

**DRUGDEX® Evaluations****ZIPRASIDONE****0.0 Overview**

- 1) Class
  - a) This drug is a member of the following class(es):
    - Antipsychotic
    - Benzisothiazoyl
- 2) Dosing Information
  - a) Ziprasidone Hydrochloride
    - 1) Adult
      - a) Bipolar I disorder, acute manic or mixed episodes
        - 1) day 1, 40 mg twice daily with food; day 2, 60 to 80 mg twice daily; then adjust to 40 to 80 mg twice daily (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005)
      - b) Schizophrenia
        - 1) initial, 20 mg ORALLY twice a day with food; may increase dosage every 2 days up to 80 mg twice a day (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005)
        - 2) maintenance, 20 to 80 mg ORALLY twice a day (MAX recommended dose is 80 mg twice a day). In order to ensure use of the lowest effective dose, ordinarily patients should be observed for improvement for several weeks before upward dosage adjustment (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005)
    - 2) Pediatric
      - a) safety and effectiveness in pediatric patients have not been established
  - b) Ziprasidone Mesylate
    - 1) Adult
      - a) Agitation, acute - Schizophrenia
        - 1) 10 mg IM every 2 hr (MAX dose 40 mg/day) OR 20 mg IM every 4 hr (MAX dose 40 mg/day); oral ziprasidone should replace IM administration as soon as possible; IM administration for more than 3 consecutive days has not been studied (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005)
    - 2) Pediatric
      - a) safety and effectiveness in pediatric patients have not been established
- 3) Contraindications
  - a) Ziprasidone Hydrochloride
    - 1) Concomitant administration with arsenic trioxide, chlorpromazine, class Ia and III anti-arrhythmics and other drugs that cause QT prolongation, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, or mefloquine
    - 2) Concomitant administration with mesoridazine, moxifloxacin, pentamidine, pimozone, probutolol, sotalol, sparfloxacin, tacrolimus, or thioridazine
    - 3) QT prolongation history including congenital long QT syndrome
    - 4) History of cardiac arrhythmias
    - 5) Hypersensitivity to ziprasidone
    - 6) Recent acute myocardial infarction
    - 7) Uncompensated heart failure
  - b) Ziprasidone Mesylate
    - 1) Concomitant administration with arsenic trioxide, chlorpromazine, class Ia and III anti-arrhythmics and other drugs that cause QT prolongation, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, or mefloquine
    - 2) Concomitant administration with mesoridazine, moxifloxacin, pentamidine, pimozone, probutolol, sotalol, sparfloxacin, tacrolimus, or thioridazine
    - 3) QT prolongation history including congenital long QT syndrome
    - 4) History of cardiac arrhythmias
    - 5) Hypersensitivity to ziprasidone
    - 6) Recent acute myocardial infarction
    - 7) Uncompensated heart failure
- 4) Serious Adverse Effects
  - a) Ziprasidone Hydrochloride
    - 1) Diabetes mellitus
    - 2) Hyperglycemia
    - 3) Neuroleptic malignant syndrome
    - 4) Prolonged QT interval
    - 5) Seizure
    - 6) Syncope
    - 7) Tachyarrhythmia
    - 8) Tardive dyskinesia
    - 9) Torsades de pointes
  - b) Ziprasidone Mesylate
    - 1) Diabetes mellitus
    - 2) Hyperglycemia
    - 3) Priapism
    - 4) Prolonged QT interval
    - 5) Seizure
    - 6) Syncope
    - 7) Tachyarrhythmia
    - 8) Tardive dyskinesia

- 5) Clinical Applications
  - a) Ziprasidone Hydrochloride
    - 1) FDA Approved Indications
      - a) Bipolar I disorder, acute manic or mixed episodes
      - b) Schizophrenia
  - b) Ziprasidone Mesylate
    - 1) FDA Approved Indications
      - a) Agitation, acute - Schizophrenia

## 1.0 Dosing Information

Drug Properties  
Storage and Stability  
Adult Dosage

### 1.1 Drug Properties

- A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
- B) Synonyms
  - Ziprasidone
  - Ziprasidone HCl
  - Ziprasidone Hydrochloride
- C) Physicochemical Properties
  - 1) Molecular Weight
    - a) 467.42(Prod Info Geodon™, 2001)

### 1.2 Storage and Stability

- A) Oral route
  - 1) Ziprasidone capsules should be protected from light and stored at a controlled room temperature between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Geodon(R), 2002ag).
- B) Parenteral route
  - 1) Ziprasidone for injection, in dry form, should be protected from light and stored at a controlled room temperature between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit). The reconstituted solution is stable for 7 days if refrigerated (2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit)) or for up to 24 hours at room temperature when protected from light (Prod Info Geodon(R), 2002ag).

### 1.3 Adult Dosage

Normal Dosage  
Dosage in Renal Failure  
Dosage in Hepatic Insufficiency  
Dosage in Geriatric Patients

#### 1.3.1 Normal Dosage

Ziprasidone Hydrochloride  
Ziprasidone Mesylate

##### 1.3.1.A Ziprasidone Hydrochloride

###### 1.3.1.A.1 Oral route

Bipolar I disorder, acute manic or mixed episodes  
Schizophrenia

###### 1.3.1.A.1.a Bipolar I disorder, acute manic or mixed episodes

- 1) For BIPOLAR MANIA, the recommended initial dose is 40 milligrams twice daily with food. On the second day of treatment, the dose should be increased to 60 or 80 milligrams twice daily and thereafter adjusted according to tolerance and efficacy within the range of 40 to 80 milligrams twice daily. There are no recommendations for maintenance treatment (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

###### 1.3.1.A.1.b Schizophrenia

- 1) For SCHIZOPHRENIA the initial daily dose is 20 milligrams (mg) twice daily with food. In some patients daily dosage may be adjusted up to 80 mg twice daily. Adjustments, if indicated, should occur at intervals of not less than 2 days. Efficacy in short-term clinical trials occurred with dosages between 20 to 100 mg twice daily. Initial dosages above 80 mg twice daily are not recommended and the safety of dosages above 100 mg twice daily have not been evaluated. To ensure the lowest effective dose, patients should be observed for improvement for several weeks before upward dosage adjustment (Prod Info Geodon(R), 2002ah).

##### 1.3.1.B Ziprasidone Mesylate

###### 1.3.1.B.1 Intramuscular route

###### 1.3.1.B.1.a Agitation, acute - Schizophrenia

- 1) For ACUTE AGITATION IN SCHIZOPHRENIA the recommended intramuscular dose is 10 to 20 milligrams (mg) as needed to a maximum daily dose of 40 mg. The 10 mg dose may be given every 2 hours and 20 mg dose may be given every 4 hours (maximum dose=40 mg/day). Intramuscular dosing of ziprasidone for more than 3 days has not been studied. If long-term therapy is indicated, oral ziprasidone should replace intramuscular administration as soon

as possible (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005).

2) Ziprasidone 10 milligrams (mg) intramuscularly (IM) produced a rapid reduction in symptoms of acute agitation and was significantly more effective ( $p$  less than 0.01) compared to a 2 mg IM dose up to 4 hours after the first injection (Lesem et al, 2001).

### 1.3.2 Dosage in Renal Failure

#### A) Ziprasidone Hydrochloride

1) No dosage adjustment should be necessary for mild-to-moderate renal impairment (creatinine clearance 10 to 60 milliliters/minute); no clinically significant effect on oral ZIPRASIDONE pharmacokinetics was found in these patients (Prod Info Geodon(R), 2002ah; Aweeka et al, 2000).

#### B) Ziprasidone Mesylate

1) Ziprasidone for injection should be used with caution in patients with impaired renal function as the injection contains a cyclodextrin sodium excipient that is eliminated by renal filtration (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005).

### 1.3.3 Dosage in Hepatic Insufficiency

#### A) Ziprasidone Hydrochloride

##### 1) ORAL

a) No dosage adjustment is necessary for mild-to-moderate hepatic impairment (chronic and stable, Child-Pugh classification A or B); the pharmacokinetics of ZIPRASIDONE were not significantly different in subjects with mild-to-moderate liver disease (Prod Info Geodon(R), 2002ah; Everson et al, 2000).

### 1.3.4 Dosage in Geriatric Patients

#### A) Ziprasidone Hydrochloride

1) No dosage adjustment is thought to be necessary for elderly patients; no clinically significant difference in ziprasidone pharmacokinetics was found between healthy young and elderly volunteers (Prod Info Geodon(R), 2002ah; Wilner et al, 2000).

#### B) Ziprasidone Mesylate

1) No dosage adjustment is thought to be necessary for elderly patients; no clinically significant difference in ziprasidone pharmacokinetics was found between healthy young and elderly volunteers (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Wilner et al, 2000).

## 2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

### 2.1 Onset and Duration

#### A) Onset

##### 1) Peak Response

a) SCHIZOPHRENIA, ORAL: 4 weeks (Harrigan et al, 1996a).

### 2.2 Drug Concentration Levels

#### A) Time to Peak Concentration

1) ORAL: 4 to 5 hours (Miceli et al, 2000; Ereshefsky, 1996; Miceli et al, 1995).

a) Fed, 4.5 hours; fasted, 3.6 hours (Hamelin et al, 1998).

2) INTRAMUSCULAR: 60 minutes (Prod Info Geodon(R), 2002aj).

#### B) Area Under the Curve

1) 627.2 ng x hr/mL fed; 371.0 ng x hr/mL fasted (Hamelin et al, 1998).

a) Oral, fed, multiple-dose: 109.8 to 1027.9 ng x hr/mL (10 to 120 mg/day) (Miceli et al, 2000).

b) Steady-state pharmacokinetics of ziprasidone did not differ between genders (Caccia, 2000).

### 2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

#### 2.3.1 Absorption

##### A) Bioavailability

1) ORAL: 60% (Ereshefsky, 1996; Miceli et al, 1995).

2) INTRAMUSCULAR: 100% (Prod Info Geodon(R), 2002aj).

##### B) Effects of Food

1) increased bioavailability (Ereshefsky, 1996; Miceli et al, 1995).

a) Dosing concurrent with high-fat meals increases systemic exposure to the drug, including area under the time-concentration curve, maximum concentration, and time to maximum concentration, while decreasing half-life (Caccia, 2000; Hamelin et al, 1998).

