical Thresholds and Increases for QTcF - A1281132

	Ziprasidone (N=140)	Placebo (N=85)
Incidence	n (%)	n (%)
QTcF ≥ 450 msec	5 (3.6)	1 (1.2)
QTcF ≥ 460 msec	2 (1.4)	0
QTcF ≥ 480 msec	0	0
QTcF ≥ 500 msec	0	0
	Increase from pre-study drug[a]	
≥ 30 msec	31 (22.1)	9 (10.6)
≥ 60 msec	1 (0.7)	0
≥ 75 msec	0	0

[a] From baseline where baseline is defined as the mean of the pre-dose triplicate at the baseline visit.
QTcF =Fridericia-corrected QT interval

Two ziprasidone-treated subjects had a QTcF ≥460 msec; no placebo-treated subject had a QTcF ≥460 msec. Of these, 1 subject in the ziprasidone group (60 mg total daily dose) had an adverse event of prolonged (greater than 460 msec) corrected QT interval. Subject 10401007, a 16-year-old female, had a QTcF of 425 msec at screening. On Day 8, she had a QTcF of 464 msec. On Day 17, her QTcF values were greater than 460 msec before, 45 minutes after, and 5 hours after dosing (Table 33). The investigator considered the event to be severe and the subject was permanently discontinued. On Day 23 she had a follow-up ECG that showed a QTcF interval increase of 18 msec over her baseline visit (Day 1, 0 hour). On Day 38, she had another follow-up ECG that showed her QTcF to be similar to the screening measurement. The subject had sinus bradycardia throughout the study. Her maximum prolonged QTcF interval was 478 msec. (Table 33)

Table 33. QTcF Intervals for Subject 10401007

Visit	Planned Time Point	QTcF (msec)
Screening (Day -3)	--	425
Day 1	0 hour	436
	2 minutes	439
	4 minutes	433
Day 8	--	464
Day 17 (ET)	0 hour	478
	45 minutes	473
	5 hours	476
Day 23 (Unplanned)	--	454
Day 38 (Unplanned)	--	439

ET = early termination

The second subject, a 17 year-old male (10671010), who was receiving 60 mg BID ziprasidone had a QTcF of ≥460 msec following the morning dose on day 29. The QTcF at screening was 406 msec. On Day 29, he had a QTcF of 461 msec. All other QTcF values were below 460 msec and the investigator did not consider this to be an adverse event. The QTcF intervals for this subject are provided in Table 34.

Table 34. QTcF Intervals for Subject 106710010

Visit	**Planned Time Point**	**QTcF (msec)**
Screening (Day -13)	--	406
Day 1	0 hour	428
	2 minutes	450
	4 minutes	422
Day 8	--	435
Day 14	--	424
Day 22	--	404
Day 29	0 hour	429
	45 minutes	461
	5 hours	449

Thirty-one (22.1%) ziprasidone-treated subjects had an increase in QTcF interval from baseline of ≥30 msec; 9 (10.6%) placebo-treated subjects had a QTcF interval increase of ≥30 msec. One ziprasidone-treated subject (10871008), who was receiving a total daily dose of 80 mg/d, experienced an increase in QTcF of ≥60 msec; no placebo-treated subject had a QTcF increase of ≥60 msec. QTcF intervals for Subject 10871008, a 12-year-old female, are presented in Table 35. A baseline QTcF of 368 msec was decreased by 62 msec from Screening (QTcF of 430 msec), but subsequently increased to a similar level at Day 8 (432 msec). Subsequent measurements showed a continued decline in QTcF values.

Table 35. QTcF Intervals for Subject 10871008

Visit	Planned Time Point	QTcF (msec)
Screening (Day -6)	--	430
Day 1	0 hour	368
	2 minutes	365
	4 minutes	362
Day 8	--	432
Day 13	--	434
Day 20	--	429
Day 27	0 hour	419
	45 minutes	412
	5 hours	416

In long-term administration of ziprasidone for subjects with Bipolar I Disorder, the mean change from baseline to last observation and mean maximum change from baseline for QTcF is summarized in Table 36. Effects on QTc in two subjects (10121004 and 10021013) from study A1281123 who overdosed on ziprasidone are described in section 5.5.1.4.

Table 36. QTcF - Mean Change at Final Visit and Maximum Change from Baseline - A1281123 and A1281133

	Ziprasidone
	QTcF Changes at Final Visit (msec)
N	188
Mean	3.6
Standard Deviation	(16.8)
Range	(-45)-(51)
	QTcF Maximum Change from Baseline (msec)
N	188
Mean	8.2
Standard Deviation	(26.2)
Range	(-49)-(69)

QTcF =Fridericia-corrected QT interval
Baseline is defined as the mean of the predose observations at the baseline visit

Table 37 summarizes the clinically significant increases in QTcF from prestudy drug. No subjects had a QTcF value ≥450 msec. Two subjects experienced an increase in QTcF of ≥60 msec and one subject reported atrial fibrillation.

Table 37. Incidence of Categorical Thresholds and Increases for QTcF[a] – A1281123 and A1281133 – Open Label

Parameter	Ziprasidone Dosage Group (mg/d) All subjects ≤160 n=188
	No. of Subjects (%)
Incidence	
QTcF ≥ 450 msec	0
QTcF ≥ 460 msec	0
QTcF ≥ 480 msec	0
QTcF ≥ 500 msec	0
≥30 msec	40 (21.3)
≥60 msec	2 (1.1)
≥75 msec	0 (0.0)

[a] Baseline is defined as the mean of the predose observations at the baseline visit.
QTcF=fridericia-corrected QT interval

Two subjects experienced a QTcF ≥60 msec. A 14 year-old female (11081003) had a baseline QTcF of 369 msec that increased to 438 msec at Week 10 while receiving 160 mg/d ziprasidone. Subsequent QTcF values were ≤44 msec increase from baseline. This subject had no associated adverse events.

The other subject with a prolonged QTc interval was a 12 year-old female (10861006), who at the Week 1 visit (Day 10) had a QTcF which was increased to greater than 60 msec from the baseline visit (from 365 to 431 msec, +66 msec) was receiving a total dose of 80 mg/d ziprasidone. Subsequent measurements indicated continued prolonged QTc and the subject was discontinued from the study. The investigator considered the prolonged QT interval to be related to the study treatment.

A 12 year-old female (11081007), who was receiving a total daily of 80 mg/d ziprasidone, experienced atrial fibrillation on day 38 that was regarded by the investigator as related to study drug. The diagnosis was supported by automated ECG interpretations but manual over-reading by the central ECG vendor indicated that the subject had intermittent junctional rhythm with artifacts on some of the tracings, but no atrial fibrillation. The subject remained on the study treatment and the event resolved 39 days later.

The effects on QTc observed in the pediatric subjects in both the short-term placebo-controlled study A1281132 and the long-term safety database were comparable to what was observed in adults treated with ziprasidone.

5.7.1.1. Pharmacokinetic-Pharmacodynamic Assessment of the QTc-Ziprasidone Concentration Relationship

Assessments for the relationship between change in QTcF and ziprasidone parent concentration have been conducted for several studies and meta-analyses. The effect of ziprasidone administration on the QT interval in pediatric patients was evaluated separately in studies A1281132 (Appendix 2.1) and A1281123 (Appendix 2.2). Population pharmacokinetic-pharmacodynamic (PKPD) assessment of the change in QTcF (Fridericia

correction) – ziprasidone concentration relationship was conducted separately for these studies. In addition, a descriptive and quantitative comparison of adult and pediatric patient data (Appendix 2.3) was also conducted across 27 adult and 4 pediatric studies.

In study A1281132, ziprasidone was associated with a concentration dependent increase in QTcF, Fridericia correction of QT for heart rate. The slope of the regression line expressed as population mean (90%CI) was 0.0852 (0.067 to 0.106) msec/ng/mL with QTcF (Appendix 2.1, Table 55). Expected QTc changes with various dose regimens were calculated providing a median maximum increase in ΔQTcF at the highest dose (160 mg/day) of approximately 14 msec, based upon a steady state median ziprasidone Cmax concentration using the final population PK model for A1281132.

Similarly, for ΔQTcF vs. ziprasidone concentration data from study A1281123, ziprasidone demonstrated a concentration dependent increase in QTcF. The slope of the regression line expressed as population mean (95% CI) was 0.139 (-0.0132 to 0.299) ng/mL (Table 56). Note that, although a positive slope was identified in this analysis, the estimated 95% CI includes the null effect of zero (-0.0132 to 0.299). Using the estimated slope of 0.139 msec/ng/mL, the expected QTcF change at the peak concentration of 118 ng/mL measured in the study was approximately 16 msec.

Graphical and quantitative comparisons (Appendix 2.3 and Figure 14) of adult and pediatric ziprasidone concentrations and associated QTcF values demonstrated that the prepared using data from the 4 pediatric studies conducted during the clinical development of ziprasidone (N=180 subjects/n= 506 concentration-ΔQTcF data pairs) and from 27 adult ziprasidone clinical studies (N=1383 Subjects/n= 2086 concentration-ΔQTcF data pairs). The distributions of pediatric and adult ΔQTcF-concentration values were similar (Figure 14).

The subset of data including only subjects with more than 1 data point was used in a regression analysis. The resulting dataset, incorporated data from 21 studies, 17 adult and 4 pediatric with a total of 2420 (1803 Adult; 617 Pediatric) ΔQTcF vs. concentration data pairs from 857 (684 Adult; 173 Pediatric) subjects.

Although the slopes estimated from the meta-analysis of observational data available for pediatric and adult subjects are numerically different (Table 38), the overall distributions of the observed change from baseline response data over the range of concentrations was similar (Appendix 2.3, Figure 14). Note also that the placebo-corrected mean maximum change from baseline QTcF for the A1281132 study was 17.8 msec similar to the 15.9 msec change observed for adult subjects administered 80 mg BID in study 128-054.

Table 38. Summary of Meta Analysis of Change in QTcF vs Ziprasidone Concentration

Parameter (Units)		Population Mean (SE*)	SD Inter-Individual Variance (SE*)
Intercept – Adult (msec)	θ1	0.744 (70.7)	9.04 (14.3)
Intercept – Pediatric (msec)	θ4	3.29 (28.5)	
Slope – Adult (msec/ng/mL)	θ2	0.0521 (11.4)	0.0601 (24.6)
Slope – Pediatric (msec/ng/mL)	θ3	0.0824 (18.0)	
Additive Residual Error (msec, as SD)		13.0 (5.01)	
* - SE expressed as %CV; SD= standard deviation			

5.7.2. Vital Signs

In the short-term, double-blind, placebo controlled study, the mean changes from baseline through Week 4 (5-7 hours after dosing) for standing and supine systolic and diastolic blood pressure and pulse rates were small and not clinically significant. Table 39 presents the categorical summary of post baseline blood pressure changes above a pre-defined threshold over baseline occurring in 5% or more of the subjects in any group. The percentage of subjects having a vital sign change within each predefined vital sign criterion was generally similar between the treated and placebo groups.

Table 39. Incidence of Clinically Significant Changes in Vital Signs (5% or Greater in Any Group) - Study A1281132

Parameter Criteria	Ziprasidone n/N (%)	Placebo n/N (%)
Standing Diastolic BP, mm Hg		
≥20 mm Hg decrease[a]	6/143 (4.2)	5/86 (5.8)
≥20 mm Hg increase[a]	12/143 (8.4)	9/86 (10.5)
Supine Systolic BP, mm Hg		
<90 mm Hg	8/144 (5.6)	2/86 (2.3)
Supine Diastolic BP, mm Hg		
≥20 mm Hg increase[a]	10/144 (6.9)	5/86 (5.8)

n = number of subjects whose maximum post baseline value met criterion
N = number of evaluable subjects
[a]from baseline where baseline is the measure taken immediately prior to randomization
BP = blood pressure, mm Hg = millimeters of mercury

In long-term administration of ziprasidone for subjects with Bipolar I Disorder, mean changes from baseline in supine blood pressure and heart rate were generally small. No subjects had a clinically significant increase or decrease in change from baseline supine systolic blood pressure (≥30 mm Hg increase or decrease), diastolic blood pressure (≥20 mm Hg increase or decrease) and heart rate (<40 bpm or >120 bpm).

5.8. Safety in Population Subgroups

5.8.1. Gender

In the double-blind placebo-controlled study, there were 84 male and 65 female ziprasidone subjects and 47 male and 41 female placebo subjects. Of these, 34.5% of ziprasidone male and female subjects and 46.8% and 35.4% of placebo subjects, male and female, respectively, discontinued from the study. The majority of both male and female ziprasidone and placebo subjects discontinued from this study due to reasons not related to study drug. Overall, there was no difference in the incidence of discontinuation from study by gender.

A summary of the all causality treatment-emergent adverse events in male and female subjects that were reported in ≥5% of all subjects is summarized in Table 40. When subjects were evaluated by gender, musculoskeletal stiffness, dystonia, and tremor were reported more commonly in males, and abdominal pain, nausea, vomiting, upper respiratory infection, akathisia, and pharyngolaryngeal pain were reported more commonly in females. These differences were not considered clinically significant.