#### 2.3.2 Distribution

##### A) Distribution Sites

##### 1) Protein Binding

a) Greater than 99% (Prod Info Geodon(R), 2002aj; Aweeka et al, 2000a; Everson et al, 2000a; Ereshefsky, 1996).

- B) Distribution Kinetics
  - 1) Volume of Distribution
    - a) 1.5 L/kg (Prod Info Geodon(R), 2002aj).

### 2.3.3 Metabolism

- A) Metabolism Sites and Kinetics
  - 1) LIVER, (Prod Info Geodon(R), 2002aj; Ereshefsky, 1996).
    - a) CYP3A4 is the predominant isoenzyme involved in ZIPRASIDONE metabolism (Prakash et al, 2000; Caccia, 2000).
    - b) ZIPRASIDONE does not cause clinically significant inhibition of CYP2D6 (Wilner et al, 2000a; Prakash et al, 2000).
- B) Metabolites
  - 1) Metabolites inactive at 5HT-2A/dopamine D2 receptors (Ereshefsky, 1996).
  - 2) Ziprasidone sulfoxide (major) (Prod Info Geodon(R), 2002aj; Prakash et al, 2000).
  - 3) Benzisothiazole sulphoxide (Prod Info Geodon(R), 2002aj).
  - 4) Benzisothiazole sulphone (Prod Info Geodon(R), 2002aj).
  - 5) S-methylidihydroziprasidone (Prod Info Geodon(R), 2002aj).
  - 6) Ziprasidone sulfone (Prakash et al, 2000).
  - 7) Oxindole acetic acid (Prakash et al, 2000).
  - 8) Benzisothiazole piperazine (Prakash et al, 2000).

### 2.3.4 Excretion

- A) Kidney
  - 1) RENAL EXCRETION: less than 1% (Prod Info Geodon(R), 2002aj).
    - a) Less than 1% of an oral dose of ziprasidone is renally excreted as unchanged drug (Prod Info Geodon(R), 2002aj).

### 2.3.5 Elimination Half-life

- A) Parent Compound
  - 1) ELIMINATION HALF-LIFE
    - a) 7 hours oral; 2 to 5 hours intramuscular (Prod Info Geodon(R), 2002aj).
      - 1) Fed, 4.65 hours; fasted, 6.63 hours (Hamelin et al, 1998).
      - 2) Half-life dose-dependent at steady-state (not observed with single doses). Single doses, 5 to 60 mg: 3 to 4 hours. Multiple dosing: 4 to 5 hours with 5 mg twice daily, 20 mg twice daily; 8.8 hours with 40 mg twice daily; 10 hours with 60 mg twice daily (Miceli et al, 2000; Miceli et al, 1995; Ereshefsky, 1996). These changes have minimal clinical relevance.
      - 3) The half-life increased from 4 to 5 hours (10 to 40 mg/day-dose) to 9 to 10 hours at 80 to 120 mg/day dosing due to an additional elimination phase that becomes apparent only after repeated administration. The extended elimination period was not due to a decrease in clearance with higher doses (Caccia, 2000).

### 2.3.6 Extracorporeal Elimination

- A) Hemodialysis
  - 1) Dialyzable: No (Aweeka et al, 2000a).

## 3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

### 3.0.A Black Box WARNING

- 1) Ziprasidone Hydrochloride
  - a) Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 times to 1.7 times that seen 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Ziprasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005).
- 2) Ziprasidone Mesylate
  - a) Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 times to 1.7 times that seen 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Ziprasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005).

## 3.1 Contraindications

- A) Ziprasidone Hydrochloride
  - 1) Concomitant administration with arsenic trioxide, chlorpromazine, class Ia and III anti-arrhythmics and other drugs that cause QT prolongation, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, or mefloquine
  - 2) Concomitant administration with mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, sotalol, sparfloxacin, tacrolimus, or thioridazine
  - 3) QT prolongation history including congenital long QT syndrome
  - 4) History of cardiac arrhythmias
  - 5) Hypersensitivity to ziprasidone
  - 6) Recent acute myocardial infarction

- 7) Uncompensated heart failure
- B) Ziprasidone Mesylate**
  - 1) Concomitant administration with arsenic trioxide, chlorpromazine, class Ia and III anti-arrhythmics and other drugs that cause QT prolongation, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, or mefloquine
  - 2) Concomitant administration with mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, sotalol, sparfloxacin, tacrolimus, or thioridazine
  - 3) QT prolongation history including congenital long QT syndrome
  - 4) History of cardiac arrhythmias
  - 5) Hypersensitivity to ziprasidone
  - 6) Recent acute myocardial infarction
  - 7) Uncompensated heart failure

### 3.2 Precautions

- A) Ziprasidone Hydrochloride**
  - 1) Diabetes mellitus (monitor for worsening of glucose control)
  - 2) Discontinue if patient develops a rash for which there is no alternative etiology identified
  - 3) Dysphagia
  - 4) Elderly patients with dementia (unapproved use); increased risk of death (1.6 to 1.7 times greater than placebo) reported when atypical antipsychotics were used off-label to treat behavioral disorders associated with dementia; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (mostly pneumonia) (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005)
  - 5) History of seizures
  - 6) Hyperprolactinemia
  - 7) May cause orthostatic hypotension
  - 8) May cause QTc prolongation associated with the occurrence of torsades de pointes and sudden unexplained death; avoid concomitant use of other drugs known to prolong QTc interval
  - 9) Patients with bradycardia, hypokalemia, and/or hypomagnesemia may be at a greater risk for torsades de pointes and/or sudden death
  - 10) Potential Neuroleptic Malignant Syndrome
  - 11) Recent history of myocardial infarction or unstable heart disease
  - 12) Suicide
  - 13) Tardive dyskinesia
  - 14) Untoward events associated with prior use of atypical antipsychotic agents, such as risperidone, clozapine
- B) Ziprasidone Mesylate**
  - 1) Diabetes mellitus (monitor for worsening of glucose control)
  - 2) Discontinue if patient develops a rash for which there is no alternative etiology identified
  - 3) Dysphagia
  - 4) Elderly patients with dementia (unapproved use); increased risk of death (1.6 to 1.7 times greater than placebo) reported when atypical antipsychotics were used off-label to treat behavioral disorders associated with dementia; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (mostly pneumonia) (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005)
  - 5) History of seizures
  - 6) Hyperprolactinemia
  - 7) May cause orthostatic hypotension
  - 8) May cause QTc prolongation associated with the occurrence of torsades de pointes and sudden unexplained death; avoid concomitant use of other drugs known to prolong QTc interval
  - 9) Patients with bradycardia, hypokalemia, and/or hypomagnesemia may be at a greater risk for torsades de pointes and/or sudden death
  - 10) Potential Neuroleptic Malignant Syndrome
  - 11) Recent history of myocardial infarction or unstable heart disease
  - 12) Suicide
  - 13) Tardive dyskinesia
  - 14) Untoward events associated with prior use of atypical antipsychotic agents, such as risperidone, clozapine

### 3.3 Adverse Reactions

Cardiovascular Effects  
 Dermatologic Effects  
 Endocrine/Metabolic Effects  
 Gastrointestinal Effects  
 Hepatic Effects  
 Musculoskeletal Effects  
 Neurologic Effects  
 Ophthalmic Effects  
 Psychiatric Effects  
 Renal Effects  
 Respiratory Effects  
 Other

#### 3.3.1 Cardiovascular Effects

Ziprasidone Hydrochloride  
 Ziprasidone Mesylate

##### 3.3.1.A Ziprasidone Hydrochloride

Cardiovascular finding

Hypotension  
Prolonged QT interval  
Torsades de pointes

### 3.3.1.A.1 Cardiovascular finding

- a) Postural hypotension and tachycardia have been reported with oral ziprasidone use; incidence was at least 1% (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).
- b) In clinical trials related to schizophrenia, mean increase in heart rate was 1.4 beats per minute (bpm) in the group treated with oral ziprasidone, compared to a 0.2 bpm decrease in those given placebo (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

### 3.3.1.A.2 Hypotension

#### a) Summary

- 1) Postural hypotension (incidence unknown) has been reported in clinical trials following therapeutic doses (Prod Info Geodon(TM), 2002)(Citrome, 1997).

### 3.3.1.A.3 Prolonged QT interval

- a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005).

### 3.3.1.A.4 Torsades de pointes

- a) In a case report of a 28 year-old female, Q-T prolongation occurred separately during two hospital admissions, and asymptomatic non-sustained polymorphic ventricular tachycardia occurred during the second admission while using ziprasidone concurrently with other potentially arrhythmogenic medications (lithium, ciprofloxacin, fluconazole, fluoxetine, and trazodone). Upon discontinuation of ziprasidone and the other medications, the patient's Q-T interval shortened. The patient had a medical history of systemic lupus erythematosus, hypothyroidism, and a complicated history of mood disorders with psychotic features, post traumatic stress disorder, and borderline personality disorder. During the first incidence of Q-T prolongation (600 milliseconds (msec) at 68 bpm) associated with ziprasidone, the patient was lithium toxic and hypokalemic; either of which have been associated with Q-T interval abnormalities and arrhythmias. Discontinuation of ziprasidone and lithium, coupled with emergency dialysis for lithium toxicity, resulted in a decrease in Q-T interval (440 msec at 77 bpm). Two weeks later, the patient was readmitted with complaints of chest pain and an electrocardiogram revealed prolonged Q-T interval (540 msec at 58 bpm). The patient experienced a gradual lowering of potassium levels and further prolongation of Q-T interval after the interchange of ziprasidone for olanzapine coupled with the concurrent initiation of fluconazole, ciprofloxacin, trazodone, and levetiracetam. On the third day, telemetry revealed an asymptomatic non-sustained polymorphic ventricular tachycardia. She was treated by discontinuing ziprasidone, trazodone, and fluconazole, and starting metoprolol. The QT interval remained prolonged at 455 to 480 msec for the remainder of her hospitalization with no subsequent arrhythmias (Heinrich et al, 2006).