Table 40. Summary of Treatment-Emergent Adverse Events (All Causality) by Gender Occurring at an Incidence of >=5% - Study A1281132

Body System and Preferred Term	Ziprasidone		Placebo	
MedDRA v. 11.0	Male N = 84 [n (%)]	Female N = 65 [n (%)]	Male N = 47 [n (%)]	Female N = 41 [n (%)]
Eye Disorders	**7 (8.3)**	**5 (5.7)**	**0 (0)**	**1 (2.4)**
Vision blurred	5 (6.0)	4 (6.2)	0 (0)	1 (2.4)
Gastrointestinal disorders	**22 (26.2)**	**27 (41.5)**	**4 (8.5)**	**10 (24.4)**
Abdominal pain	0 (0)	5 (7.7)	0 (0)	0 (0)
Abdominal pain upper	5 (6.0)	3 (4.6)	1 (2.1)	2 (4.9)
Nausea	7 (8.3)	13 (20.0)	1 (2.1)	5 (12.2)
Vomiting	4 (4.8)	7 (10.8)	0 (0)	1 (2.4)
General disorders and administration site conditions	**14 (16.7)**	**14 (21.5)**	**10 (21.3)**	**4 (9.8)**
Fatigue	11 (13.1)	9 (13.8)	3 (6.4)	3 (7.3)
Pyrexia	0 (0)	2 (3.1)	3 (6.4)	0 (0)
Irritability	1 (1.2)	1 (1.5)	3 (6.4)	1 (2.4)
Infections and infestations	**13 (15.5)**	**3 (6.4)**	**9 (13.8)**	**3 (7.3)**
Upper respiratory tract infection	2(2.4)	5 (7.7)	0 (0)	0(0)
Injury, poisoning and procedural complications	**5 (6.0)**	**5 (7.7)**	**4 (8.5)**	**2 (4.9)**
Overdose	4 (4.8)	3 (4.6)	4 (8.5)	1 (2.4)
Musculoskeletal and connective tissue disorders	**13 (15.5)**	**9 (13.8)**	**2 (4.3)**	**8 (19.5)**
Musculoskeletal stiffness	6 (7.1)	2 (3.1)	0 (0)	0(0)
Pain in Extremity	1 (1.2)	0(0)	0(0)	3 (7.3)
Nervous system disorders	**66 (78.6)**	**49 (75.4)**	**16 (34.0)**	**15 (36.6)**
Akathisia	2 (2.4)	5 (7.7)	0 (0)	1 (2.4)
Dystonia	5 (6.0)	1 (1.5)	0 (0)	1 (2.4)
Tremor	6 (7.1)	2 (3.1)	0 (0)	0 (0)
Dizziness	9 (10.7)	7 (10.8)	2 (4.3)	0 (0)
Sedation	28 (33.3)	21 (32.3)	2 (4.3)	2 (4.9)
Somnolence	19 (22.6)	18 (27.7)	6 (12.8)	1 (2.4)
Headache	19 (22.6)	12 (18.5)	7 (14.9)	12 (29.3)
Psychiatric disorders	**19 (22.6)**	**15 (23.1)**	**11 (23.4)**	**10 (24.4)**
Bipolar disorder	1 (1.2)	0 (0)	4 (8.5)	0 (0)
Restlessness	4 (4.8)	4 (6.2)	1 (2.1)	0 (0)
Insomnia	6 (7.1)	7 (10.8)	0 (0)	3 (7.3)
Respiratory, Thoracic, & Mediastinal	**7 (8.3)**	**5(7.7)**	**3 (6.4)**	**3 (7.3)**
Pharyngolaryngeal pain	1 (1.2)	4 (6.2)	2 (4.3)	2 (4.9)

The incidence of laboratory abnormalities for subjects with either a normal baseline or without regard to baseline abnormality was greater in females than in males in both the ziprasidone and placebo treatment groups. The higher incidence of laboratory abnormalities in older females was due to hematuria associated with menses.

There were no notable differences in categorical increases in QTcF or mean maximum change in QTcF interval between genders.

During long-term administration of ziprasidone to subjects with Bipolar I Disorder, a comparable percentage of male (85.2%) and female (88.8%) subjects experienced at least one, all-causality treatment-emergent adverse event. A summary of the all-causality treatment-emergent adverse events in male and female subjects that were reported in ≥5% of subjects that received ziprasidone is summarized in Table 41. When the subjects were

evaluated by gender, irritability and rash were reported more commonly in males, and akathisia, abdominal pain upper, chest pain, and vision blurred were reported more commonly in females. These differences were not considered clinically significant. None of these events occurred in ≥10 subjects.

Fifty-six (51.9%) of 108 males discontinued the study and 53 (66.3%) of 80 females discontinued the study. Of these, 18 males (16.7%) and 16 (20.0%) females discontinued due to reasons related to study drug.

Table 41. Summary of Treatment-Emergent Adverse Events (All Causality) by Gender, Reported in >=5% of Bipolar Mania I Subjects - Studies A1281123 and A1281133 – Open Label

Body System and Preferred Terms	Ziprasidone	
MedDRA v. 11		
	Male N=108	**Female** n=80
Nervous system	**73 (67.6)**	**50 (62.5)**
Sedation	29 (26.9)	25 (31.3)
Somnolence	27 (25.0)	13 (16.3)
Headache	21 (19.4)	13 (16.3)
Dizziness	8 (7.4)	6 (7.5)
Extrapyramidal disorder	6 (5.6)	2 (2.5)
Tremor	4 (3.7)	4 (5.0)
Akathisia	1 (0.9)	4 (5.0)
Psychiatric	**37 (34.3)**	**24 (30.0)**
Insomnia	11 (10.2)	7 (8.8)
Irritability	7 (6.5)	1 (1.3)
Depression	3 (2.8)	4 (5.0)
Gastrointestinal	**24 (22.2)**	**29 (36.3)**
Abdominal pain upper	5 (4.6)	8 (10.0)
Nausea	9 (8.3)	8 (10.0)
Stomach discomfort	5 (4.6)	5 (6.3)
Vomiting	6 (5.6)	6 (7.5)
General/ administration site conditions	**20 (18.5)**	**14 (17.5)**
Fatigue	8 (7.4)	8 (10.0)
Chest Pain	2 (1.9)	4 (5.0)
Investigations	**16 (14.8)**	**9 (11.3)**
Weight increased	7 (6.5)	3 (3.8)
Respiratory, thoracic and mediastinal	**14 (13.0)**	**11 (13.8)**
Nasal congestion	6 (5.6)	6 (7.5)
Cough	5 (4.6)	4 (5.0)
Skin and subcutaneous tissue	**10 (9.3)**	**5 (6.3)**
Rash	6 (5.6)	1 (1.3)
Eye disorders	**3 (2.8)**	**6 (7.5)**
Vision blurred	2 (1.9)	5 (6.3)

The incidence of laboratory abnormalities without regard to baseline abnormality was greater in females (83%) than in males (68%). For most parameters, laboratory abnormalities occurred at a similar rate between females and males. Females experienced a greater

incidence of abnormal values for thyroid stimulating hormone (increased and decreased), urine microscopy abnormalities and urine ketones. In addition, a larger proportion of (8/63, 13%) of females than males (8/95, 8%) had elevated prolactin.

5.8.2. Age

In double-blind placebo-controlled study A1281132, the mean duration of treatment/exposure was comparable for subjects between the ages of 10<14 years (24.2 days vs 23.5 days for placebo) and 14-17 years (21.7 days vs 23.8 for placebo) who received ziprasidone treatment. Of the subjects who discontinued from the study, 28.4% of ziprasidone subjects and 42.9% of placebo subjects were between the ages 10 - <14 years, and 41.3% of ziprasidone subjects and 41.5% of placebo subjects were between the ages of 14 to ≤17 years. In both age groups, most ziprasidone and placebo subjects discontinued for reasons not related to study drug.

Analysis of adverse event data by age group indicated that a larger percentage of ziprasidone subjects experienced all causality adverse events than placebo in both age categories (93.2% vs 60.0% placebo in subjects 10-<14 and 89.3% vs placebo 69.8% in subjects 14-17 years. A summary of the all causality treatment-emergent adverse events in subjects that were reported in ≥5% of subjects by age category is summarized in Table 42. When incidence of adverse events between younger and older ziprasidone-treated subjects were compared, younger subjects had a greater incidence of abdominal pain, headache, dystonia, and dizziness and older subjects had a greater incidence of nausea, akathisia, and restlessness. The incidence of sedation, somnolence, and insomnia was comparable between the ziprasidone-treated age groups.

Table 42. Summary of Treatment-emergent Adverse Events (All Causalities) by Age Reported in >=5% of Bipolar Mania I Subjects - Study A1281132

Body System and Preferred Term	Ziprasidone		Placebo	
MedDRA v 11.0	10-<14 yrs N = 74 [n (%)]	≥14-≤18 yrs N = 75 [n (%)]	10-<14 yrs N = 35 [n (%)]	≥14-≤18 yrs N = 53 [n (%)]
Eye Disorders	**4 (5.4)**	**8 (10.7)**	**0**	**1 (1.9)**
Vision blurred	2 (2.7)	7 (9.3)	0	1 (1.9)
Gastrointestinal disorders	**26 (35.1)**	**23 (30.7)**	**7 (20)**	**7 (13.2)**
Abdominal pain	4 (5.4)	1 (1.3)	0	0
Abdominal pain upper	8 (10.8)	0	3 (8.6)	0
Nausea	6 (8.1)	14 (18.7)	2 (5.7)	4 (7.5)
Vomiting	4 (5.4)	7 (9.3)	0	1 (1.9)
General disorders and administration site conditions	**13 (17.6)**	**15 (20.0)**	**2 (5.7)**	**12 (22.6)**
Fatigue	10 (13.5)	10 (13.3)	1 (2.9)	5 (9.4)
Infections and infestations	**10 (13.5)**	**12 (16.0)**	**1 (2.9)**	**5 (9.4)**
Sinusitis	4 (5.4)	0	0	0
Upper respiratory tract infection	2 (2.7)	5 (6.7)	0	0
Injury, poisoning and procedural complications	**7 (9.5)**	**3 (4.0)**	**3 (8.6)**	**3 (5.7)**
Overdose	5 (6.8)	2 (2.7)	2 (5.7)	3 (5.7)
Metabolism and nutrition disorders	**8 (10.8)**	**3 (4.0)**	**1 (2.9)**	**5 (9.4)**
Decreased appetite	4 (5.4)	2 (2.7)	1 (2.9)	1 (1.9)
Musculoskeletal and connective tissue disorders	**9 (12.2)**	**13 (17.3)**	**4 (11.4)**	**6 (11.3)**
Musculoskeletal stiffness	3 (4.1)	5 (6.7)	0	0
Nervous system disorders	**59 (79.7)**	**56 (74.7)**	**9 (25.7)**	**22 (41.5)**
Akathisia	1 (1.4)	6 (8.0)	0	1 (1.9)
Dystonia	5 (6.8)	1 (1.3)	0	1 (1.9)
Extrapyramidal disorder	4 (5.4)	3 (4.0)	0	1 (1.9)
Tremor	5 (6.8)	3 (4.0)	0	0
Dizziness	11 (14.9)	5 (6.7)	0	2 (3.8)
Sedation	26 (35.1)	23 (30.7)	0	4 (7.5)
Somnolence	16 (21.6)	21 (28.0)	2 (5.7)	5 (9.4)
Headache	19 (25.7)	12 (16.0)	8 (22.9)	11 (20.8)
Psychiatric disorders	**15 (20.3)**	**19 (25.3)**	**6 (17.1)**	**15 (28.3)**
Bipolar disorder	1 (1.4)	0	1 (2.9)	3 (5.7)
Restlessness	2 (2.7)	6 (8.0)	0	1 (1.9)
Insomnia	6 (8.1)	7 (9.3)	0	3 (5.7)

The incidence of laboratory abnormalities for subjects without regard to baseline by age group was greater in ziprasidone subjects in the 14-17 year old age group compared with subjects in the 10-<14 year age group (74% vs 58%, respectively). In placebo-treated subjects, the incidence of abnormalities was also greater in the older age group as compared to the younger age group (80% vs 69%, respectively). For mean maximum change from baseline in QTcF intervals that were noted to be prolonged in the ziprasidone group relative to the placebo group, no differences in age were evident.

During long-term administration of ziprasidone to subjects with Bipolar I Disorder, a comparable percentage of subjects aged 10 - <14 (87.8%) years and 14-17 (85.6%) years experienced at least one all causality adverse event. A summary of the all-causality treatment-emergent adverse events in subjects aged 10 to <14 and 14 to ≤18 years reported in ≥5% of all subjects is summarized in Table 43. When incidence of adverse events between younger and older ziprasidone-treated subjects were compared, younger subjects had a greater incidence of Bipolar disorder, suicidal ideation, nausea, abdominal pain upper, vomiting, upper respiratory tract infection, weight increased, rash, and increased appetite. Older subjects had a greater incidence of nasal congestion and fatigue. Overall, there does not appear to be a clinically significant difference with regard to age for these events.