## 3.3.1.B Ziprasidone Mesylate

Orthostatic hypotension  
Prolonged QT interval

### 3.3.1.B.1 Orthostatic hypotension

#### a) Summary

- 1) Postural hypotension (incidence unknown) has been reported in clinical trials following therapeutic doses (Prod Info Geodon(TM), 2002)(Citrome, 1997).

#### b) Incidence: 5%

### 3.3.1.B.2 Prolonged QT interval

- a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005).

## 3.3.2 Dermatologic Effects

### 3.3.2.A Ziprasidone Hydrochloride

Dermatological finding  
Rash

#### 3.3.2.A.1 Dermatological finding

- a) Rash has been reported with ziprasidone use.
- b) Fungal dermatitis was reported among patients treated with oral ziprasidone in schizophrenia trials; incidence was at least 1% (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

#### 3.3.2.A.2 Rash

##### a) Summary

- 1) Rashes have been reported in 5% of patients using ziprasidone (Prod Info Geodon(R), 2002ag; Reeves &

Harrigan, 1996).

### 3.3.3 Endocrine/Metabolic Effects

Ziprasidone Hydrochloride  
Ziprasidone Mesylate

#### 3.3.3.A Ziprasidone Hydrochloride

Diabetes mellitus  
Endocrine finding  
Increased prolactin level  
Metabolic finding  
Weight gain

##### 3.3.3.A.1 Diabetes mellitus

a) Incidence: rare

b) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004). Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not.

##### 3.3.3.A.2 Endocrine finding

a) Small increases in prolactin levels have been reported with high doses of ziprasidone. Because of reports of hyperglycemia and diabetes mellitus with the use of other atypical antipsychotics, it is assumed that an increased risk for hyperglycemia and diabetes mellitus may occur with ziprasidone treatment.

##### 3.3.3.A.3 Increased prolactin level

a) Summary

1) Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Prod Info Geodon (R), 2002ag; Anon, 1996a; Kerwin & Taylor, 1996a). The changes are transient and return to baseline within 12 hours of ziprasidone administration (Miceli et al, 2000a; Goff et al, 1998a).

##### 3.3.3.A.4 Metabolic finding

a) Ziprasidone has been associated with a low risk of weight gain.

##### 3.3.3.A.5 Weight gain

a) Summary

1) Based on 4 short-term clinical trials (4 to 6 week duration) related to schizophrenia, incidence of weight gain amounting to 7% or more of baseline body weight was 10% for subjects receiving oral ziprasidone compared with 4% for those receiving placebo. Median weight gain of 0.5 kg and 0 kg occurred in the ziprasidone and placebo groups, respectively. Data collected during LONG-TERM therapy showed mean weight gain from baseline to be 1.4 kg for patients with initial low BMI (less than 23), no mean weight change for those with normal BMI (23 to 27), and 1.3 kg weight loss for patients with initially high BMI (greater than 27) (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

2) Compared to other atypical antipsychotics in a systemic review, ziprasidone is associated with a low risk of weight gain (Prod Info Geodon(R), 2002ag; Kingsbury et al, 2001; Taylor & McAskill, 2000).

b) Incidence: 0.4%

#### 3.3.3.B Ziprasidone Mesylate

Diabetes mellitus  
Endocrine finding  
Increased prolactin level  
Metabolic finding

##### 3.3.3.B.1 Diabetes mellitus

a) Incidence: rare

b) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone, increased risk has been clearly associated with other drugs of this class (atypical antipsychotics). Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004). Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not.

##### 3.3.3.B.2 Endocrine finding

a) Small increases in prolactin levels have been reported with high doses of ziprasidone. Because of reports of hyperglycemia and diabetes mellitus with the use of other atypical antipsychotics, it is assumed that an increased risk for hyperglycemia and diabetes mellitus may occur with ziprasidone treatment.

##### 3.3.3.B.3 Increased prolactin level

a) Summary

1) Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Prod Info Geodon (R), 2002ag; Anon, 1996a; Kerwin & Taylor, 1996a). The changes are transient and return to baseline within 12 hours of ziprasidone administration (Miceli et al, 2000a; Goff et al, 1998a).

**3.3.3.B.4 Metabolic finding**

a) Ziprasidone has been associated with a low risk of weight gain.

**3.3.4 Gastrointestinal Effects**

Ziprasidone Hydrochloride  
Ziprasidone Mesylate

**3.3.4.A Ziprasidone Hydrochloride**

Gastrointestinal tract finding  
Loss of appetite

**3.3.4.A.1 Gastrointestinal tract finding**

a) Constipation, dyspepsia, nausea and vomiting have been reported with ziprasidone use.

b) CONSTIPATION, DYSPEPSIA, NAUSEA and VOMITING are seen with ziprasidone use in 5% to 20% of patients (Prod Info Geodon(R), 2002ag; Harrigan et al, 1996; Kerwin & Taylor, 1996a; Reeves & Harrigan, 1996).

**3.3.4.A.2 Loss of appetite**

a) Anorexia was reported among patients treated with oral ziprasidone in schizophrenia trials; incidence was at least 1% (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

**3.3.4.B Ziprasidone Mesylate**

**3.3.4.B.1 Gastrointestinal tract finding**

a) Constipation, dyspepsia, nausea and vomiting have been reported with ziprasidone use.

b) CONSTIPATION, DYSPEPSIA, NAUSEA and VOMITING are seen with ziprasidone use in 5% to 20% of patients (Prod Info Geodon(R), 2002ag; Harrigan et al, 1996; Kerwin & Taylor, 1996a; Reeves & Harrigan, 1996).

**3.3.6 Hepatic Effects**

Ziprasidone Hydrochloride  
Ziprasidone Mesylate

**3.3.6.A Ziprasidone Hydrochloride**

**3.3.6.A.1 Increased liver enzymes**

a) Summary

1) No overt cases of hepatotoxicity have been reported. Occasional rises in liver enzymes have been reported with ziprasidone use but have not been clinically significant (Brown et al, 1999; Citrome, 1997; Kerwin & Taylor, 1996a).

b) LITERATURE REPORTS

1) Two patients in a clinical trial of ziprasidone were discontinued because of abnormal laboratory results. One patient had elevated gamma-glutamyl transpeptidase (GGT) and serum glutamic-pyruvic transaminase (SGPT/ALT) after 7 days of treatment with ziprasidone 10 milligrams/day, and one patient showed elevations of both serum glutamic-oxaloacetic transaminase (SGOT/AST) and SGPT/ALT after 8 days of treatment with ziprasidone 40 milligrams/day. Both patients had elevated GGT values at baseline. At follow-up, all values had returned or were returning to normal (Goff et al, 1998a).

**3.3.6.B Ziprasidone Mesylate**

**3.3.6.B.1 Increased liver enzymes**

a) Summary

1) No overt cases of hepatotoxicity have been reported. Occasional rises in liver enzymes have been reported with ziprasidone use but have not been clinically significant (Brown et al, 1999; Citrome, 1997; Kerwin & Taylor, 1996a).

**3.3.8 Musculoskeletal Effects**

**3.3.8.A Ziprasidone Hydrochloride**

Myalgia  
Rhabdomyolysis, following correction of hyponatremia secondary to psychogenic polydipsia

**3.3.8.A.1 Myalgia**

a) Myalgia was reported among patients treated with oral ziprasidone in schizophrenia trials; incidence was at least 1% (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004)

**3.3.8.A.2 Rhabdomyolysis, following correction of hyponatremia secondary to psychogenic polydipsia**

a) Rhabdomyolysis, possibly complicated by ziprasidone therapy, was observed in one patient following the correction of hyponatremia secondary to psychogenic polydipsia. The 50-year-old Caucasian male had begun ziprasidone therapy (40 mg twice daily) for the treatment of chronic paranoid schizophrenia three weeks before presenting with hyponatremia secondary to psychogenic polydipsia. Following the discontinuation of ziprasidone and the correction of hyponatremia via sodium chloride 0.9% administration and oral water restriction, the man developed rhabdomyolysis secondary to hyponatremia correction which manifested as an unexplained increase in serum alanine and aspartate aminotransferase

levels and total serum creatine kinase elevated to 67,259 International Units/L. Following resolution of rhabdomyolysis, ziprasidone therapy was reinitiated at a dose of 80 mg twice daily with no recurrence of increased serum creatine kinase levels. While the author notes that hyponatremia secondary to psychogenic polydipsia or its correction was most likely the primary cause of rhabdomyolysis in this patient, he also asserts that a review of the literature allows supposition that the development of rhabdomyolysis may have been complicated by the prior use of ziprasidone. The use of the Naranjo probability scale indicated a possible relationship between the use of ziprasidone and the subsequent development of rhabdomyolysis (Zaidi, 2005).

### 3.3.9 Neurologic Effects

Ziprasidone Hydrochloride  
Ziprasidone Mesylate

#### 3.3.9.A Ziprasidone Hydrochloride

Extrapyramidal disease  
Neuroleptic malignant syndrome  
Neurological finding

##### 3.3.9.A.1 Extrapyramidal disease

###### a) Summary

1) In short-term trials, the incidence of extrapyramidal symptoms (EPS) was 14% among ziprasidone-treated (oral form) subjects versus 8% in placebo-treated subjects. Terms used to describe these extrapyramidal symptoms were hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis, and twitching. However, objectively collected data on the Simpson-Angus Rating Scale for EPS and the Barnes Akathisia Scale did not generally indicate a difference between the ziprasidone and placebo groups in these trials. (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

2) AKATHISIA is the most frequently reported extrapyramidal symptom (up to 14%). The incidence of parkinsonian symptoms, dystonia, hypertonia is 0 to 6% (relative to placebo) (Prod Info Geodon(R), 2002ag); (Citrome, 1997; Reeves & Harrigan, 1996)(Harrigan et al, 1996; Kerwin & Taylor, 1996a).

3) TARDIVE DYSKINESIA developed in a 70-year-old woman nine weeks following the initiation of ziprasidone therapy (100 milligrams/day) for the treatment of major depression with mood-congruent psychotic features. Symptoms included repetitive, involuntary jaw and toe movements (Keck et al, 2004).