Table 43. Summary of Treatment-Emergent Adverse Events (All Causalities) by Age Reported in >=5% of Bipolar I Disorder Subjects - Studies A1281123 and A1281133 –Open-label

Body System and Preferred Terms	Ziprasidone N=188	
MedDRA v. 11		
	Aged 10 to <14 years n=98	**Aged 14 to ≤18 years n=90**
Gastrointestinal	**29 (29.6)**	**24 (26.7)**
Nausea	12 (12.2)	5 (5.6)
Vomiting	8 (8.2)	4 (4.4)
Abdominal pain upper	9 (9.2)	4 (4.4)
Stomach discomfort	5 (5.1)	5 (5.6)
General and administration site conditions	**16 (16.3)**	**18 (20.0)**
Fatigue	6 (6.1)	10 (11.1)
Infections and infestations	**25 (25.5)**	**14 (15.6)**
Upper respiratory tract infection	6 (6.1)	2 (2.2)
Investigations	**18 (18.4)**	**7 (7.8)**
Weight increased	9 (9.2)	1 (1.1)
Metabolism and nutrition	**8 (8.2)**	**3 (3.3)**
Increased appetite	5 (5.1)	0 (0.0)
Nervous system	**65 (66.3)**	**58 (64.4)**
Sedation	28 (28.6)	26 (28.9)
Somnolence	25 (25.5)	15 (16.7)
Headache	17 (17.3)	17 (18.9)
Dizziness	6 (6.1)	8 (8.9)
Extrapyramidal disorder	5 (5.1)	3 (3.3)
Psychiatric	**37 (37.8)**	**24 (26.7)**
Insomnia	9 (9.2)	9 (10.0)
Bipolar disorder	5 (5.1)	1 (1.1)
Suicidal ideation	5 (5.1)	1 (1.1)
Respiratory, thoracic and mediastinal	**11 (11.2)**	**14 (15.6)**
Cough	5 (5.1)	4 (4.4)
Nasal congestion	4 (4.1)	8 (8.9)
Skin and subcutaneous tissue	**10 (10.2)**	**5 (5.6)**
Rash	6 (6.1)	1 (1.1)

The rate of discontinuation from the long-term studies for reasons related to the study drug was generally similar (18.4% 10<14 years vs 17.8% 14-17 years) between the age groups (ziprasidone ≤160 mg/day).

A comparable percentage of subjects aged 10 to ≤14 years (61%) and aged 14 to ≤18 years (64%) experienced at least one laboratory abnormality in the ziprasidone group. The incidence of laboratory abnormalities without regard to baseline abnormality was also comparable between subjects aged 10 to ≤14 years (75%) and aged 14 to ≤18 years (74%). In laboratory tests where a 3 fold increase in incidence occurred between the age groups, the number of events was too small to draw any meaningful conclusions.

5.8.3. Weight

The majority of subjects (115/149, 77%) in the double-blind placebo-controlled study weighed ≥45 kg. The percentage of subjects who weighed ≥45 kg and discontinued from the study was comparable between both the ziprasidone (38.3%) and placebo (41.1%) treatment groups, while the percentage of subjects weighing <45 kg who discontinued from the study was less in the ziprasidone (23.5%) group compared with the placebo (46.7%) group.

Subjects <45 kg had a higher incidence of gastrointestinal adverse events (abdominal pain upper, vomiting), dystonia, extrapyramidal disorder, tremor, dizziness, and anxiety compared to subjects ≥45 kg, while the subjects weighing ≥45 kg had a greater incidence of akathisia and fatigue.

A summary of the all causality treatment-emergent adverse events in subjects by weight reported in ≥5% of all subjects is summarized in Table 44.

Table 44. Summary of Treatment-emergent Adverse Events (All Causalities) by Weight Reported in >=5% of Bipolar I Disorder Subjects - Study A1281132

Body System and Preferred Term	Ziprasidone		Placebo	
MedDRA v. 11.0	<45 kg N = 34 [n (%)]	≥45 kg N = 115 [n (%)]	<45 kg N = 15 [n (%)]	≥45 kg N = 73 [n (%)]
Eye Disorders	**3 (8.8)**	**9 (7.8)**	**0**	**1 (1.4)**
Vision blurred	1 (2.9)	8 (7.0)	0	1 (1.4)
Gastrointestinal disorders	15 (44.1)	34 (29.6)	1 (6.7)	13 (17.8)
Abdominal pain upper	5 (14.7)	3 (2.6)	1 (6.7)	2 (2.7)
Nausea	5 (14.7)	15 (13.0)	0	6 (8.2)
Stomach discomfort	2 (5.9)	4 (3.5)	0	2 (2.7)
Vomiting	4 (11.8)	7 (6.1)	0	1 (1.4)
General disorders and administration site conditions	**6 (17.6)**	**22 (19.1)**	**1 (6.7)**	**13 (17.8)**
Fatigue	3 (8.8)	17 (14.8)	0	6 (8.2)
Irritability	0	2 (1.7)	0	4 (5.5)
Infections and infestations	**5 (14.7)**	**17 (14.8)**	**1 (6.7)**	**5 (6.8)**
Upper respiratory tract infection	2 (5.9)	5 (4.3)	0	0
Injury, poisoning and procedural complications	**4 (11.8)**	**6 (5.2)**	**2 (13.3)**	**4 (5.5)**
Overdose	4 (11.8)	3 (2.6)	2 (13.3)	3 (4.1)
Medication error	2 (5.9)	1 (0.9)	0	1 (1.4)
Musculoskeletal and connective tissue disorders	**5 (14.7)**	**17 (14.8)**	**0**	**10 (13.7)**
Myalgia	1 (2.9)	2 (1.7)	0	4 (5.5)
Musculoskeletal stiffness	1 (2.9)	7 (6.1)	0	0
Nervous system disorders	**25 (73.5)**	**90 (78.3)**	**1 (6.7)**	**30 (41.1)**
Akathisia	0	7 (6.1)	0	1 (1.4)
Dystonia	4 (11.8)	2 (1.7)	0	1 (1.4)
Extrapyramidal disorder	3 (8.8)	4 (3.5)	0	1 (1.4)
Tremor	4 (11.8)	4 (3.5)	0	0
Dizziness	6 (17.6)	10 (8.7)	0	2 (2.7)
Sedation	10 (29.4)	39 (33.9)	0	4 (5.5)
Somnolence	7 (20.6)	30 (26.1)	0	7 (9.6)
Headache	9 (26.5)	22 (19.1)	1 (6.7)	18 (24.7)
Psychiatric disorders	**9 (26.5)**	**25 (21.7)**	**2 (13.3)**	**19 (26.0)**
Anxiety	2 (5.9)	0	0	1 (1.4)
Agitation	0	1 (0.9)	0	4 (5.5)
Bipolar I disorder	0	0	1 (6.7)	0
Bipolar disorder	1 (2.9)	0 (0)	0 (0)	4 (5.5)
Insomnia	4 (11.8)	9 (7.8)	0	3 (4.1)
Respiratory, thoracic, and mediastinal disorders	**4 (11.8)**	**8 (7.0)**	**1 (6.7)**	**5 (6.8)**
Epistaxis	2 (5.9)	0	1 (6.7)	0

The incidence of laboratory abnormalities for subjects without regard to baseline abnormality by weight group was slightly greater in both the ziprasidone- and placebo-treatment groups for subjects weighing ≥45 kg compared with subjects weighing <45 kg. For mean maximum change from baseline QTcF intervals that were noted to be prolonged in the ziprasidone group relative to the placebo group, no differences in weight were evident.

During long-term administration of ziprasidone to subjects with Bipolar I Disorder, the majority (144/188, 77%) of the subjects weighed ≥45 kg. Subjects <45 kg had a higher incidence of gastrointestinal events (abdominal pain, vomiting) and rash compared to subjects ≥45 kg, while the subjects weighing ≥45 kg had a greater incidence of fatigue.

A summary of the all causality treatment-emergent adverse events reported in ≥5% of all subjects, by weight, is summarized in Table 45.

Table 45. Summary of Treatment-Emergent Adverse Events (All Causality) by Weight Reported in >=5% of Subjects with Bipolar I Disorder - Studies A1281123 and A1281133 - Open-label

Body System and Preferred Terms	Ziprasidone N=188	
MedDRA v. 11.0	**<45 kg N=44**	**≥45 kg N=144**
Gastrointestinal	**13 (29.5)**	**40 (27.8)**
Nausea	5 (11.4)	12 (8.3)
Vomiting	5 (11.4)	7 (4.9)
Abdominal pain upper	5 (11.4)	8 (5.6)
Stomach discomfort	3 (6.8)	7 (4.9)
General and administration site conditions	**7 (15.9)**	**27 (18.8)**
Fatigue	1 (2.3)	15 (10.4)
Investigations	**7 (15.9)**	**18 (12.5)**
Weight increased	3 (6.8)	7 (4.9)
Nervous system	**31 (70.5)**	**92 (63.9)**
Sedation	13 (29.5)	41 (28.5)
Somnolence	11 (25.0)	29 (20.1)
Headache	9 (20.5)	25 (17.4)
Dizziness	2 (4.5)	12 (8.3)
Extrapyramidal disorder	3 (6.8)	5 (3.5)
Psychiatric	**17 (38.6)**	**44 (30.6)**
Insomnia	5 (11.4)	13 (9.0)
Skin and subcutaneous tissue	**6 (13.6)**	**9 (6.3)**
Rash	4 (9.1)	3 (2.1)

5.8.4. Race

In double-blind placebo-controlled study A1281132 the majority of subjects were White, and there were too few subjects from the other races to draw any conclusions about differences between the ziprasidone and placebo treatment groups among different races for study discontinuations. No conclusions could be drawn regarding the incidence of laboratory test abnormalities in subjects with a normal baseline, due to the small number of subjects who were Black, Asian, or of Other races.

During long-term administration of ziprasidone to subjects with Bipolar I Disorder, >80% of subjects were White, therefore, no meaningful comparison could be made with the use of ziprasidone by race.

5.9. Effects on Sexual Maturation, Growth, and Learning and Memory

Specific safety assessments were included in both the short-term, double-blind, placebo-controlled study A1281132 and its 26-week, open-label extension study A1281133 to evaluate the potential effects of ziprasidone on the sexual maturation, growth, and learning and memory function of the pediatric subjects with Bipolar I Disorder who were enrolled in these studies. The assessments used and results generated with them are described in detail below.

5.9.1. Sexual Maturation

Sexual maturation was assessed using a validated self-report version of the Tanner scale for assessment of adolescent development which subjects completed at the Baseline visit for A1281132 and at the Week 26 visit for A1281133. In addition, hormone assessments, including testosterone and prolactin measurements, were obtained prior to treatment, at the end of the 4-week double-blind treatment period, and at weeks 6 and 26 in the open-label extension trial.

5.9.1.1. Tanner Self-Ratings

Self-assessments of Tanner stage of sexual maturation were obtained at baseline of study A1281132 in 147 of 149 subjects randomized to ziprasidone and 87 of 88 subjects randomized to placebo. In the extension study A1281133, Tanner self-assessments were obtained in 21 girls and 45 boys, who completed the entire 26 weeks of open label treatment with ziprasidone, following their participation in the 4-week double-blind controlled study A1281132. Additional assessments were obtained from 32 girls and 34 boys who terminated early from the A1281133 study.

Table 46 provides the Tanner stage results for all subjects who provided self-ratings at both the baseline of study A1281132 and at their end of study visit in study A1281133 (at week 26 or early termination). The table shows the proportion of subjects who fell into each Tanner stage at baseline of study A1281132 and at their end of study visit in study A1281133. In general, the results appear to be consistent with normal sexual maturation.

Table 46. Tanner Stages of Development – Study A1281133

Tanner Stage	Baseline* N (%)	End of Study (Week 26 + ET) N (%)
Pubic Hair (Males)		
N	89	79
Stage 1	11 (12.4)	5 (6.3)
Stage 2	17 (19.1)	16 (20.3)
Stage 3	19 (21.3)	18 (22.8)
Stage 4	30 (33.7)	21 (26.6)
Stage 5	12 (13.5)	19 (24.1)
Genitalia (Males)		
N	90	79
Stage 1	8 (8.9)	7(8.9)
Stage 2	18 (20.0)	11(13.9)
Stage 3	22 (24.4)	22 (27.8)
Stage 4	28 (31.1)	21 (26.6)
Stage 5	14 (15.6)	18 (22.8)
Pubic Hair (Females)		
N	70	53
Stage 1	4 (5.7)	3 (5.7)
Stage 2	3 (4.3)	4 (7.5)
Stage 3	10 (14.3)	5 (9.4)
Stage 4	28 (40.0)	19 (35.8)
Stage 5	25 (35.7)	22 (41.5)
Breasts (Females)		
N	70	53
Stage 1	4 (5.7)	2 (3.8)
Stage 2	3 (4.3)	3 (5.7)
Stage 3	12 (17.1)	9 (17.0)
Stage 4	31 (44.3)	20 (37.7)
Stage 5	20 (28.6)	19 (35.8)

*A1281132 baseline Tanner data serves as the baseline for A1281133

In the majority of cases, most subjects either remained at their baseline stage or shifted to a later developmental stage, whether based on self-assessment of pubic hair, breast development or genital development.

Taken together these results are consistent with the fact that there were no adverse events of delayed puberty in subjects treated with ziprasidone in either study A1281132 or A1281133 and suggest that treatment with ziprasidone up to 30 weeks in duration did not appear to have any consistent effect on the pubertal development of the pediatric subjects with Bipolar I Disorder who were enrolled into studies A1281132 and A1281133.

5.9.1.2. Sexual Hormone Assessments

As part of the assessment of sexual maturation, plasma testosterone and prolactin levels also were obtained at baseline and week 4 or at early termination in study A1281132 and at weeks 6 and 26 or at early termination in the open-label extension study A1281133.