##### 3.3.9.A.2 Neuroleptic malignant syndrome

###### a) Incidence: rare

b) Neuroleptic malignant syndrome (NMS) developed in a 49-year-old female patient after receiving ziprasidone (20 to 60 milligrams twice daily) for the treatment of recurrent psychotic depression. Symptoms included agitation, disorganized thoughts, sweating, tachycardia, hypertension, elevated liver enzymes, and hyponatremia. Although there was no evidence of fever or muscle rigidity, a diagnosis of rhabdomyolysis secondary to NMS was made. All medications were stopped and the symptoms resolved over the next 6 days following aggressive treatment including intravenous hydration and electrolyte replacement (Murty et al, 2002).

##### 3.3.9.A.3 Neurological finding

###### a) Summary

1) SOMNOLENCE has been reported in up to 20% of patients using ziprasidone and HEADACHE has been reported up to 30% (Prod Info Geodon(R), 2002ag; Brown et al, 1999; Anon, 1996a; Reeves & Harrigan, 1996; Citrome, 1997; Kerwin & Taylor, 1996a). Less commonly reported symptoms include DIZZINESS (up to 16%), lightheadedness, insomnia, agitation, anxiety, asthenia (Citrome, 1997; Reeves & Harrigan, 1996).

b) Akathisia, tardive dyskinesia, and parkinsonian related effects have been reported with ziprasidone use. Seizures occurred in 0.4% of patients during clinical trials. Other neurologic effects include somnolence and headache with less frequent reporting of dizziness, insomnia, agitation, mania, anxiety and asthenia.

#### 3.3.9.B Ziprasidone Mesylate

Extrapyramidal disease  
Neurological finding

##### 3.3.9.B.1 Extrapyramidal disease

###### a) Summary

1) AKATHISIA is the most frequently reported extrapyramidal symptom (up to 14%). The incidence of parkinsonian symptoms, dystonia, hypertonia is 0 to 6% (relative to placebo) (Prod Info Geodon(R), 2002ag); (Citrome, 1997; Reeves & Harrigan, 1996)(Harrigan et al, 1996; Kerwin & Taylor, 1996a).

##### 3.3.9.B.2 Neurological finding

###### a) Summary

1) SOMNOLENCE has been reported in up to 20% of patients using ziprasidone and HEADACHE has been reported up to 30% (Prod Info Geodon(R), 2002ag; Brown et al, 1999; Anon, 1996a; Reeves & Harrigan, 1996; Citrome, 1997; Kerwin & Taylor, 1996a). Less commonly reported symptoms include DIZZINESS (up to 16%), lightheadedness, insomnia, agitation, anxiety, asthenia (Citrome, 1997; Reeves & Harrigan, 1996).

b) Akathisia, tardive dyskinesia, and parkinsonian related effects have been reported with ziprasidone use. Seizures occurred in 0.4% of patients during clinical trials. Other neurologic effects include somnolence and headache with less frequent reporting of dizziness, insomnia, agitation, mania, anxiety and asthenia.

### 3.3.10 Ophthalmic Effects

#### 3.3.10.A Ziprasidone Hydrochloride

**3.3.10.A.1 Oculogyric crisis**

a) Oculogyric crisis developed in an 11-year-old boy after receiving ziprasidone 20 milligrams (mg) twice daily for the treatment of pervasive developmental disorder and psychotic symptoms. Six weeks following initiation of ziprasidone therapy, the child had a sudden onset of dystonic upward deviation of the eyes. Ziprasidone was discontinued and the patient was treated with oral diphenhydramine 50 mg every 4 hours. Symptoms subsided within 30 minutes of the first dose and completely resolved within 24 hours (Ramos et al, 2003).

**3.3.12 Psychiatric Effects**

Ziprasidone Hydrochloride

Ziprasidone Mesylate

**3.3.12.A Ziprasidone Hydrochloride**

At risk for suicide

Mania

**3.3.12.A.1 At risk for suicide**

a) Because an attempt at suicide is inherently possible in patients with a psychotic illness or bipolar disorder, high-risk patients on drug therapy should receive close supervision. Also, in order to reduce the risk of overdose, ziprasidone prescriptions should be written for the smallest quantity of capsules consistent with good patient management (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

**3.3.12.A.2 Mania**

a) Summary

1) There have been several reports of mania associated with the initiation of ziprasidone therapy in bipolar patients.

b) LITERATURE REPORTS

1) HYPOMANIA developed in a 40-year-old man on two occasions following the initiation and reinitiation of ziprasidone therapy for the treatment bipolar schizoaffective disorder. Hypomania developed eight days after ziprasidone (100 milligrams (mg)/day) was initiated with ongoing venlafaxine (150 mg/day) and valproate (1200 mg/day) therapy. Symptoms included decreased need for sleep, recklessness, talkativeness, high self-esteem and racing thoughts. Ziprasidone was stopped on day 10 after a worsening of symptoms. However, 6 weeks later, the patient was restarted on ziprasidone treatment (120 mg/day) and again developed a hypomanic episode after eight days of treatment. A dysphoric mood rather than euphoric mood marked this episode and ziprasidone was again discontinued. Symptoms of hypomania resolved within 24 hours on both occasions (Brieger, 2004).

2) Four cases of mania related to the initiation of ziprasidone administration have been reported in bipolar patients. Three of the cases occurred in males 25, 26 and 45 years of age and the other case occurred in a 29-year-old female. In each case the patients were receiving multiple psychotropic medications prior to ziprasidone administration. Each patient received an initial ziprasidone dose of 20 milligrams (mg) twice a day. Manic symptoms occurred within 3 to 7 days in each of the male patients at this dosage. With the woman patient, ziprasidone dosage was increased to 100 mg/day over a period of 5 days and on the fifth day of treatment she developed manic symptoms. Within 3 to 7 days of dosage reduction or discontinuation of ziprasidone, all of the patient's manic symptoms improved. The authors speculated that ziprasidone's potent inhibition of noradrenergic and serotonergic reuptake sites may play a role in the observed switch from bipolar depression to mania (Baldassano et al, 2003).

**3.3.12.B Ziprasidone Mesylate****3.3.12.B.1 At risk for suicide**

a) Because an attempt at suicide is inherently possible in patients with a psychotic illness or bipolar disorder, high-risk patients on drug therapy should receive close supervision (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004).

**3.3.13 Renal Effects****3.3.13.A Ziprasidone Hydrochloride****3.3.13.A.1 Urogenital finding**

a) Summary

1) Priapism has been reported in a patient receiving ziprasidone 4 milligrams twice daily (Reeves et al, 2002).

b) LITERATURE REPORTS

1) An African American male developed PRIAPISM on two occasions after receiving risperidone and again after receiving ziprasidone for the treatment of schizophrenia. Following risperidone treatment (4 milligrams (mg) twice daily) the man developed an erection lasting 13 hours, which resolved upon irrigation of the corpora with phenylephrine 200 micrograms. Following discontinuation of risperidone, the patient developed another unwanted erection after an increase in his ziprasidone dose from 20 mg twice daily to 40 mg twice daily. This erection lasted 2 hours and resolved upon urination. He experienced several more unwanted erections until the ziprasidone was discontinued and the priapism quickly resolved (Reeves et al, 2002).

**3.3.15 Respiratory Effects****3.3.15.A Ziprasidone Hydrochloride****3.3.15.A.1 Rhinitis**

a) Summary

1) Rhinitis, along with unspecified respiratory symptoms have been reported with ziprasidone use (Prod Info Geodon

(R), 2002ag; Reeves &amp; Harrigan, 1996).

**3.3.16 Other****3.3.16.A Ziprasidone Hydrochloride****3.3.16.A.1 Dead**

a) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI=1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI=1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI=1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI=1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI=1.15 to 1.45), without dementia (RR, 1.45; 95% CI=1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI=1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI=1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI=1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

**3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding****A) Teratogenicity/Effects in Pregnancy****1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Geodon(R), 2002ai) (All Trimesters)**

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

**2) Crosses Placenta: Unknown****3) Clinical Management**

a) There is insufficient clinical experience with the use of ziprasidone in pregnant patients to confirm its safety in that patient population. Until additional data are available, caution should be exercised with the use of ziprasidone in pregnancy. Detailed fetal ultrasonography is recommended for monitoring fetal outcome following inadvertent exposure (Schaefer, 2001).

**4) Literature Reports**

a) No human studies of pregnancy outcomes after exposure to ziprasidone have been published, and there are no reports of outcomes after inadvertent exposure during pregnancy.

**B) Breastfeeding****1) Thomson Lactation Rating: Infant risk cannot be ruled out.**

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

**2) Clinical Management**

a) It is not known whether ziprasidone or its metabolites are excreted into human breast milk, and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. The manufacturer recommends that women receiving ziprasidone not breast feed their infants (Prod Info Ziprasidone(R), 2002).

**3) Literature Reports**

a) No reports describing the use of ziprasidone during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

**3.5 Drug Interactions****3.5.1 Drug-Drug Combinations**

Acecaïnide  
Ajmaline  
Amiodarone  
Amisulpride  
Amitriptyline  
Amoxapine  
Aprindine  
Arsenic Trioxide  
Astemizole  
Azimilide  
Bepidil  
Bretylium  
Chloral Hydrate  
Chloroquine  
Chlorpromazine  
Cisapride  
Clarithromycin  
Desipramine  
Dibenzepin  
Disopyramide  
Dofetilide  
Dolasetron

Doxepin  
 Droperidol  
 Enflurane  
 Erythromycin  
 Flecainide  
 Fluconazole  
 Fluoxetine  
 Foscarnet  
 Gatifloxacin  
 Gemifloxacin  
 Halofantrine  
 Haloperidol  
 Halothane  
 Hydroquinidine  
 Ibutilide  
 Imipramine  
 Isoflurane  
 Isradipine  
 Levofloxacin  
 Levomethadyl  
 Lidoflazine  
 Lorcainide  
 Mefloquine  
 Mesoridazine  
 Moxifloxacin  
 Nortriptyline  
 Octreotide  
 Pentamidine  
 Pimozide  
 Pirmenol  
 Prajmaline  
 Probuco  
 Procainamide  
 Prochlorperazine  
 Propafenone  
 Protriptyline  
 Quinidine  
 Ranolazine  
 Risperidone  
 Sematilide  
 Sertindole  
 Sotalol  
 Sparfloxacin  
 Spiramycin  
 Sulfamethoxazole  
 Sultopride  
 Tacrolimus  
 Tedisamil  
 Telithromycin  
 Terfenadine  
 Thioridazine  
 Trifluoperazine  
 Trimethoprim  
 Trimipramine  
 Vasopressin  
 Venlafaxine  
 Zolmitriptan  
 Zotepine

### 3.5.1.A Acecainide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

**3.5.1.B Ajmaline**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.C Amiodarone**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

**3.5.1.D Amisulpride**

- 1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Coadministration of ziprasidone with other drugs that potentially prolong the QTc interval, such as amisulpride, is contraindicated (Prod Info Solian(R), 1999a; Prod Info Geodon(R), 2002w).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as amisulpride, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon (R), 2002v).