In the 4-week, double-blind, placebo-controlled study A1281132, baseline and follow-up plasma testosterone measurements were obtained in 46 boys and 45 girls randomized to ziprasidone and 30 boys and 29 girls randomized to placebo. A total of 8 of the 92 (9%) boys and girls treated with ziprasidone had a testosterone level greater than 1.2 X the upper limit of normal (for age and sex) at any time in study A1281132 compared with 5 of 60 (8%) treated with placebo. No subject had a testosterone level <0.8 X the lower limit of normal (for age and sex) at any time in the study.

To further explore the testosterone data, testosterone measurements from boys enrolled in studies A1281132 and A1281133, who had testosterone measured at baseline of study A1281132 and at week 26 or early termination in study A1281133, were analyzed by stratifying the data according to the subjects' Tanner stage at baseline and end of study. Mean testosterone levels generally increased with increase in Tanner stage, as would be expected in the course of normal sexual maturation (Table 47).

Table 47. Testosterone (ng/dL) by Tanner Stage of Development – Study A1281133

Tanner Stage	Baseline Testosterone (ng/dL) Mean (SD)	End of Study (Week 26 + ET) Testosterone (ng/dl) Mean (SD)
Pubic Hair (Males)		
N	89	79
Stage 1	32.5 (34.9)	20.0 (0.0)
Stage 2	25.6 (10.5)	38.6 (35.0)
Stage 3	145.8 (178.0)	97.6 (76.5)
Stage 4	423.1 (208.7)	310.5 (175.4)
Stage 5	368.6 (123.7)	376.1 (178.7)
Genitalia (Males)		
N	90	79
Stage 1	36.4 (41.0)	20.7 (1.9)
Stage 2	31.2 (29.5)	39.0 (39.0)
Stage 3	119.1 (170.4)	101.8 (86.2)
Stage 4	404.9 (193.2)	304.6 (176.9)
Stage 5	419.4 (171.8)	389.8 (174.8)

A1281132 baseline Testosterone and Tanner Data serves as the baseline for A1281133

Taken together, it is difficult to draw firm conclusions from these data due to the variability of single time-point measurements of plasma testosterone and the wide variability at which children reach different stages of puberty and in the rates at which they pass from one stage of development to the next (Marshall & Tanner, 1969; Marshall & Tanner, 1970). In general, treatment with ziprasidone for up to 30 weeks duration was not associated with any systematic effects on testosterone plasma levels. Moreover, none of the subjects with elevated testosterone levels on any occasion in either study A1281132 or A1281133 had adverse events in the endocrine disorder or reproductive organ system class, other than menstrual cramps and one case of sexual assault.

5.9.1.3. Prolactin Assessments

In study A1281132, elevated blood prolactin occurred more frequently in the ziprasidone group (14/120 subjects, 12%) compared to the placebo group (2/75 subjects, 3%). None of the subjects having elevated blood prolactin had an adverse event of hyperprolactinemia and none had adverse events in the reproductive organ system class. The types of adverse events reported in these subjects were similar to adverse events reported in the ziprasidone treated group overall (ie, adverse events commonly related to stomach upset/nausea, sedation, and somnolence). One subject in the ziprasidone group had an adverse event of elevated blood prolactin that was clinically significant. This subject (11241010), a 15 year-old male, had a prolactin level of 39.8 ng/mL (normal range = 2.1-17.7 ng/mL) on Day 31. His Day -6 and Day 1 prolactin levels were below the normal range (ie, 0.5 and 0.8 ng/mL, respectively).

In the 26-week open-label study A1281133, elevated prolactin occurred in 7% (10/134) of the subjects. Two subjects had adverse events of elevated prolactin, which were considered related to the study treatment. Neither subject had an adverse event of the reproductive organ system class.

In summary, although ziprasidone treatment up to 30 weeks in duration was associated with elevated prolactin levels in some patients, as outlined in Sections 5.9.1.1 and 5.9.1.2, there were no noticeable effects on sexual maturation or hormones.

5.9.2. Growth

Potential effects of ziprasidone treatment on subjects' growth were assessed by measurement of body weight, height, BMI, BMI-Z scores based on CDC growth charts, and waist circumference. These parameters were obtained at screening, at the end of the 4-week double-blind treatment period in study A1281132 and at the end of the 26-week open-label extension trial A1281133.

5.9.2.1. Weight and BMI Z-Score

In the 4-week, randomized, placebo-controlled study A1281132, there were no clinically meaningful changes in height, weight, BMI, BMI Z-scores derived from CDC growth charts, or waist circumference.

BMI Z-score was used to evaluate changes in body weight. No subject had an increase in BMI Z-score (adjusted for age) of 1 or higher during the study. At Week 4, the majority of the subjects in each group (98%) had a change from baseline in BMI Z-score of ≥ -1 to 0 and from 0 to <1. At Week 4, 98% of the subjects in each group had less than a 1-point increase from baseline.

Section 6.6.4 (Table 29) presents the mean baseline and mean change from baseline for body weight and BMI Z-score from study A1281132. Both treatment groups were comparable with respect to these measurements.

One subject in each treatment group had an AE of weight increase and 1 subject in the placebo group had an AE of weight decrease during the study. A 10-year-old male in the

ziprasidone group (40 mg) had weight gain (+4.99 kg from screening) on Day 30 that the investigator considered to be mild and which was still present at study termination. The investigator considered the AE to be related to the study treatment. The second subject, an 11- year-old male in the placebo group, had weight gain (+9.8 kg from screening) on Day 29 that the investigator considered to be mild and which was still present at study termination. The investigator attributed the weight gain to the subject's discontinuation of a stimulant prior to admission into the study. A 14-year-old male in the placebo group had weight loss (-9.23 kg from screening) on Day 29 that the investigator considered to be moderate and which was still present at study termination. The investigator attributed the weight loss to the study treatment.

In the 26-week, open-label study A1281133, there also were no clinically meaningful changes in height, weight, BMI, BMI Z-scores derived from CDC growth charts, or waist circumference.

In the A1281133 study, there was an increase in body weight at Week 6 (+1.3 kg) and Week 26 (+3.9 kg) with a simultaneous increase in height that kept BMI unchanged. Table 48 summarizes the mean baseline (last available observation in the preceding double-blind study) and mean change from baseline for body weight and BMI Z-scores. The majority of the subjects had a BMI Z-score between -1 and less than 1 at Weeks 6 (99%) and 26 (97%). The changes in BMI derived Z-scores, which adjust for age and sex, showed little or no change throughout the study. One subject had a change from baseline in BMI Z-score of 1 or higher at Weeks 6 and 26.

Table 48. Mean Baseline and Mean Change from Baseline for Body Weight and BMI-Z Score in Study A1281133 – Open-label

	N	Mean (SD)
Weight, kg		
Mean baseline	162	57.6 (14.9)
Change from baseline		
Week 6	119	1.3 (3.0)
Week 26	68	3.9 (5.4)
ET	74	1.4 (2.8)
BMI-derived Z-score[a]		
Mean baseline	162	0.8 (0.9)
Change from baseline		
Week 6	119	0.0 (0.3)
Week 26	68	0.1 (0.5)
ET	74	0.0 (0.3)

Baseline is the last available observation in the preceding double-blind study (A1281132).
[a]Derived from CDC growth charts.
BMI = body mass index, CDC = Centers for Disease Control,
N = number of evaluable subjects, SD = standard deviation.

Taken together, these results indicate that ziprasidone treatment up to 30 weeks in duration was not associated with any systematic effects on the growth trajectories of the youth enrolled in studies A1281132 and A1281133.

5.9.3. Hormones Involved in Growth and Development

As part of the assessment of potential effects on growth and development of treatment with ziprasidone, free T4 (thyroxine), thyroid stimulating hormone (TSH), insulin like growth factor (ILGF) and insulin like growth factor binding protein 3 (ILGFBP3) also were assessed at baseline and week 4 or at early termination in study A1281132 and at weeks 6 and 26 or at early termination in the open-label extension study A1281133. The results suggest that ziprasidone treatment up to 30 weeks in duration has no systematic or clinically relevant effect on thyroxine, TSH, insulin growth factor, and insulin like growth factor binding protein 3. Along with the clinical measurements of height, weight, BMI, BMI-Z scores, and waist circumference previously described, the weight of evidence from the A1281132 and A1281133 studies in children and adolescents with Bipolar I Disorder suggests that ziprasidone treatment up to 6 months in duration is not associated with clinically relevant effects on growth.

5.9.4. Learning and Development

A computerized cognitive battery was included in the A1281132 and A1281133 trials as a special safety assessment to determine the impact of ziprasidone treatment on learning and memory. Based on the results, it appears that there were no changes (ie, no improvement or worsening) in cognitive performance with ziprasidone treatment on the domains assessed by the CNS Vital Signs battery. Similarly, there appear to be no changes in the sedation rating completed just prior to the administration of the cognitive battery. In study A1281133, there were few changes in the cognitive domains over the 26-week open-label study period. Only visual memory showed a slight decline. The mean level of sedation reported by subjects also dropped slightly during this open-label phase.

5.10. Safety in Supplementary Studies with Ziprasidone in the Pediatric Population

As previously noted, one of the studies supporting the safety of ziprasidone in pediatric subjects with Bipolar I Disorder also enrolled subjects with schizophrenia and schizoaffective disorder (A1281123) (Table 1). Other supplementary studies provided additional pharmacokinetic data in pediatric subjects (Table 2). Summaries of the safety findings in each of these studies are as follows:

Study A1281123 included 17 subjects with schizophrenia and schizoaffective disorder for up to 27 weeks of treatment with ziprasidone. Data from the long term extension studies (A1281123 and A1281133) with Bipolar I Disorder subjects alone compared with data from the long-term extension studies from Bipolar I Disorder, schizophrenia, and schizoaffective disorder subjects did not identify any new or unexpected safety findings.

Study 128-044, a Phase 1 open-label, single-dose, oral study to evaluate the pharmacokinetics of ziprasidone in children and adolescents with Tourette's Syndrome enrolled 24 subjects between the ages of 7-16 years who received between 5-20 mg ziprasidone. No serious adverse events were reported. Treatment-emergent adverse events included somnolence, emotional lability, dizziness, postural hypotension, and nausea. The mean change in QTcF in this small subject population ranged from -1.5 msec to 11.8 msec.

Using QTcF, no QTc value exceeded 450 msec and no subject demonstrated an increase in QTc of ≥30 msec. In summary, ziprasidone was well tolerated and no new safety concerns were noted in this study.

Study 128-122, a Phase 2, 8-week, double-blind, placebo-controlled study in children and adolescents with Tourette's Syndrome, enrolled 28 subjects (27 with Tourette's Syndrome; 1 with chronic motor or vocal tic disorder). Sixteen subjects were randomized to ziprasidone (maximum dose 20 mg BID) and 12 subjects were randomized to placebo. There were no serious adverse events in the study. The majority of the treatment-emergent adverse events were associated with the nervous system, including somnolence, insomnia, dizziness, twitching, and akathisia. A QTc interval of ≥450 msec was reported in one subject; no subject had an increase in QTc interval ≥480 msec or QT interval increase ≥20% from baseline. There were no clinically significant mean changes observed in scores from the Simpson-Angus Rating Scale, Barnes Akathisia Scale or Abnormal Involuntary Movement Scale. In summary, no new safety concerns were noted in this study.

5.11. Post marketing

A search of the sponsor's global safety database for ziprasidone pediatric cases from 5 February 1998 – 30 April 2008 identified the following information: Overall key characteristics reported in the HCP and non HCP cases were similar. Of 809 cases, 85% were reported by health-care professionals and 15% were reported by consumers. Of the cases that reported an exact age, mean age was 13 years. About 68% of the patients were between 12-<18 years. Of the cases that reported an indication, bipolar disorder was the most commonly reported indication (13%), followed by schizophrenia (6%) and psychotic disorder (4.3%). Of the cases that reported a total daily dose, 40 mg was the most commonly reported total daily dose (17%). A total of eight cases reported death. Cause of death for these eight cases includes: asphyxia, completed suicide, neuroleptic malignant syndrome, cardiopulmonary failure, aspiration secondary to convulsion, and cause unknown (3 cases). None were attributed to the use of ziprasidone. The greatest number of events reported were associated with the Nervous System and included Dystonia (10.4%), Somnolence (9.8%), and Extrapyramidal disorder (5.9%). A review of cases reporting suicidality, QT-related events, and dystonia, did not identify safety concerns in the pediatric population. A review of cases reporting drug interaction, overdose, exposure in utero, drug abuse/misuse/dependence, and intramuscular route did not identify any safety concerns in the pediatric population. When comparing the pediatric group with the non-pediatric group, the only adverse event having a 3-fold greater reporting proportion was Dystonia in the pediatric group (2.9% vs 10.4%). Overall, key characteristics including the number of serious cases and case outcome reported in the pediatric and non-pediatric cases, reporting Dystonia were similar. The distribution of serious and non-serious events across system organ classes was similar in both groups.

A search of the post-marketing safety database from 5 February 1998 – 28 February 2009 identified 56 additional pediatric cases. A review of the adverse events for these new cases did not identify any unexpected safety issues.

A review of the post-marketing data revealed that that safety profile of ziprasidone in pediatric patients is comparable to that of the non-pediatric patients. No new or unanticipated safety issues were identified in the pediatric population with ziprasidone use.