**3.5.1.E Amitriptyline**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.F Amoxapine**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.G Aprindine**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambocor(R) flecainide acetate, 1998).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.H Arsenic Trioxide**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs, such as arsenic trioxide, which are also known to prolong the QTc interval (Prod Info Geodon(R), 2002i; Prod Info Trisenox(R), 2000).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as arsenic trioxide, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002h).
  - b) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001).

**3.5.1.I Astemizole**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including astemizole (Prod Info Geodon (TM), 2002z).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and astemizole is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.J Azimilide**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

**3.5.1.K Bepridil**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002d; Agelink et al, 2001; Owens, 2001a; Prod Info Orap(R), 1999c; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999c).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999b).

b) Sometimes fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999a; Ravin & Levenson, 1997a).

### 3.5.1.L Bretylium

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

### 3.5.1.M Chloral Hydrate

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloral hydrate (Prod Info Geodon(TM), 2002k; Young et al, 1986).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and chloral hydrate is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.N Chloroquine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloroquine (Prod Info Geodon(TM), 2002l). Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Aralen(R), 1999).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and chloroquine is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.O Chlorpromazine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002z).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
- 7) Probable Mechanism: additive QT prolongation

### 3.5.1.P Cisapride

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002a; Owens, 2001; Prod Info Orap(R), 1999a). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).
  - b) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone (Duenas-Laita et al, 1999; Ravin & Levenson, 1997).

### 3.5.1.Q Clarithromycin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including clarithromycin (Prod Info Geodon(TM), 2002s; Prod Info Biaxin(R), 2002).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and clarithromycin is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.R Desipramine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.S Dibenzepin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.T Disopyramide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.U Dofetilide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

### 3.5.1.V Dolasetron

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(R), 2002f).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as dolasetron, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14

msec less than that observed with thioridazine (Prod Info Geodon(R), 2002e).

### 3.5.1.W Doxepin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.X Droperidol

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Droperidol has been shown to prolong the QTc interval at the recommended therapeutic dose. Even though no formal drug interaction studies have been done, the coadministration of droperidol and other drugs known to prolong the QTc interval, including ziprasidone, is contraindicated (Prod Info Inapsine(R), 2001; Prod Info Geodon(TM), 2002c).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as droperidol and ziprasidone, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(TM), 2002b).

### 3.5.1.Y Enflurane

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including enflurane (Prod Info Geodon(R), 2002o; Owens, 2001d).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as enflurane, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002n).

### 3.5.1.Z Erythromycin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002t). Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

### 3.5.1.AA Flecainide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambocor(R) flecainide acetate, 1998).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.AB Fluconazole

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002). Case reports have described QT prolongation and torsades de pointes associated with fluconazole (Khazan & Mathis, 2002; Wassmann et al, 1999).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluconazole, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002).

#### 3.5.1.AC Fluoxetine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including fluoxetine (Prod Info Geodon(TM), 2002v; Prod Info Prozac(R), 2001).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluoxetine, is not recommended.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002r).

#### 3.5.1.AD Foscarnet

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002u; Prod Info Foscavir(R), 2000).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as foscarnet, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.AE Gatifloxacin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including gatifloxacin (Prod Info Geodon(TM), 2002i).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and gatifloxacin is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.AF Gemifloxacin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Although pharmacokinetic studies between ziprasidone and gemifloxacin, which may prolong the QT interval, have not been performed, gemifloxacin should not be used in patients receiving ziprasidone (Prod Info Factive(R), 2003; Prod Info Geodon(R), 2002a).

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of ziprasidone with a drug that may prolong the QT interval, such as gemifloxacin, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.AG Halofantrine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Halofantrine can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Because ziprasidone may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of halofantrine with ziprasidone is contraindicated (Prod Info Halfan(R), 1998; Prod Info Geodon(TM), 2002n).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as halofantrine, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.AH Haloperidol

- 1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). Coadministration of ziprasidone with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Geodon(R), 2002d).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as haloperidol, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993; Wilt et al, 1993). Torsades de pointes developed in 8 of 223 critically ill patients in intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998).
  - b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).
  - c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002c).

### 3.5.1.AI Halothane

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Prod Info Geodon(R), 2002af; Owens, 2001g).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as halothane, is contraindicated.
- 7) Probable Mechanism: additive effect on QT interval
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002ae).

### 3.5.1.AJ Hydroquinidine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.AK Ibutilide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

### 3.5.1.AL Imipramine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.AM Isoflurane

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including isoflurane (Prod Info Geodon(R), 2002y; Owens, 2001e).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as isoflurane, is contraindicated.
- 7) Probable Mechanism: additive effect on QT interval
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002x).

### 3.5.1.AN Isradipine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including isradipine (Prod Info Geodon(TM), 2002q; Prod Info DynaCirc(R), 2000).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as isradipine, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(TM), 2002p).

### 3.5.1.AO Levofloxacin

- 1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Although no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including levofloxacin (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004; Prod Info Levaquin, 2004).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and levofloxacin is not recommended.
- 7) Probable Mechanism: additive QT prolongation effects

### 3.5.1.AP Levomethadyl

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as ziprasidone that prolong the QT interval (Prod Info Orlaam(R), 2001).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Levomethadyl is contraindicated in patients being treated with ziprasidone as it may precipitate QT prolongation and interact with levomethadyl.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002m).

### 3.5.1.AQ Lidoflazine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Lidoflazine has been shown to prolong the QTc interval at the recommended therapeutic dose (Hanley & Hampton, 1983). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including lidoflazine, is contraindicated (Prod Info Geodon(TM), 2002f).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as lidoflazine, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.AR Lorcaïnide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambacor(R) flecainide acetate, 1998).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.AS Mefloquine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including mefloquine (Prod Info Geodon(TM), 2002o; Davis et al, 1996).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and mefloquine is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.AT Mesoridazine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002z).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
- 7) Probable Mechanism: additive QT prolongation

**3.5.1.AU Moxifloxacin**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including moxifloxacin (Prod Info Geodon(TM), 2002g).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and moxifloxacin is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.AV Nortriptyline**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.AW Octreotide**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Octreotide has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Sandostatin(R), 1999). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including octreotide, is contraindicated (Prod Info Geodon(TM) ziprasidone, 2002c).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as octreotide, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.AX Pentamidine**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and pentamidine is contraindicated (Prod Info Geodon(TM) ziprasidone, 2002). Pentamidine has been shown to prolong the QTc interval at the recommended therapeutic dose (Lindsay et al, 1990).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as pentamidine, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation

**3.5.1.AY Pimozide**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including pimozide (Prod Info Geodon(TM), 2002w).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and pimozide is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.AZ Pirmenol**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.BA Prajmaline**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
- 3) Severity: contraindicated
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.BB Probuco

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including probuconol (Prod Info Geodon(TM), 2002y). Probuconol has been shown to prolong the QTc interval (Gohn & Simmons, 1992; Prod Info Lorelco(R), 1991).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as probuconol, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.BC Procainamide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.BD Prochlorperazine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002z).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
- 7) Probable Mechanism: additive QT prolongation

#### 3.5.1.BE Propafenone

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambacor(R) flecainide acetate, 1998).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.BF Protriptyline

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.BG Quinidine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

#### 3.5.1.BH Ranolazine

- 1) Interaction Effect: an increase in ziprasidone serum concentration and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

- 2) Summary: Ranolazine, and/or its metabolites, partially inhibit cytochrome P450-2D6-mediated ziprasidone metabolism resulting in increased ziprasidone exposure. Concurrent administration of ranolazine and antipsychotics that could prolong the QTc interval, such as ziprasidone, is contraindicated (Prod Info RANEXA(TM) extended-release tablets, 2006).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Using ranolazine and ziprasidone together is contraindicated due to the additive effects on QTc prolongation.
- 7) Probable Mechanism: ranolazine inhibition of cytochrome P450-2D6-mediated metabolism of ziprasidone and additive effects on QTc prolongation

### 3.5.1.BI Risperidone

- 1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Coadministration of ziprasidone with other drugs that potentially prolong the QTc interval, such as risperidone, is contraindicated (Prod Info Geodon(R), 2002q; Prod Info Risperdal(R), 2002).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as risperidone is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Fatal QRS prolongation and QTc prolongation have been reported in patients taking risperidone therapeutically (Duenas-Laita et al, 1999c; Ravin & Levenson, 1997b; Gesell & Stephen, 1997; Lo Vecchio et al, 1996; Brown et al, 1993).
  - b) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon (R), 2002p).

### 3.5.1.BJ Sematilide

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

### 3.5.1.BK Sertindole

- 1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Brown & Levin, 1998a; Prod Info Geodon(R), 2002ad).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as sertindole is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) The overall incidence of QT interval prolongation with sertindole is estimated at 1.9% to 4%, and the potential risk of developing torsades de pointes has been estimated at 0.13% to 0.21% (Brown & Levin, 1998). Periodic electrocardiographic monitoring is required in the United Kingdom per sertindole's official labeling (Cardoni & Myer, 1997).
  - b) Thirty, otherwise healthy, schizophrenic patients participated in an open, dose titration (4 to 16 mg/day) study to determine the cardiovascular effects of sertindole. At the end of the 3-week study it was concluded that resting heart rate and frequency corrected QT times increased in a dose-related manner, while there was no change in PQ-conduction times, autonomic parasympathetic tone, or blood pressure. Conduction times increased an average 3.5% to 6.5% over the dosing range (Agelink et al, 2001a).
  - c) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon (R), 2002ac).