5.12. Safety Summary and Conclusions

- During the double-blind placebo-controlled study, commonly occurring adverse events were attributed to the known pharmacologic effects of ziprasidone in adults. The pediatric safety profile was similar to the adult profile, except for an increased incidence of sedation and somnolence. The effects on QTc observed in the pediatric subjects were comparable to what was observed in adults treated with ziprasidone. Ziprasidone had minimal effects on weight and metabolic parameters.

- Long-term administration of ziprasidone in open-label safety and tolerance studies to pediatric subjects with Bipolar I Disorder did not identify new or unexpected safety findings as compared with the safety profile observed in adult patients with bipolar mania. For QTcF intervals during long-term administration of ziprasidone, no differences emerged when data were evaluated by age and gender.

- A review of the post-marketing data revealed that the safety profile of ziprasidone in pediatric patents is comparable to that of the non-pediatric patients. No new or unanticipated safety issues were identified in the pediatric population with ziprasidone use.

- Overall, ziprasidone was generally well-tolerated. Data from children and adolescents aged 10-17 years in the double-blind placebo-controlled study and from the two open-label, long-term safety and tolerance studies did not reveal any new or unexpected safety findings compared with the safety profile observed in adult patients with bipolar mania.

6. CONCLUSIONS

Efficacy

- Based on the primary efficacy endpoint (change from baseline to Week 4 in YMRS total score), there was a statistically significant treatment effect (p=0.0005) for ziprasidone over placebo.

- Results from the analysis of the key secondary efficacy endpoint, the change from baseline in CGI-S score at Week 4, were consistent with the findings in YMRS total score. Ziprasidone demonstrated a statistically significant (favorable) difference from placebo (p=0.0001).

- Ziprasidone was shown to be effective in the treatment of children and adolescents with Bipolar I Disorder (manic or mixed).

Safety

- Ziprasidone was generally well tolerated in a 4-week controlled trial in children and adolescents with Bipolar I Disorder: The adverse event profile was consistent with studies in adults with bipolar disorder. There were no new or unexpected adverse events, including in QTc changes. There were no unexpected laboratory abnormalities.

- There was a low propensity for weight gain. In the ziprasidone group, 7% of subjects had weight gain ≥7% as compared to 4% in the placebo group.

- There was minimal effect on lipid profiles.

- Ziprasidone was generally well tolerated in up to 30 weeks of continued open-label treatment.

- There were no evident effects on growth, sexual maturation, or cognition.

Overall Conclusions

- Ziprasidone was efficacious in the treatment of children and adolescents aged 10-17 with Bipolar I Disorder (manic or mixed) at doses from 40 – 160 mg/day. There was significant improvement in YMRS and CGI-S vs. placebo at 4 weeks.

- Ziprasidone was generally well tolerated in up to 30 weeks of treatment. The pediatric safety profile was similar to the adult profile, except for an increased incidence of sedation and somnolence. There were no clinically significant effects on weight. Ziprasidone was metabolically neutral.

7. REFERENCES

Beedham C, Miceli JJ, Obach RS (2003) Ziprasidone metabolism, aldehyde oxidase, and clinical implications. J Clin Psychopharmacol 23:229-232.

Birmaher B (2007) Longitudinal course of pediatric bipolar disorder. Am J Psychiatry 164:537-539.

Blader JC, Carlson GA (2007) Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. Biol Psychiatry 62:107-114.

Carter TD, Mundo E, Parikh SV, et al. (2003) Early age at onset as a risk factor for poor outcome of bipolar disorder. J Psychiatr Res 37:297-303.

Case BG, Olfson M, Marcus SC, et al. (2007) Trends in the inpatient mental health treatment of children and adolescents in US community hospitals between 1990 and 2000. Arch Gen Psychiatry 64:89-96.

Correll CU (2007) Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. J Am Acad Child Adolesc Psychiatry 46:687-700.

Duax JM, Youngstrom EA, Calabrese JR, et al. (2007) Sex differences in pediatric bipolar disorder. J Clin Psychiatry 68:1565-1573.

Fagiolini A, Chengappa KN, Soreca I, et al. (2008) Bipolar disorder and the metabolic syndrome: causal factors, psychiatric outcomes and economic burden. CNS Drugs 22:655-669.

Faraone SV, Glatt SJ, Tsuang MT (2003) The genetics of pediatric-onset bipolar disorder. Biol Psychiatry 53:970-977.

Findling RL, Gracious BL, McNamara NK, et al. (2001) Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disord 3:202-210.

Freeman AJ, Youngstrom EA, Michalak E, et al. (2009) Quality of life in pediatric bipolar disorder. Pediatrics 123:e446-452.

Geller B, Tillman R, Craney JL, Bolhofner K (2004) Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 61:459-467.

Geller B, Tillman R, Bolhofner K, et al. (2008) Child bipolar I disorder: prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Arch Gen Psychiatry 65:1125-1133.

Goldstein BI, Birmaher B, Axelson DA, et al. (2008) Preliminary findings regarding overweight and obesity in pediatric bipolar disorder. J Clin Psychiatry 69:1953-1959.

Goldstein TR, Birmaher B, Axelson D, et al. (2009) Psychosocial functioning among bipolar youth. J Affect Disord 114:174-183.

Hirshfeld RM, Lewis L, Vornik LA (2003) Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic depressive association 2000 survey of individuals with bipolar disorder. J Clin Psychiatr 64:161-174.

Jerrell JM, Prewette ED, 2nd (2008) Outcomes for youths with early- and very-early-onset bipolar I disorder. J Behav Health Serv Res 35:52-59.

Joshi G, Wilens T (2009) Comorbidity in pediatric bipolar disorder. Child Adolesc Psychiatr Clin N Am 18:291-319, vii-viii.

Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. Arch Gen Psychiat 1998; 51 :8-19.

Leibenluft E, Rich BA (2008) Pediatric bipolar disorder. Annu Rev Clin Psychol 4:163-187.

Lewinsohn PM, Klein DN, Seeley JR (1995) Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry 34:454-463.

Lish JD, Dime-Meenan S, Whybrow PC, et al. (1994) The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J Affect Disord 31:281-294.

McClellan J, Kowatch R, Findling RL (2007) Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 46:107-125.

McElroy SL, Frye MA, Suppes T, et al. (2002) Correlates of overweight and obesity in 644 patients with bipolar disorder. J Clin Psychiatry 63:207-213.

Moreno C, Laje G, Blanco C, et al. (2007) National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry 64:1032-1039.

Nandagopal JJ, DelBello MP, Kowatch R (2009) Pharmacologic treatment of pediatric bipolar disorder. Child Adolesc Psychiat Clin N Am 18:455-469, x.

Ogden CL, Carroll MD, Curtin LR, et al. (2006) Prevalence of overweight and obesity in the United States, 1999-2004. Jama 295:1549-1555.

Patel NC, Keck PE, Jr. (2006) Ziprasidone: efficacy and safety in patients with bipolar disorder. Expert Rev Neurother 6:1129-1138.

Perlis RH, Miyahara S, Marangell LB, et al. (2004) Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 55:875-881.

Pini S, et al. Prevelance and burden of bipolar disorders in European countries. Eur Neuropsychopharmacol. 2005; 15 (4) :425-34.

Rademacher J, DelBello MP, Adler C, et al. (2007) Health-related quality of life in adolescents with bipolar I disorder. J Child Adolesc Psychopharmacol 17:97-103.

Safer DJ (2004) A comparison of risperidone-induced weight gain across the age span. J Clin Psychopharmacol 24:429-436.

Schmidt AW, Lebel LA, Howard HR, Jr., et al. (2001) Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 425:197-201.

Smarty S, Findling RL (2007) Psychopharmacology of pediatric bipolar disorder: a review. Psychopharmacology (Berl) 191:39-54.

Strober M, Morrell W, Burroughs J, et al. (1988) A family study of bipolar I disorder in adolescence. Early onset of symptoms linked to increased familial loading and lithium resistance. J Affect Disord 15:255-268.

Suppes T, Leverich GS, Keck PE Jr, et al. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. J Affect Disord 2001; 67 (1/3) :45-59.

Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996; 276 (4):293-9.

Youngstrom E, Youngstrom JK, Starr M (2005) Bipolar diagnoses in community mental heath; Achenback Child Behavior Checklist profiles and patterns of comorbidity, Biol Psychiatry 58:569-575.

Appendices

Appendix 1. Summaries of Studies Contributing Pharmacokinetic Data

Appendix 1.1. Summaries of Pediatric Studies Contributing Pharmacokinetic Data

A1281132: Four Week, Double-blind, Placebo Controlled Phase III Trial Evaluating the Efficacy, Safety and Pharmacokinetics of Flexible Doses of Oral Ziprasidone in Children and Adolescents with Bipolar I Disorder (Manic or Mixed)

Study A1281132 is a pivotal phase 3, 4 week randomized, double-blind, placebo-controlled safety, tolerability and efficacy trial conducted in patients age 10-18 years with bipolar disorder. Oral ziprasidone was administered as capsules twice daily (BID) with meals, titrated up to 120 – 160 mg/day depending on body weight (120 – 160 mg/day for subjects ≥45 kg; 60 – 80 mg/day for subjects <45 kg) over the first 1-2 weeks of treatment and flexibly dosed through weeks 3 and 4. Sparse sampling for measurement of ziprasidone and its major metabolites, S-methyldihydroziprasidone (M9) and ziprasidone sulfoxide (M10), was performed and the data treated by population PK analysis. One hundred and forty nine (149) subjects were treated with ziprasidone of which 128 subjects provided 413 concentration observations in this study.

A1281123: A 27-Week Open-Label Trial to Characterize the Safety and Tolerability of Orally Administered Ziprasidone in Children and Adolescent Subjects with Bipolar I Disorder (Manic and Mixed), Schizophrenia or Schizoaffective Disorder

Study A1281123 was a dose ranging trial which assessed tolerability and pharmacokinetics in patients age 10-17 years with schizophrenia, schizoaffective disorder or bipolar disorder. This study provided support for the design of study A1281132. The study consisted of a screening period to determine eligibility and two open-label treatment periods, Periods 1 and 2. In Period 1, subjects were randomly assigned to one of two treatment groups and were to achieve the maximum allowable dose in their assigned group and remain at that dose through the Week 3 visit. Ziprasidone was administered as oral suspension for Groups 1 and 2 as follows:

Group 1 (low dose titration): Start at 10 mg BID and titrate to 40 mg BID to achieve the maximum dose by Day 10.

Group 2 (high dose titration): Start at 20 mg BID and titrate to 80 mg BID to achieve the maximum dose by Day 10.

Following the Week 3 visit or at early termination from Period 1, subjects could enter Period 2 for up to an additional 24 weeks for a maximum treatment duration of 27 weeks. During Period 2, subjects could remain on oral suspension or be switched to oral capsules. Dosing in Period 2 was flexible and could cover the dose range of 10-80 mg BID based upon clinical need. Dosing in both Periods 1 and 2 was to be under fed conditions.

During Period 1, subjects weighing less than 45 kg received one-half the starting dose associated with their group assignment. During Period 2, these subjects could receive the full dose strength of ziprasidone and be titrated through the entire dose range of 10-80 mg BID based upon clinical need.

Sparse sampling for measurement of ziprasidone and metabolite concentration and assessment of pharmacokinetics was performed. Sixty three (63) subjects were assigned to ziprasidone treatment with 57 subjects providing 210 observed ziprasidone concentration measurements for assessment of pharmacokinetics.

128-044: Phase I Open, Single Dose, Oral Study to Evaluate the Pharmacokinetics of Ziprasidone in Children and Adolescents with Tourette's Syndrome

Study 128-044 is a single dose oral pharmacokinetic study conducted in patients age 7-16 years meeting DSM-IV criteria for Tourette's syndrome or chronic motor or vocal tic disorder (CTD). A total of 24 patients were assigned by weight to three treatment groups and received single suspension doses of 5, 10 or 20 mg ziprasidone hydrochloride under fed conditions followed by intensive pharmacokinetic collections up to 32 hours postdose. Subjects greater than 60 kg were assigned to Group 1 and received 20 mg doses of ziprasidone. Group 2 subjects were 31 to 60 kg and assigned to 10 mg doses and Group 3 were 16 to 30 kg and assigned to receive 5 mg doses of ziprasidone. Pharmacokinetic data was collected and analyzed from 23 subjects contributing 171 ziprasidone concentration measurements. Only ziprasidone (parent drug) was measured.

128-122: Phase II, Eight -Week, Double-Blind, Placebo-Controlled Pilot Study Evaluating the Toleration, Safety, and Efficacy of Oral Ziprasidone (CP-88,059-1) in Children and Adolescents with Tourette's Syndrome

Study 128-122 was a 56 day, double-blind, randomized, placebo-controlled, flexible dose-escalating phase 2 study examining safety, efficacy and pharmacokinetics in patients age 7-16 years with Tourette's syndrome, or chronic vocal or motor tic disorders. This study provided an early evaluation of ziprasidone PK in pediatric subjects. A total of 16 patients received ziprasidone treatment under fed conditions on a flexible dose schedule starting at 5 mg QD, with increases allowed up to a maximum of 20 mg BID. Forty five (45) of 73 serum samples collected from random sampling windows following administration of the morning dose on days 29 and 57 were evaluable for pharmacokinetic assessment of ziprasidone. Individual pharmacokinetic parameters were predicted using a population pharmacokinetic approach. Only ziprasidone (parent drug) was measured.

Appendix 1.2. Summaries of Adult Studies Contributing Pharmacokinetic Data and Supporting Ziprasidone Population Pharmacokinetic Analyses

A1281037: Phase I, Open, 4-Period, 2-Treatment, Multiple-Dose Study to Compare the Pharmacokinetics of 20 mg Ziprasidone Administered as a Suspension and as a Capsule in the Fed State to Healthy Subjects

Study A1281037 was a 4-period, repeated measure, cross-over, multiple dose study to compare the pharmacokinetics of 20 mg ziprasidone administered as suspension and capsule in the fed state to healthy adult subjects over 3 days. This study was incorporated into the population pharmacokinetic analysis of adult and pediatric PK data in order to take into account any potential PK differences between formulations. Seventeen (17) subjects contributed 657 ziprasidone concentration observations, using a rich sampling design, of which 639 were available for pharmacokinetic assessment.

128-109: A Double-Blind Study Comparing the Efficacy and Safety of Two Doses of Oral CP-88,059 in the Acute Exacerbation of Schizophrenia and Schizoaffective Disorder

Study 128-109 was a 6 week study conducted to evaluate safety and efficacy of ziprasidone administered either as 20 mg QID or 80 mg BID to patients with acute exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder. Serum samples were collected at trough on days 7, 14, 21, 28, 35 and 42 and samples at the expect time of maximal ziprasidone concentration collected on days 7 and 14. Of the 35 subjects that entered and were administered ziprasidone, 21 subjects contributed 107 ziprasidone concentration data values for pharmacokinetic assessment.

128-114: Phase III, Six-Week, Double-Blind, Multicenter, Placebo-Controlled Study Evaluating the Efficacy and Safety of Two Fixed Doses of Oral Ziprasidone (CP-88,059-1) (40 mg BID and 80 mg BID) Acute Exacerbation of Schizophrenia and Schizoaffective Disorder

Study 128-114 was a 6 week double-blind, placebo-controlled, parallel group, fix-dose trial in adult patients. Subjects (males or females, ≥18 years of age; not resistant to neuroleptics) were to have had a recent exacerbation of chronic or subchronic (duration ≥6 months) schizophrenia or schizoaffective disorder. Treatment was 40 or 80 mg ziprasidone or placebo taken orally twice daily (BID). Subjects were evaluated at screening, prior to the start of double-blind dosing, and at regular intervals throughout the study. Serum samples were collected at trough on days 7, 14, 21, and 42 for determination of ziprasidone concentration. Of the 210 subject who were administered ziprasidone treatment, 132 contributed 334 samples for pharmacokinetic assessment.

128-115: Phase III, Six-Week, Double-Blind, Multicenter, Placebo-Controlled Study Evaluating the Efficacy and Safety of Three Fixed Doses of Oral Ziprasidone (CP-88,059-1) (20 mg BID, 60 mg BID and 100 mg BID) and Haloperidol in the Acute Exacerbation of Schizophrenia and Schizoaffective Disorder

The primary objective of this study was to determine the dose response relationship among three dose regimens of ziprasidone and placebo; to compare the therapeutic effect of ziprasidone with placebo and haloperidol with placebo in subjects with an acute exacerbation of schizophrenia or schizoaffective disorder. This study enrolled only adult subjects.

This randomized trial began with a single-blind 3-7-day placebo washout period and continued with a 42-day double-blind, placebo-controlled, parallel group, fixed-dose

treatment period. Subjects (males or females, ≥18 years of age; not resistant to neuroleptics) were to have had a recent exacerbation of chronic or subchronic (duration ≥6 months) schizophrenia or schizoaffective disorder. Treatment was 20, 60, or 100 mg ziprasidone taken orally twice daily, haloperidol (oral; 5 mg AM, 10 mg PM), or placebo taken orally twice daily. Subjects were evaluated at screening, prior to the start of double-blind dosing, and at regular intervals throughout the study. Pharmacokinetic parameters were determined using blood samples on days 7, 14, 21 and 42. One hundred and fifty four (154) subjects contributed 550 ziprasidone concentration values for pharmacokinetic assessment.

128-303: Multicentre Double-Blind Study of Ziprasidone versus Placebo in Relapse Prevention for Hospitalized Patients with Chronic or Subchronic Schizophrenia

The primary objectives of this study were to compare the efficacy of ziprasidone 40 mg BID with placebo; investigate the dose-response relationship of three fixed dose regimens of, ziprasidone (20, 40 and 80 mg BID) in the prevention of psychotic relapse; evaluate the treatment effects on a subgroup of subjects with predominantly negative symptoms (Protocol Amendments III and IV); measure concentrations of ziprasidone in the serum and provide data for the evaluation of the population pharmacokinetics of ziprasidone; and assess the safety and toleration of the three ziprasidone doses.

This inpatient trial began with a placebo run-in followed by double-blind, randomized treatment up to 52 weeks. Subjects were men or women (child-bearing or non-child bearing potential) aged >18 years. Subjects had a DSM-III-R diagnosis of chronic or subchronic schizophrenia, had been hospitalized for not less than 2 months and had a Clinical Global Impression (Severity) Scale score of 5 (markedly ill) or less at baseline. Blood specimens for ziprasidone concentration analysis were obtained throughout the study with 145 subjects contributing 427 ziprasidone concentration values for pharmacokinetic assessment.

Appendix 1.3. Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone

A population pharmacokinetic analysis of ziprasidone concentration data from the 2 smaller pediatric studies (128-044 and 128-122) and 5 adult studies (A1281037, 128-109, 128-114, 128-115, and 128-303) with 507 subjects ranging in age from 7 to 82 years was conducted. This analysis was conducted prior to the availability of the A1281123 and A1281132 data.

A notable characteristic apparent from this combined analysis of pediatric and adult patients is that pediatric patients exhibit similar PK to adults once weight and age differences are considered.

The structural pharmacokinetic model identified was a one-compartment model with first order absorption and linear clearance, parameterized in terms of apparent oral clearance (CL/F), the volume of distribution of the central (V/F) compartments and the first order absorption rate constant (Ka). Parameter estimates and associated standard errors for final pharmacokinetic model are shown below.

Table 49. Final Parameter Estimates and Variability - Retrospective Pooled Population Pharmacokinetic Analysis

Parameter (Units)		Population Mean (s.e.)		Inter-Individual Variability* (s.e.)
CL/F (L/h)	Θ_1	54.1 (2.8)	η_1	34.06 (11.6)
Effect of Weight	Θ_5	0.412 (18.1)		
Effect of Age	Θ_6	0.152 (29.6)		
V/F (L)	Θ_2	67.6 (11.1)	η_2	83.34 (19.0)
KA Capsule (h-1)	Θ_3	0.073 (7.8)	η_3	54.77 (16.8)
KA Oral Suspension (h-1)	Θ_4	0.128 (14.3)	η_4	26.04 (55.2)
Effect of Age on KA	Θ_7	-0.288 (33.9)		
ALAG1 Oral Suspension (h)	Θ_8	0.855 (3.5)		NE
F1 Oral Suspension (%BA)	Θ_9	0.906 (3.4)		NE
CCV Residual Error (%CV)			41.11 (7.0)	
Additive Residual Error (ug/L)			0.85 (68.5)	

* - given as %CV s.e. – standard error given as %CV NE – not estimated

With respect to covariate influences, age and body weight were found to significantly impact the apparent clearance and age the absorption rate of ziprasidone. Over the range of weights in the evaluated population (22 – 160 kg), typical values of clearance ranged from 26.8 L/h to 76.1 L/h. For adults aged 35 years, over a weight range of 50 to 160 kg, clearance is estimated to range from 44.6 L/h – 72.0 L/h. For subjects weighing 70 kg, over the age range of 35 to 80 years of age, calculated values of clearance ranged from 51.2 L/h to 58.1 L/h. The model predicts that pediatric patients had substantially higher absorption rate constants, suggesting faster absorption. A notable characteristic apparent from this combined analysis of pediatric and adult patients in that pediatric patients exhibit similar PK to adults once weight and age differences are considered. There is no apparent discontinuity or change in properties between PK of adults and that of children or adolescents across the age range examined.

It is important to note that although age was identified as a significant covariate impacting clearance in this pooled analysis, its influence on overall exposure was minor, representing an approximate 12% change in clearance across ages 10 to 17. The impact of weight and age in pediatric subjects can be illustrated as follows:

Table 50. Projected Clearance: Change with Body Weight and Age - Retrospective Pooled Population Pharmacokinetic Analysis

	Apparent Clearance (L/h)		
Age (yr)	WT = 30 kg	WT = 40 kg	WT = 60 kg
8	28.9	32.5	38.4
9	29.4	33.1	39.1
10	29.9	33.6	39.8
11	30.3	34.1	40.3
12	30.7	34.6	40.9
13	31.1	35.0	41.4
14	31.4	35.4	41.8
15	31.8	35.8	42.3
16	32.1	36.1	42.7
17	32.4	36.5	43.1

Since two different formulations (capsule and oral suspension) were used in the study database, the effect of formulation was incorporated into the pharmacokinetic models developed for the capsule and oral suspension. A comparison showed that the pharmacokinetics of the oral solution had a shorter lag time and a faster absorption rate constant than the capsule and the relative bioavailability was found to be slightly lower (~10%) for the oral suspension. These findings are similar to those for study A1281123 in which both formulations were used and compared, and are also similar to PK findings in adult subjects in study A1281037.

Appendix 1.4. Population Pharmacokinetic Analysis for Ziprasidone Study A1281132

A population PK model was developed to describe the ziprasidone concentration data obtained in study A1281132 and to identify and characterize patient characteristics which influence the variability in ziprasidone pharmacokinetics. The final pharmacokinetic model for ziprasidone was a one compartment model with first order input, a lag time and linear elimination. The final parameter estimates and variances are shown in Table 51.

Table 51. Final Model Parameter Estimates: Study A1281132

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)
CL/F (L/h)	Θ_1	55.1 (7.4)	54.4 (19.8)
Effect of Weight		0.75 FIX	
V2/F (L)	Θ_2	439 (14.6)	70.4 (19.8)
Effect of Weight		1 FIX	
Ka (1/h)	Θ_3	0.292 (13.1)	
ALAG (h)	Θ_4	0.259 (24.3)	
LTBS (CCV + Additive)			
Residual Error			
CCV	Θ_5		56.9 (15.9)
Additive	Θ_6		8.34 (27.1)

* - SE given as %CV, Source: Population Pharmacokinetic Analysis for Ziprasidone Study A1281132

The ziprasidone concentration time data from the present study were well described by the final pharmacokinetic model. Body weight was identified as a significant covariate affecting clearance and volume of distribution. The model used for both the retrospective pooled population PK analyses and the separate analysis of data from A1281132 was similar but the final model in the A1281132 analysis included an absorption lag while the pooled analysis did not.

The two analyses gave generally similar results. Age had an effect on CL/F in the pooled analysis but not in A1281132. This was probably a result of the much narrower age range in A1281132 (10-18 yr vs. 7-82 yr). Body size was a significant covariate of clearance in both analyses. The inclusion of an absorption lag time in the current model for the capsule formulation resulted in a difference in the parameter estimates for KA and V/F.

Appendix 1.5. Population Pharmacokinetic Analysis for Ziprasidone Study A1281123

A population pharmacokinetics model using nonlinear mixed effects modeling (NONMEM) describing the pharmacokinetics of ziprasidone was utilized to assess the data that arose from A1281123. Separate model development was not conducted but rather a preliminary model developed and described during the Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone was applied to the data from A1281123 for comparison of individual parameter estimates and concentration profiles.

The population pharmacokinetic model utilized was a one compartment model with first order input following a lag time for the oral suspension and linear elimination. The final parameter estimates and variances are provided in the following table.

Table 52. Ziprasidone Pharmacokinetic Model Parameters: Study A1281123

Parameter (Units)	Population Mean	Inter-Individual Variability*
CL/F (L/h)	49.3	33.8
Effect of weight	0.46	
Effect of age	0.0747	
V/F (L)	68.1	34.9
Ka Capsule (1/h)	0.065	63.2
Effect of age	-0.253	
Ka Oral Suspension (1/h)	0.109	43.0
ALAG1 Oral Suspension (h)	1.41	NE
F1 Oral Suspension (%BA)	0.889	NE
CCV Residual Error (%CV)	44.0	
Additive Residual Error (µg/L)	0.731	

BA = bioavailability, CV = coefficient of variability, * = % CV, NE = not estimated

In the model used, the remaining inter-individual variability was relatively low although the residual error was still pronounced. In this model, the clearance of ziprasidone increases as body weight increases and also increases slightly as age increases. This preliminary model utilized for comparison of the A1281123 data indicated that the absorption of ziprasidone decreases as age increases. Overall the pharmacokinetic data from A1281123 was described well utilizing the previously developed preliminary retrospective model.