### 3.5.1.BL Sotalol

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc

interval , including ziprasidone (Yamreudeewong et al, 2003a).

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

### 3.5.1.BM Sparfloxacin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including sparfloxacin (Prod Info Geodon(TM), 2002x).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and sparfloxacin is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.BN Spiramycin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Spiramycin has been shown to prolong the QTc interval at the recommended therapeutic dose (Stramba-Badiale et al, 1997). Even though no formal drug interaction studies have been done, the coadministration of ziprasidone and other drugs known to prolong the QTc interval, including spiramycin, is not recommended (Prod Info Geodon(TM) ziprasidone, 2002b).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as spiramycin, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation

### 3.5.1.BO Sulfamethoxazole

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including cotrimoxazole (Prod Info Geodon (TM) ziprasidone, 2002a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and cotrimoxazole is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.BP Sultopride

- 1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Lande et al, 1992a; Montaz et al, 1992a; Harry, 1997a; Prod Info Geodon(R), 2002l).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that prolong the QT interval, such as sultopride, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Sultopride may induce prolongation of the QT interval and ventricular arrhythmias including torsades de pointes following therapeutic or toxic doses (Lande et al, 1992; Montaz et al, 1992; Harry, 1997).
  - b) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon (R), 2002k).

### 3.5.1.BQ Tacrolimus

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including tacrolimus (Prod Info Geodon(TM), 2002r).
- 3) Severity: contraindicated
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tacrolimus is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

**3.5.1.BR Tedisamil**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval, including ziprasidone (Yamreudeewong et al, 2003a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.
- 7) Probable Mechanism: additive QT prolongation
- 8) Literature Reports
  - a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

**3.5.1.BS Telithromycin**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including telithromycin (Prod Info Geodon(TM), 2002h; Owens, 2001b).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as telithromycin, is contraindicated.
- 7) Probable Mechanism: additive effect on QT interval
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002g).

**3.5.1.BT Terfenadine**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002aa; Owens, 2001f; Prod Info Orap(R), 1999e). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
- 7) Probable Mechanism: additive effect on QT interval
- 8) Literature Reports
  - a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

**3.5.1.BU Thioridazine**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001c), risperidone (Duenas-Laita et al, 1999b), and sultopride (Lande et al, 1992b).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and thioridazine, is contraindicated.
- 7) Probable Mechanism: additive QT prolongation

**3.5.1.BV Trifluoperazine**

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002; Prod Info Geodon(R), 2002z).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: The concurrent administration of ziprasidone and other drugs that may prolong the QT interval, such as phenothiazines, is contraindicated.
- 7) Probable Mechanism: additive QT prolongation

### 3.5.1.BW Trimethoprim

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Cotrimoxazole has been shown to prolong the QTc interval at the recommended therapeutic dose (Lopez et al, 1987). Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including cotrimoxazole (Prod Info Geodon (TM) ziprasidone, 2002a).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and cotrimoxazole is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.BX Trimipramine

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including tricyclic antidepressants (Prod Info Geodon(R), 2002u; Marshall & Forker, 1982).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone and tricyclic antidepressants is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

### 3.5.1.BY Vasopressin

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including vasopressin (Prod Info Geodon(TM), 2002e; Jacoby & Wiegman, 1990).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as vasopressin, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) Ziprasidone prolongs the QTc and an increased risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002b).

### 3.5.1.BZ Venlafaxine

- 1) Interaction Effect: QT prolongation and increased risk of cardiotoxicity (torsades de pointes, cardiac arrest)
- 2) Summary: Additive QTc-prolonging effects cannot be excluded when ziprasidone and venlafaxine are administered concomitantly. QTc interval prolongation has occurred during stand-alone treatment with venlafaxine; however, it is not listed among agents specifically contraindicated during ziprasidone therapy. Although formal drug interaction studies are lacking, other drugs that prolong QTc should generally be avoided during ziprasidone administration (Prod Info Geodon(TM), 2003; Prod Info Effexor(R) XR, 2003).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use of ziprasidone with other QT-prolonging drugs should generally be avoided where possible; concomitant use of venlafaxine is not specifically contraindicated, however. Defer to clinical judgement for individual patient benefits and risks with concomitant drug treatment.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) Given alone, ziprasidone may prolong QTc interval. QTc prolongation due to other drugs has been associated with clinical events such as torsades de pointes or sudden death. It is not known if the QTc prolonging effects of ziprasidone monotherapy are associated with such events, nor if the risk of such events would be changed when ziprasidone is combined with other QTc-prolonging drugs. QTc prolongation generally increases the risk of potentially fatal ventricular dysrhythmias in a dose-related manner (Anon, 2000). In clinical trials, ziprasidone increased the QTc interval (compared to placebo) by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2003). Based on the metabolic pathways of both venlafaxine and ziprasidone, concomitant use is unlikely to cause clinically significant pharmacokinetic interactions; venlafaxine is metabolized primarily via CYP2D6 and ziprasidone is metabolized largely via aldehyde oxidase and to a lesser extent CYP3A4 (Anon, 2004). These metabolic routes do not overlap.
  - b) QT interval prolongation occurred in patients treated with venlafaxine (extended-release form). In several randomized, double-blind trials, patients treated with extended-release venlafaxine (aggregate n=357) showed a mean increase of 4.7

milliseconds (msec) in corrected QT interval (QTc) after 8-12 weeks of therapy. Patients receiving placebo (aggregate n=285) showed a mean decrease of 1.9 msec in the QTc interval. Concurrently, heart rate in patients receiving venlafaxine showed a mean increase from baseline of 4 beats per minute, compared with an increase of 1 beat per minute for patients receiving placebo (Prod Info Effexor(R) XR, 2003).

### 3.5.1.CA Zolmitriptan

- 1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including zolmitriptan (Prod Info Geodon(R), 2002ab; Prod Info Zomig(R), 2001).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as zolmitriptan, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects
- 8) Literature Reports
  - a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002aa).

### 3.5.1.CB Zotepine

- 1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
- 2) Summary: Coadministration of ziprasidone with other drugs that potentially prolong the QTc interval, such as zotepine, is contraindicated (Prod Info Geodon(R), 2002t; Sweetman, 2003).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of ziprasidone with other agents that prolong the QT interval, such as zotepine, is contraindicated.
- 7) Probable Mechanism: additive effects on QT prolongation
- 8) Literature Reports
  - a) Ziprasidone prolongs the QTc in some patients in a dose-related manner. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams) (Prod Info Geodon (R), 2002s).
  - b) Since zotepine can prolong the QT interval it is recommended that an ECG is performed before starting treatment. Patients with pre-existing prolongation of the QT interval should not be given zotepine (Sweetman, 2003).

## 4.0 Clinical Applications

Monitoring Parameters  
 Patient Instructions  
 Place In Therapy  
 Mechanism of Action / Pharmacology  
 Therapeutic Uses  
 Comparative Efficacy / Evaluation With Other Therapies

### 4.1 Monitoring Parameters

- A) Ziprasidone Hydrochloride
  - 1) Therapeutic
    - a) Physical Findings
      - 1) Improvement of psychotic symptomatology (positive, negative symptoms)
  - 2) Toxic
    - a) Laboratory Parameters
      - 1) Complete blood counts, liver function tests, ECG, serum prolactin, routine chemistry during prolonged therapy
    - b) Physical Findings
      - 1) Signs/symptoms of adverse effects (eg, akathisia, abnormal movements, persistent constipation)

### 4.2 Patient Instructions

- A) ZIPRASIDONE (By mouth)  
 Ziprasidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an allergic reaction to ziprasidone, if you have uncontrolled heart failure, recently had a heart attack, or if you are using certain heart medicines. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome).

How to Use This Medicine:  
 Capsule

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

It is best to take this medicine with food or milk at the same time every day. Swallow the capsule whole. Do not break, crush, or chew it.

Keep using this medicine for the full treatment time, even if you feel better after the first few doses.

#### If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

#### How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep all medicine away from children and never share your medicine with anyone.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.

#### Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are also using medicine for a heart rhythm problem such as amiodarone, dofetilide, procainamide, quinidine, or sotalol. Make sure your doctor knows if you are also using blood pressure medicine or diuretics ("water pills") such as furosemide, hydrochlorothiazide, Aldactazide®, Aldactone®, Lasix®, or Maxzide®.

Tell your doctor if you are also using levodopa, carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®). Tell your doctor if you are also taking other medicines for a mood disorder such as thioridazine or chlorpromazine (Thorazine®).

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

There are many other medicines that you should not use while you are taking ziprasidone. Taking ziprasidone with certain other medicines may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other medicines you are using.

Do not drink alcohol while you are using this medicine.

#### Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breast feeding, or if you have heart problems, Alzheimer's disease, seizures, or trouble swallowing. Tell your doctor if you have a history of stroke, breast cancer, or low potassium or magnesium levels in your blood. Make sure your doctor knows if you have thoughts of hurting yourself. Tell your doctor if you or anyone in your family has a history of diabetes.

Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are using medicine for diabetes, your doctor may need to change your dose.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.

Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills.

Make sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia").

#### Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Fast, slow, irregular (uneven), or pounding heartbeat.

Fever, sweating, confusion, muscle stiffness.

In males: Painful, prolonged erection of your penis.

Increase in thirst, hunger, or urination.

Lightheadedness, fainting, or seizures.

Severe diarrhea, vomiting, or stomach pain.

Skin rash.

Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:

Problems with balance or walking.

Severe tiredness.

Sneezing, cough, stuffy nose.

Weight gain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

#### **B) ZIPRASIDONE (Injection)**

## Ziprasidone

Treats schizophrenia and certain problems caused by bipolar disorder. Treats an episode of agitation (excessive movement, tension, or anxiety) in a person who has schizophrenia. This medicine is given to people who cannot take ziprasidone by mouth.

### When This Medicine Should Not Be Used:

You should not use this medicine if you have had an allergic reaction to ziprasidone. You should not use this medicine if you have recently had a heart attack, are using certain heart medicines, or if you have uncontrolled heart failure. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome).

### How to Use This Medicine:

#### Injectable

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.

A nurse or other trained health professional will give you this medicine.

### Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Before taking this medicine, tell your doctor if you are also using medicine for a heart rhythm problem such as dofetilide, sotalol, quinidine, procainamide, or amiodarone. Make sure your doctor knows if you are also using medicine to lower blood pressure. Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, and Zestril®.

Tell your doctor if you are also using levodopa, carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®). Make sure your doctor knows if you are using diuretics ("water pills") such as furosemide, Aldactazide®, Aldactone®, Dyazide®, Lasix®, Moduretic®, or Maxzide®.

Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

There are many other medicines that you should not use while you are taking ziprasidone. Taking ziprasidone with certain other medicines may be dangerous, even life-threatening. Make sure your doctor and your pharmacist knows about all other medicines you are using.

Do not drink alcohol while you are using this medicine.

### Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breast feeding, or if you have heart problems, Alzheimer's disease, seizures, or trouble swallowing. Tell your doctor if you have a history of stroke, breast cancer, or low potassium or magnesium levels in your blood. Tell your doctor if you or anyone in your family has a history of diabetes.

Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.

This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are taking medicine for diabetes, your doctor may need to change your dose.

This medicine may cause you to become overheated more easily than usual. Be careful when exercising, or when you are outdoors in hot or humid weather.

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.

### Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Fast, slow, uneven, or pounding heartbeat.

Fever, sweating, confusion, muscle stiffness.

In males: painful, prolonged erection of your penis.

Increase in thirst, hunger, or urination.

Lightheadedness, fainting, or seizures.

Severe diarrhea, vomiting, or stomach pain.

Skin rash.

Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:

Headache.

Pain where the shot was given.

Problems with balance or walking.

Severe tiredness.

Sneezing, cough, stuffy nose.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

## 4.3 Place In Therapy

**A) General (atypical agents):** patients resistant to standard antipsychotic agents; patients with therapy-limiting extrapyramidal symptoms, other adverse effects.

**B)** Specific: comparisons of ziprasidone with clozapine, risperidone, olanzapine, and sertindole in refractory patients are needed to determine potential advantages. Disadvantages of ziprasidone: prolongation of QT/QTc interval, shorter half-life, twice-daily dosing usually required (olanzapine, sertindole may be given once daily).

#### 4.4 Mechanism of Action / Pharmacology

##### A) MECHANISM OF ACTION

- 1) Atypical antipsychotic (benzisothiazoyl piperazine derivative); serotonin (5HT)-2A/dopamine D2 antagonist. Also a 5HT-1A agonist (property may confer greater protection against adverse extrapyramidal effects) (Kerwin & Taylor, 1996; Bench et al, 1993; Fischman et al, 1996; Owens, 1996; Lieberman, 1993; Pickar, 1995; Anon, 1996a; Schotte et al, 1996).
- 2) Modest-to-low affinity for alpha-1, H1 receptors (Kerwin & Taylor, 1996). Inhibits norepinephrine reuptake (Pickar, 1995; Seeger et al, 1995).
- 3) In vitro: ratio of 5HT-2A/dopamine D2 receptor affinity greater than clozapine (2-fold), haloperidol (680-fold) (Seeger et al, 1995).

##### B) REVIEW ARTICLES

- 1) Focus on Ziprasidone (Green B, 2001).
- 2) Treatment of schizophrenia (includes use of atypical agents) (Marder, 1996; Fleischhacker, 1995; Meltzer et al, 1994; Lieberman, 1996; Weiden et al, 1996; Jeste et al, 1996).
- 3) Psychosis in mania (use of atypical agents) (McElroy et al, 1996).
- 4) Mechanism of action with respect to neurotransmitter pathways in the brain utilized by atypical antipsychotics, including ZIPRASIDONE (Kendrick, 1999).
- 5) A brief introductory review of ziprasidone is available (Tandon, 2000).

#### 4.5 Therapeutic Uses

Ziprasidone Hydrochloride  
Ziprasidone Mesylate

##### 4.5.A Ziprasidone Hydrochloride

Bipolar I disorder, acute manic or mixed episodes  
Major depressive disorder, Treatment-resistant; Adjunct  
Schizoaffective disorder  
Schizophrenia

##### 4.5.A.1 Bipolar I disorder, acute manic or mixed episodes

FDA Labeled Indication

###### a) Overview

FDA Approval: Adult, yes; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class IIa  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

###### b) Summary:

Indicated for the treatment of acute manic or mixed episodes in patients with bipolar disorder, with or without psychotic features (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005)  
Effective for treating acute mania in patients with bipolar I disorder

###### c) Adult:

1) Ziprasidone was more effective than placebo for treating acute bipolar mania. In a randomized, double-blind, multicenter, placebo-controlled trial, 210 bipolar inpatients, currently in a manic or mixed episode, underwent single-blind placebo treatment for a one-week washout and were then randomized 2:1 to receive ziprasidone (n=140) or placebo (n=70) for 3 weeks. Ziprasidone, given with meals, was started at 40 milligrams (mg) twice daily on day 1, raised to 80 mg twice daily on day 2, and then adjusted if necessary during the trial to a final range of 80 to 160 mg/day. Data from 131 ziprasidone-treated patients and 66 placebo-treated patients were used for determining efficacy. On the 11-item Mania Rating Scale, a significantly greater improvement with ziprasidone compared to placebo was evident by day 2 (p less than 0.003) and remained apparent throughout the study (p less than 0.001 at the end of weeks 1, 2, and 3). By the end of the study, significant differences between the groups, favoring ziprasidone over placebo, were evident on the Clinical Global Impressions (CGI) severity scale, the CGI improvement scale, the Positive and Negative Syndrome Scale, and the Global Assessment of Functioning Scale. Fifty percent of patients receiving ziprasidone and 35% receiving placebo were classified as responders (p less than 0.05). In the ziprasidone group, 6.4% of patients (9 of 140) withdrew because of adverse events, compared to 4.3% (3 of 70) of the placebo group. None of the treatment-related adverse events in either group was serious. The most commonly occurring adverse events were somnolence (ziprasidone vs placebo: 37% vs 13%), headache (21% vs 19%), dizziness (22% vs 10%), and akathisia (11% vs 6%). Movement disorders were uncommon. No change in weight was associated with ziprasidone treatment. Ziprasidone treatment showed a mean prolongation in QT(c) interval of 11 milliseconds (msec). No patient had a QT(c) interval of 500 msec or higher (Keck et al, 2003).

##### 4.5.A.2 Major depressive disorder, Treatment-resistant; Adjunct

###### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence is inconclusive  
Recommendation: Adult, Class IIb  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

###### b) Summary:

Ziprasidone augmentation may be effective in the treatment of major depression resistant to SSRI therapy

###### c) Adult:

1) Ziprasidone augmentation of selective serotonin reuptake inhibitor (SSRI) therapy may be an effective option for patients with treatment-resistant major depression. In a prospective, open-label trial (n=20), patients with MAJOR DEPRESSIVE DISORDER resistant to SSRI therapy and a Hamilton Rating Scale for Depression (HAM-D) score of at least 14 received ziprasidone (initial, 20 milligrams (mg) twice daily, titrated in 20 mg/week increments to a maximum of 80 mg twice daily; mean dose, 82.1 mg/day) in addition to continued SSRI therapy with citalopram, fluoxetine, paroxetine, or sertraline for 6 weeks. At endpoint, 10 (50%) patients achieved response (defined as at least a 50% reduction in the HAM-D score from baseline to endpoint) and 5 (25%) patients achieved remission (defined as a HAM-D score of 7 or less at endpoint). Overall, the mean HAM-D score was reduced from 21.8 to approximately 12 from baseline to week 6, respectively. The most common adverse events included fatigue (50%), sleep disturbance (30%), restlessness (15%), tremor (15%), bruxism (15%), headache (10%), dry mouth (20%), gastrointestinal distress (20%), and urinary frequency (10%). No patient had a QTc interval greater than 500 milliseconds; however, a QTc interval increase of 30 milliseconds was observed in two patients. Placebo-controlled trials are needed to clarify the efficacy of ziprasidone augmentation therapy in SSRI-resistant depression (Papakostas et al, 2004).

#### 4.5.A.3 Schizoaffective disorder

##### a) Overview

FDA Approval: Adult, no; Pediatric, no  
Efficacy: Adult, Evidence favors efficacy  
Recommendation: Adult, Class IIa  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Oral ziprasidone has been shown to be effective in the short term treatment of patients with an acute episode of schizoaffective disorder.

##### c) Adult:

1) Significant dose-related improvements on all primary efficacy variables (BPRS total, BPRS Core, CGI-S and BPRS Manic scores) were observed in patients receiving ziprasidone compared to placebo in 2 multicenter double-blind placebo-controlled clinical trials (n=115). Inclusion criteria consisted of hospitalized patients with an acute exacerbation of schizoaffective disorder, bipolar or depressive subtype. Patients were required to have a minimum duration of illness of at least 6 months or 1 year. In one study patients were randomized to receive ziprasidone 20 milligrams (mg) twice daily or placebo for 4 weeks. In the second study, patients were randomized to receive ziprasidone 40 mg twice daily, 80 mg twice daily or placebo for 6 weeks. The incidence of individual adverse events was generally low in all treatment groups (Keck et al, 2001).