Appendix 1.6. Pharmacokinetic Assessment of Study 128-044

In addition to being incorporated into the Retrospective Pooled Population Pharmacokinetic Analysis of Ziprasidone (Appendix 1.3), the single dose concentration data from study 128-044 was assessed using non-compartmental analysis methods. Summary PK parameters from this study for the 3 dose groups are shown in the table below, as is the ziprasidone dose adjusted for body weight. After adjusting for body weight, the mean doses in Groups 2 and 3 were 19% and 38% lower, respectively, than the dose administered to Group 1. Consistent with this difference in dose, the mean AUC(0-∞) and Cmax values for Groups 2 and 3 were 26% and 46% lower and 12% and 29% lower, respectively, than those in Group 1. For the range of body weights included in this study (25.8 kg to 63.4 kg), exposure to ziprasidone (as measured by AUC(0-∞) and Cmax) increased with increasing dose (measured in mg/kg).

Table 53. Pharmacokinetic Results Summary: Study 128-044

Mean (%CV) of Pharmacokinetic Parameters									
Dose Group/N		**BW (kg)**	**Dose (mg/kg)**	**AUC(0-∞)[a] (ng·hr/ml)**	**Cmax[a] (ng/ml)**	**Tmax (hr)**	**Kel (1/hr)**	**T1/2[b] (hr)**	**Cl/F[a] (ml/min/kg)**
Group 1 20 mg	8	63.4(6)	0.32(6)	457(25)	51(44)	5.5(57)	0.171(21)	4.1	11.5(21)
Group 2[c] 10 mg	7	40.8(25)	0.26(22)	338(30)	45(45)	5.1(21)	0.210(27)	3.3	12.4(19)
Group 3 5 mg	8	25.8(8)	0.20(9)	247(30)	36(38)	5.0(57)	0.213(45)	3.3	13.1(27)

BW = Body weight, [a] geometric mean, [b] $T_{1/2}$ = 0.693/mean Kel
[c] Summary statistics exclude Subject 7440011. Exclusion was based on systemic exposure being greater than 8 times the Group 2 mean. Pharmacokinetic data for this 13 year old female subject were as follows: Body weight: 38.3 kg; dose: 0.26 mg/kg; AUC(0-∞): 3748 ng·hr/ml; Cmax: 366 ng/ml; Tmax: 4.0 hr; Kel: 0.240 1/hr; T1/2: 2.9 hr; Cl/F: 1.2 ml/min/kg.

Across the range of mean ages (7.6 to 14.1) and mean body weights (25.8 kg to 63.4 kg) included in this study, oral clearance, Tmax, and terminal elimination half life were comparable across study groups. Exposure to ziprasidone increased in a linear fashion with increasing weight-adjusted dose. When converted to units of L/h utilizing the mean body weights in each group, the typical clearance values become 43.7, 30.4 and 20.3 L/h for the 20 (58 – 69 kg), 10 (31 – 56 kg) and 5 (22 – 29 kg) mg dose groups, respectively, generally consistent with values obtained across all four pediatric studies, indicating a similar increase with increasing body weight.

Appendix 1.7. Population Pharmacokinetic Assessment of Study 128-122

The ziprasidone serum concentration data from this study was assessed using a two compartment population pharmacokinetic model previously developed with preliminary data from study 128-044. The data from 128-122 was assessed by comparison of the observed concentration data to the concentrations predicted using the population PK model. The 2 compartment pharmacokinetic model used was parameterized using clearance (CL/F), volume of the central compartment (Vc/F), volume of the peripheral compartment (Vp/F), the absorption coefficient (Ka), intercompartmental clearance (Q) and an absorption lag time (Alag1). The model included log-linear interindividual variance parameters on CL/F, Vc/F, Ka and Alag1 and employed a proportional residual error model. The model was developed previously to the models identified with either the Retrospective Pooled Population PK Analysis or the analyses for studies A1281132 or A1281123 was parameterized differently in terms of age and body size. Covariate analysis revealed that subjects younger than 10 years had a systemic clearance of approximately half that of subjects greater than 10 years old. The estimated pharmacokinetic parameters that were used to predict individual concentrations from study 128-122 are as follows:

Table 54. Estimated Pharmacokinetic Parameters: Study 128-122

Pharmacokinetic Parameter		Estimated Value	% CV
Systemic clearance; Age <10	CL/F (L/hr)	23.1	3.1
Systemic clearance; Age >10	CL/F (L/hr)	41.8	10
Volume of central compartment	V_C/F (L)	187	28
Volume of peripheral compartment	V_P/F (L)	27.1	82
Absorption coefficient	Ka (1/hr)	0.334	9.8
Intercompartmental clearance	Q (L/hr)	8.28	65
Absorption lag time	Alag1 (hr)	0.787	11
Random effects terms	$\eta_{CL/F}$	0.0252	60
	$\eta_{Vc/F}$	0.179	59
	η_{Ka}	0.726	79
	η_{Alag1}	0.0782	110
	ε_1 (ng/ml)	0.143	36

Predictions of clearance was related to both subject age and weight, consistent with the correlation of age and weight in subjects in this age range (7-14 years). Prediction of clearance and volume of distribution in the central compartment (Vc/F) were not related to gender. However, there was some suggestion that Vc/F is related to subject weight and/or age. This was consistent with the analysis of previous study data from 128-044 which indicated that, although both age and subject weight appeared to be related to prediction of volume in the central compartment, neither variable was significant once age was included as a covariate in the prediction of clearance. Note that identification of age as the primary patient characteristic determining variability in clearance for data from study 128-122 was likely due to the small number of patients and very small number of observations available for analysis. Subsequent analyses with data from a wider range of data and subjects indicate that weight is the primary covariate in describing clearance of ziprasidone (Appendices 1.3 - 1.5).

Appendix 2. Summaries of Pharmacokinetic/Pharmacodynamic Assessments of the Effect of Ziprasidone Concentration on QT

Appendix 2.1. PKPD QTc Concentration Analysis for Study A1281132

In study A1281132, ziprasidone was associated with a concentration dependent increase in QTcF, Fridericia correction of QT for heart rate. The slope of the regression line expressed as population mean (90%CI) was 0.0852 (0.067 to 0.106) msec/(ng/mL) with QTcF (Table 55). Expected QTc changes with various dose regimens were calculated. For example, in children and adolescents, ziprasidone showed a similar median maximum increase in ΔQTcF at the highest dose (160 mg/day) of approximately 14 msec, based upon a steady state median ziprasidone Cmax concentration using the final population PK model for A1281132.

Table 55. Ziprasidone ΔQTcF vs Concentration Final Model Parameter Estimates (Study A1281132)

Parameter (Units)		Population Mean (90% CI)	SD Inter-Individual Variance (90% CI)
Intercept (msec)	θ1	$-2.6e^{-7}$ (-0.325 to $2.75e^{-9}$)*	10.9 (9.42 to 13.56)
Slope (msec/(ng/mL)	θ2	0.0852 (0.067 to 0.106)	0.0223 (0.0018 to 0.0620)
Weight Effect on Intercept	θ3	42.8 (-0.526 to 51.8)	NA
Additive Residual Error (msec, as SD)		9.96 (9.19 to 10.583)	
* intercept parameter estimate divided by 100,000			

Appendix 2.2. PKPD QTc Concentration Analysis for Study A1281123

The relationship between measured ziprasidone concentrations and change in QT interval from baseline was evaluated using a model developed on time-matched QT and concentration data from study A1281123. The primary endpoint was the ΔQTcF, the time-matched change from baseline Fridericia correction of the QT interval (msec). The final model parameter estimates and associated 95% confidence intervals are provided in the following table.

Table 56. Ziprasidone ΔQTcF vs Concentration Final Model Parameter Estimates (Study A1281123)

Parameter (Units)	Population Mean (95% CI)	SD Inter-Individual Variance (95% CI)
Intercept (msec)	0.846 (-6.47 to 8.64)	11.3 (7.64 to 14.1)
Slope (msec/(ng/mL)	0.139 (-0.0132 to 0.299)	0.0768 (~ 0 to 0.159)
Additive Residual Error (msec as SD)		14.0 (12.0 to 15.7)

CI = confidence interval, SD = standard deviation

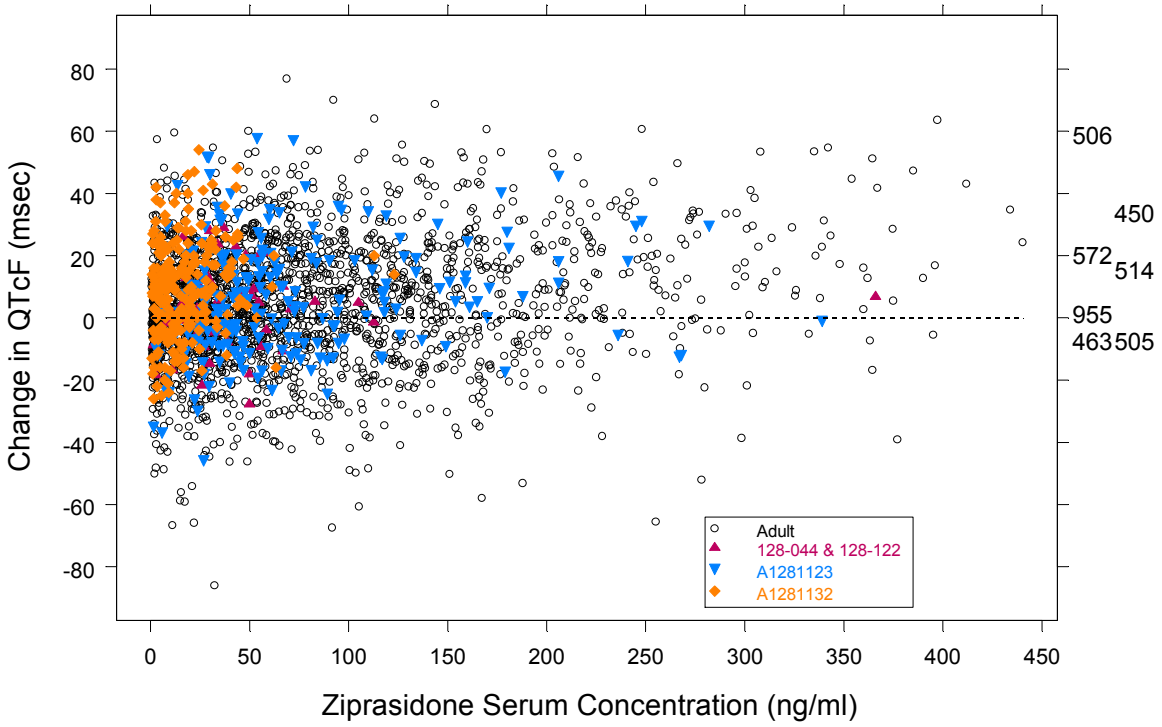
Ziprasidone was associated with a concentration dependent increase in QTcF. The slope of the regression line expressed as population mean (95% CI) was 0.139 (-0.0132 to 0.299) ng/mL. Note that, although a positive slope was identified in this analysis, the estimated 95% CI includes the null effect of zero (-0.0132 to 0.299). Expected QTcF change at the peak concentration of 118 ng/mL measured in the study was approximately 16 msec.

Appendix 2.3. Comparison of ΔQTcF Ziprasidone Concentration Relationships in Pediatric and Adult Patients

Graphical and numerical comparisons of adult and pediatric ziprasidone concentrations and associated QTcF values were conducted using data from 4 pediatric studies (N=180 subjects/n= 506 concentration-ΔQTcF data pairs) and from 27 adult ziprasidone studies (N=1383 Subjects/n= 2086 concentration-ΔQTcF data pairs). Observed pediatric ziprasidone concentrations were contained within the range of adult values. When pediatric patient

concentration-QTcF values were plotted, the distributions of pediatric and adult values were similar (Figure 14).

Figure 14. Ziprasidone Concentration versus Change in QTcF



Note that Figure 14 graphically presents the range of Change from QTcF from Baseline vs. ziprasidone concentration data observed from a wide range of studies, both adult and pediatric to illustrate the similar distribution of response across the observed concentration ranges for both patient populations and not necessarily present a particular pharmacokinetic-pharmacodynamic relationship. Figure 14 includes subjects with a single Change from Baseline QTcF and ziprasidone concentration pair in the graphical distribution. As a consequence, as a naïve pooled presentation of the data, data from 573 subjects without corresponding concentrations at the baseline ECG measurement as well as from 797 subjects with only a single observation are incorporated in the graphical representation.

Although the original dataset utilized data from a total of 31 studies, in order to assess potential differences in the ΔQTcF-concentration relationship between adults and pediatric subjects, a subset including only data from subjects with more than 1 data point were used in a regression analysis. In addition, this analysis dataset retained subjects without concentration data at baseline and note that concentration values were not imputed. The resulting analysis dataset, incorporates data from 21 studies, 17 (128-015, 054, 101, 102, 106, 106E, 108, 108E, 109, 114, 115, 116B, 117, 120, 303, 306, 601) adult and 4 (128-044, 128-122, A1281123, A1281132) pediatric with a total of 2420 (1803 Adult; 617 Pediatric) ΔQTcF vs. concentration data pairs from 857 (684 Adult; 173 Pediatric) subjects. Of these

857 subjects, 419 (309 Adult; 110 Pediatric) had no paired baseline concentration-ECG measurements but otherwise had more than one datapair for the regression. Four hundred thirty eight (438; 375 Adult; 63 Pediatric) did have baseline data pairs.

The concentration response has been characterized for the ΔQTcF – concentration relationship for ziprasidone in pediatric subjects. Although the slopes estimated from the meta-analysis of observational data (Section 5.7.1.1) available for pediatric and adult subjects are numerically different (Table 38), the overall distributions of the observed change from baseline response data over the range of concentrations was similar (Figure 14). Note also that the placebo-corrected mean maximum change from baseline QTcF for the A1281132 study was 17.8 msec similar to the 15.9 msec change observed for adult subjects administered 80 mg BID in study 128-054.

Appendix 2.4. US Prescribing Information

GEODON®
(ziprasidone HCl)
Capsules

GEODON®
(ziprasidone mesylate)
for Injection
FOR IM USE ONLY

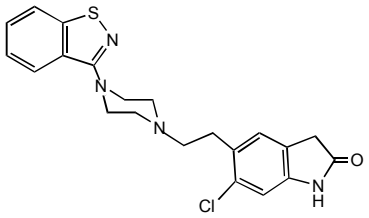
WARNING

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).

DESCRIPTION

GEODON® is available as GEODON Capsules (ziprasidone hydrochloride) for oral administration and as GEODON for Injection (ziprasidone mesylate) for intramuscular injection. 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 **Preparation for Administration**) for intramuscular administration. 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).

CLINICAL PHARMACOLOGY

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).

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.

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.

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.

Special Populations

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.

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

Race - No specific pharmacokinetic study was conducted to investigate the effects of race. Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences in the pharmacokinetics of ziprasidone. Dosage modifications for race are, therefore, not recommended.

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.

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 BID 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.

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 BID 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.

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.

Drug-Drug Interactions

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. *In vivo* studies have revealed no effect of ziprasidone on the pharmacokinetics of dextromethorphan, estrogen, progesterone, or lithium (see **Drug Interactions** under **PRECAUTIONS**).

In vivo studies have revealed an approximately 35% decrease in ziprasidone AUC by concomitantly administered carbamazepine, an approximately 35-40% increase in ziprasidone AUC by concomitantly

administered ketoconazole, but no effect on ziprasidone's pharmacokinetics by cimetidine or antacid (see **Drug Interactions** under **PRECAUTIONS**).

Clinical Trials

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 long-term (52-week) trial. All trials were in 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:
(1) In a 4-week, placebo-controlled trial (n=139) comparing 2 fixed doses of ziprasidone (20 and 60 mg BID) with placebo, only the 60 mg BID 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.

(2) In a 6-week, placebo-controlled trial (n=302) comparing 2 fixed doses of ziprasidone (40 and 80 mg BID) 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 BID had a numerically greater effect than 40 mg BID, the difference was not statistically significant.

(3) In a 6-week, placebo-controlled trial (n=419) comparing 3 fixed doses of ziprasidone (20, 60, and 100 mg BID) 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 BID 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 BID to 100 mg BID dose range.

(4) In a 4-week, placebo-controlled trial (n=200) comparing 3 fixed doses of ziprasidone (5, 20, and 40 mg BID), none of the dose groups was statistically superior to placebo on any outcome of interest.

(5) A study was conducted in chronic, symptomatically stable schizophrenic inpatients (n=294) randomized to 3 fixed doses of ziprasidone (20, 40, or 80 mg BID) or placebo and followed for

52 weeks. Patients were observed for "impending psychotic relapse," defined as CGI-improvement score of ≥6 (much worse or very much worse) and/or scores ≥6 (moderately severe) on the hostility or uncooperativeness items of the PANSS on two consecutive days. Ziprasidone was significantly superior to placebo in both time to relapse and rate of 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.

Bipolar Mania
The efficacy of ziprasidone in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder with an acute 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 bipolar mania follow:
(1) In a 3-week placebo-controlled trial (n=210), the dose of ziprasidone was 40 mg BID on Day 1 and 80 mg BID on Day 2. Titration within the range of 40-80 mg BID (in 20 mg BID 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.

(2) In a second 3-week placebo-controlled trial (n=205), the dose of ziprasidone was 40 mg BID on Day 1. Titration within the range of 40-80 mg BID (in 20 mg BID 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.

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 pre-marketing 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.

INDICATIONS AND USAGE

Schizophrenia
Ziprasidone is indicated for the treatment of schizophrenia. When deciding among the alternative treatments available for this condition, 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**). 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**).

The efficacy of oral ziprasidone was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**).

In a placebo-controlled trial involving the follow-up for up to 52 weeks of stable schizophrenic inpatients, GEODON was demonstrated to delay the time to and rate of relapse. The physician who elects to use GEODON for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar Mania
Ziprasidone is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. A manic episode is a distinct period of abnormally and persistently elevated, expansive, or irritable mood. A mixed episode is characterized by the criteria for a manic episode in conjunction with those for a major depressive episode (depressed mood, loss of interest or pleasure in nearly all activities).

The efficacy of ziprasidone in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see **CLINICAL**

PHARMACOLOGY).

The effectiveness of ziprasidone for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use ziprasidone for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Acute Agitation in Schizophrenic Patients
Ziprasidone 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 the agitation. "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. The efficacy of intramuscular ziprasidone for acute agitation in schizophrenia was established in single-day controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY**). 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.

CONTRAINDICATIONS

QT Prolongation
Because of ziprasidone's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, ziprasidone is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**).

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. Ziprasidone is also contraindicated with 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**).

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

WARNINGS

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 (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING).

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, and see Drug Interactions under PRECAUTIONS). 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).

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 BID).

In placebo-controlled trials, oral ziprasidone increased the QTc interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials with oral ziprasidone, the electrocardiograms of 2/2988 (0.06%) patients who received 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, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of ziprasidone at recommended doses 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; Other Events Observed During Post-marketing Use).

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).

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.

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.

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.

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 events is not completely understood. However, epidemiological studies, which did not include GEODON, suggest an increased risk of treatment-emergent hyperglycemia-related adverse events 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 events 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.

PRECAUTIONS

General
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 events were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, ziprasidone should be discontinued.

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).

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.

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 also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis)**.

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 **Carcinogenesis**). 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.

Potential for Cognitive and Motor Impairment - Somnolence was a commonly reported adverse event 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.

Priapism - One case of priapism was reported in the premarketing database. While the relationship of the event 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.

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.

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.

Use in Patients with Concomitant Illness - Clinical experience with ziprasidone in patients with certain concomitant systemic illnesses (see **Renal Impairment** and **Hepatic Impairment** under **CLINICAL PHARMACOLOGY**, **Special Populations**) is limited.

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 **QTc Prolongation** under **WARNINGS** and **Orthostatic Hypotension** under **PRECAUTIONS**).

Information for Patients
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.

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 repleted 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).**

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:

Pharmacodynamic Interactions
(1) Ziprasidone should not be used with any drug that prolongs the QT interval **(see CONTRAINDICATIONS).**
(2) Given the primary CNS effects of ziprasidone, caution should be used when it is taken in

combination with other centrally acting drugs.

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

(4) Ziprasidone may antagonize the effects of levodopa and dopamine agonists.

Pharmacokinetic Interactions

The Effect of Other Drugs on Ziprasidone

Carbamazepine - Carbamazepine is an inducer of CYP3A4; administration of 200 mg BID 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 coadministration of 30 mL of Maalox® with ziprasidone did not affect the pharmacokinetics of ziprasidone.

In addition, 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.

Effect of Ziprasidone on Other Drugs

In vitro studies revealed little potential for ziprasidone to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with ziprasidone due to displacement (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**).

Lithium - 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.

Oral Contraceptives - Ziprasidone at a dose of 20 mg BID did not affect the pharmacokinetics of concomitantly administered oral contraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg).

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.

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 **Hyperprolactinemia** under **PRECAUTIONS**, **General**).

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.

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.

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

Nursing Mothers - It is not known whether, and if so in what amount, ziprasidone or its metabolites are excreted in human milk. It is recommended that women receiving ziprasidone should not breast feed.

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

Geriatric Use - Of the approximately 4500 patients treated with ziprasidone in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability of ziprasidone or for reduced clearance of ziprasidone in the elderly compared to younger adults. 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.

ADVERSE REACTIONS

Premarketing experience

The premarketing development program 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. 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.

The premarketing development program 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 events 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. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART dictionary terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment

emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

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.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials of Oral Ziprasidone
Schizophrenia--Approximately 4.1% (29/702) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among ziprasidone patients (1%) compared to no placebo patients (see **PRECAUTIONS**).

Bipolar Mania--Approximately 6.5% (18/279) of ziprasidone-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the ziprasidone-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among ziprasidone patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials--The most commonly observed adverse events 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) are shown in Tables 1 and 2.

Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of Ziprasidone in 4- and 6-Week Trials -- SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Adverse Event	Ziprasidone (N=702)	Placebo (N=273)
Somnolence	14	7
Respiratory Tract Infection	8	3

Table 2: Common Treatment-Emergent Adverse Events Associated with the Use of Ziprasidone in 3-Week Trials -- BIPOLAR MANIA

	Percentage of Patients Reporting Event	
Adverse Event	Ziprasidone (N=279)	Placebo (N=136)
Somnolence	31	12
Extrapyramidal Symptoms*	31	12
Dizziness**	16	7
Akathisia	10	5
Abnormal Vision	6	3
Asthenia	6	2
Vomiting	5	2

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

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

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

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) in predominantly patients with schizophrenia, including only those events 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 3. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials -- SCHIZOPHRENIA

	Percentage of Patients Reporting Event	
Body System/Adverse Event	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 event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 5% in schizophrenia trials.

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

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 3 weeks) in patients with bipolar mania, including only those events 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 4. Treatment-Emergent Adverse Event Incidence In Short-Term Oral Placebo-Controlled Trials – BIPOLAR MANIA

	Percentage of Patients Reporting Event	
Body System/Adverse Event	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 event terms: extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis and twitching. None of these adverse events occurred individually at an incidence greater than 10% in bipolar mania trials.

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

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

Dose Dependency of Adverse Events 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 event to dose for the following events: 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 event 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 **PRECAUTIONS**).

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 event 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**). 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 Events Observed During the Premarketing Evaluation of Oral Ziprasidone
Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with ziprasidone in schizophrenia trials at multiple doses >4 mg/day within the database of 3834 patients. All reported events are included except those already listed in Table 3 or elsewhere in labeling, those event terms that were so general as to be uninformative, events reported only once and that did not have a substantial probability of being acutely life-threatening, events that are part of the illness being treated or are otherwise common as background events, and events considered unlikely to be drug-related. It is important to emphasize that, although the events reported occurred during treatment with ziprasidone, they were not necessarily caused by it.

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

Body as a Whole: *Frequent:* abdominal pain, 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.

Adverse Findings Observed in Trials of Intramuscular Ziprasidone

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

Table 5 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy with intramuscular ziprasidone in 1% or more of patients.

In these studies, the most commonly observed adverse events 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 5. Treatment-Emergent Adverse Event Incidence In Short-Term

Fixed-Dose Intramuscular Trials

	Percentage of Patients Reporting Event		
Body System/Adverse Event	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

Other Events Observed During Post-marketing Use

Adverse event reports not listed above that have been received since market introduction include rare occurrences of the following (no causal relationship with ziprasidone has been established): *Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors - see **WARNINGS**); *Digestive System Disorders:* Swollen tongue; *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; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *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.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class - Ziprasidone is not a controlled substance.

Physical and Psychological 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).

OVERDOSAGE

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, 3240 mg, the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

In post-marketing use, adverse events reported in association with ziprasidone overdose generally included extrapyramidal symptoms, somnolence, tremor, and anxiety.

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.

DOSAGE AND ADMINISTRATION

Schizophrenia
When deciding among the alternative treatments available for schizophrenia, 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**).

Initial Treatment
GEODON® Capsules should be administered at an initial daily dose of 20 mg BID with food. In some patients, daily dosage may subsequently be adjusted on the basis of individual clinical status up to 80 mg BID. 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, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment.

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

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, systematic evaluation of ziprasidone has shown that its efficacy in schizophrenia is maintained for periods of up to 52 weeks at a dose of 20 to 80 mg BID (see **CLINICAL PHARMACOLOGY**). No additional benefit was demonstrated for doses above 20 mg BID. Patients should be periodically reassessed to determine the need for maintenance treatment.

Bipolar Mania
Initial Treatment
Oral ziprasidone should be administered at an initial daily dose of 40 mg BID with food. The dose should then be increased to 60 mg or 80 mg BID on the second day of treatment and subsequently adjusted on the basis of toleration and efficacy within the range 40-80 mg BID. In the flexible-dose clinical trials, the mean daily dose administered was approximately 120 mg (see **CLINICAL PHARMACOLOGY**).

Maintenance Treatment
There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of mania with ziprasidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of ziprasidone in such longer-term treatment (i.e., beyond 3 weeks).

Intramuscular Administration for Acute Agitation in Schizophrenia
The recommended dose is 10 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.

Dosing in Special Populations
Oral: Dosage adjustments are generally not required on the basis of age, gender, race, or renal or hepatic impairment.

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.

Preparation for Administration
GEODON® for Injection (ziprasidone mesylate) should only be administered by intramuscular injection. 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.

HOW SUPPLIED

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

Storage and Handling — 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 **Preparation for Administration**) for intramuscular administration. 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

Storage and Handling - 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).

Rx only

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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.

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 acute manic or mixed episodes associated with 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
- Abnormal muscle movements, including tremor, shuffling, and uncontrolled involuntary movements
- Diarrhea

- Restlessness
- 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 events 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 events. 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.

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