#### 4.5.A.4 Schizophrenia

FDA Labeled Indication

##### a) Overview

FDA Approval: Adult, yes; Pediatric, no  
Efficacy: Adult, Effective  
Recommendation: Adult, Class I  
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

##### b) Summary:

Positive/negative symptom improvement  
Relatively low incidence of extrapyramidal symptoms  
Causes more QT/QTc prolongation than other atypical antipsychotic drugs  
Decreased the rate of relapse in patients with chronic, stable schizophrenia

##### c) Adult:

1) Results of the Ziprasidone Extended Use in Schizophrenia (ZEUS) study indicate that ziprasidone treatment decreased the rate of relapse in patients with chronic, stable schizophrenia. In this randomized, double-blind, placebo-controlled study, markedly ill (score of 5 or lower on the Clinical Global Impression Severity scale) patients with chronic, stable schizophrenia in extended-stay, inpatient settings received twice daily doses of ziprasidone 40 milligrams (mg)/day (n=72), ziprasidone 80 mg/day (n=68), ziprasidone 160 mg/day (n=67) or placebo (n=71) for up to 1 year. Patients were allowed to receive anticholinergics, lorazepam, and temazepam, but no other psychotropic medications were permitted during the study. The likelihood of relapse at 1 year was significantly lower in patients treated with ziprasidone 40 mg/day (43%), 80 mg/day (35%) or 160 mg/day (36%) as compared with placebo (77%) (p=0.002, p less than 0.001, p less than 0.001, respectively). Of the ziprasidone-treated patients who relapsed during the study, most (61/71) did so in the first 6 months. However, of patients who stayed in the study for at least 6 months only 9% (10/110) of patients in the ziprasidone groups eventually relapsed, as compared with 42% (8/19) of placebo-treated patients (p=0.001). Patients in all three ziprasidone treatment groups showed significantly better improvements in negative symptoms as compared with placebo beginning at week 16 and continuing until the end of the study. Ziprasidone was generally well tolerated, however, one patient had a grand mal seizure and another experienced extrapyramidal symptoms during treatment (Arato et al, 2002); (2002).

2) Placebo-controlled, double-blind studies (acute exacerbation of schizophrenia or schizophreniform disorder): 80 to 160 milligrams (mg) daily effective in significantly improving positive/negative symptoms. Relatively low incidence of extrapyramidal symptoms (Reeves & Harrigan, 1996a; Harrigan et al, 1996b; Citrome, 1997a; Kerwin & Taylor, 1996b; Anon, 1996b).

3) With 80/160 milligrams (mg) daily (6 weeks): reduction in Positive and Negative Syndrome Scale (PANSS) total scores by 12.4/17.1 (-5.4 with placebo), negative subscale scores by 3.2/3.9 (-0.9 with placebo); significant improvement in BPRSd total score (18-item Brief Psychiatric Rating Scale derived from PANSS) (Reeves & Harrigan, 1996a).

4) Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the 2 dose groups in a 52-week, placebo-controlled trial (n = 294). Inpatients were randomized to receive ziprasidone 20 milligrams (mg) twice daily, 40 mg twice daily, 80 mg twice daily or placebo (Prod Info Geodon(R), 2002ah).

## 4.5.B Ziprasidone Mesylate

### 4.5.B.1 Agitation, acute - Schizophrenia

FDA Labeled Indication

#### a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class I

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

#### b) Summary:

Intramuscular ziprasidone is effective for the treatment of acute agitation in schizophrenic patients

#### c) Adult:

1) The efficacy of intramuscular ziprasidone for the treatment of acute agitation in schizophrenia was established in two double-blind, randomized, single-day trials. Acutely agitated schizophrenic patients with a score of 3 or higher on at least three Positive and Negative Syndrome Scale (PANSS) items (anxiety, tension, hostility, and excitement) received either a control dose (2 milligrams) or a higher dose of ziprasidone. In the first study, patients (n=79) received 20 mg or 2 mg of intramuscular ziprasidone up to four times in 24 hours at intervals of at least 4 hours. The higher dose of ziprasidone was statistically superior to the control dose as assessed by the area under the curve (AUC) of the Behavioral Activity Rating Scale (BARS) at 0 to 4 hours and by the Clinical Global Impression (CGI) severity rating at 4 hours and at endpoint. In the second study, patients (n=117) received 10 mg or 2 mg of intramuscular ziprasidone up to four times in 24 hours at intervals of at least 2 hours. The 10 mg dose of ziprasidone was statistically superior to the 2 mg dose as assessed by the AUC of the BARS at 0 to 2 hours, but not by the CGI severity rating (Prod Info Geodon(R), 2002ah).

## 4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Perphenazine

Quetiapine

Risperidone

### 4.6.A Chlorpromazine

#### 4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo- controlled, fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of ziprasidone was 120 milligrams/day (equivalent to chlorpromazine 200 milligrams/day) (Woods SW, 2003).

### 4.6.B Haloperidol

Chronic schizophrenia

Schizophrenic episode, acute

#### 4.6.B.1 Chronic schizophrenia

a) Ziprasidone was as effective as haloperidol in treating overall symptomatology, was more effective in the treatment of negative symptoms, and was better tolerated, in the long-term treatment of outpatients with stable schizophrenia. In a 28-week, double-blind, flexible-dose, parallel-group clinical trial, ziprasidone and haloperidol both improved overall symptomatology in 227 patients with chronic or subchronic schizophrenia. Patients who received ziprasidone had a significantly higher rate of improvement in the treatment of negative symptoms (48% of patients showed improvement) compared to patients who received haloperidol (33% of patients showed improvement). For patient assessment, the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), and the Montgomery-Asberg Depression Rating Scale (MADRS) were used at baseline and weeks 3, 6, 16, and 28. In the ziprasidone group, patients received a starting dose of 40 milligrams per day (mg/d) on the first 2 days and 80 mg/d on day 3. The ziprasidone dose could be increased to a maximum of 120 mg/d in the second week and up to 160 mg/d in the third week. For the haloperidol group, patients received a starting dose of 5 mg/d, which could be increased to a maximum of 10 mg/d during the second week and 15 mg/d during the third week of treatment. At week 28, the mean doses of ziprasidone and haloperidol were 116.5 mg/d and 8.6 mg/d, respectively. Adverse events were evaluated using the Simpson-Angus scale, the Barnes Akathisia scale, and the Abnormal Involuntary Movement Scale (AIMS). Adverse events were reported in 85% of patients in the haloperidol group and 77% in the ziprasidone group; twice as many patients receiving haloperidol (16%) compared to ziprasidone (8%) discontinued the study due to treatment-related adverse events. There was also a distinct difference in the percentage of patients who developed movement disorders; 41% in the haloperidol group compared to 15% in the ziprasidone group, although this difference was not statistically significant (Hirsch et al, 2002).

#### 4.6.B.2 Schizophrenic episode, acute

a) Acute exacerbations: ziprasidone 160 mg daily, haloperidol 15 mg daily comparable in efficacy (reduction of BPRS scores). Ziprasidone 4 to 40 mg/day less effective (Anon, 1996).

b) Ziprasidone 160 milligrams (mg) and haloperidol 15 mg were both effective in improving overall psychopathology in patients with an acute exacerbation of schizophrenia or schizoaffective disorder (Goff et al, 1998). In a double-blind, dose-ranging study, patients received either haloperidol 15 mg/day (n=17), or ziprasidone 4 mg (n=19), ziprasidone 10 mg (n=17), ziprasidone 40 mg (n=17), or ziprasidone 160 mg (n=20). Despite 46 patients failing to complete the study, intention-to-treat analysis showed a trend toward significance for the ziprasidone dose response on the Brief Psychiatric Rating scale (p=0.08) and a statistically significant dose response for the Clinical Global Impression (CGI) scale (p less than 0.001). Changes in the CGI severity score were significantly changed from baseline as compared to the ziprasidone 4 mg group for both the

haloperidol group ( $p$  less than 0.01) and the ziprasidone 160 mg group ( $p=0.001$ ). Study termination was due to 18 patients having a lack of efficacy (4 in the haloperidol group), 7 due to liver transaminase elevations in ziprasidone groups, and 23 for unrelated reasons.

**c)** In hospitalized patients, the mean reductions in BPRS total, BPRS agitation items, and CGI were statistically greater after INTRAMUSCULAR (IM) ziprasidone than IM haloperidol, and this continued following conversion to oral treatment. The study was a multicenter, 7-day, randomized, open-label, parallel-group study in 7 countries ( $n=132$ ). Patients received either an initial dose of ziprasidone 10 milligrams (mg) IM, followed by up to 3 days of flexible-dose IM ziprasidone (5 mg to 20 mg every 4 to 6 hours prn) and continued with oral treatment (80 mg to 200 mg/day) to day 7 ( $n = 90$ ), or haloperidol IM (2.5 mg to 10 mg) on entry, followed by 2.5 mg to 10 mg IM every 4 to 6 hours prn up to 3 days followed by oral haloperidol 10 mg/day to 80 mg/day to day 7 ( $n = 32$ ). Ziprasidone was associated with a lower incidence of movement disorders compared to haloperidol (Brook et al, 2000).

#### 4.6.C Olanzapine

Chronic schizophrenia

Schizophrenia

##### 4.6.C.1 Chronic schizophrenia

**a)** When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients ( $n=1493$ ) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76;  $p$  less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90;  $p=0.002$ ). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine ( $p=0.04$ ). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

##### 4.6.C.2 Schizophrenia

**a)** In a randomized, double-blind trial ( $n=269$ ), six-week courses of OLANZAPINE and ZIPRASIDONE had comparable efficacy for treatment of schizophrenia or schizoaffective disorder (DSM-IV), while the side effects profile of ziprasidone appeared to be more favorable with respect to metabolic indicators but less favorable related to QT interval prolongation. Enrollees were acutely ill, recently admitted inpatients. During the first week, subjects received fixed doses of study drugs: olanzapine 5 milligrams (mg) on days 1 and 2 and 10 mg/day on days 3 to 7 ( $n=133$ ); ziprasidone 40 mg twice daily on days 1 and 2 and 80 mg twice daily on days 3 to 7 ( $n=136$ ). Dosing was flexible over weeks 2-6 (olanzapine 5 to 15 mg/day; ziprasidone 40 to 80 mg twice daily); overall median daily doses were 12.4 mg for olanzapine and 138.6 mg for ziprasidone (the latter in 2 divided doses daily). Efficacy measures included the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) severity and improvement scales, Positive and Negative Syndrome Scale, and the Calgary Depression Scale for Schizophrenia. At study end, there were no significant differences on any rating scale between improvements in the olanzapine group and those in the ziprasidone group. At endpoint, 36.8% of the olanzapine group and 48.5% of the ziprasidone group had discontinued. Overall, 39.8% and 46.3% of the olanzapine and ziprasidone groups, respectively, had experienced adverse events that were considered treatment related. No between-group differences were seen related to dyskinesia, dystonia, or extrapyramidal symptoms. Weight gain amounted to approximately 3.5 kilograms (kg) and 1 kg for olanzapine- and ziprasidone-treated patients, respectively ( $p$  less than 0.0001). Total cholesterol, low-density lipoprotein cholesterol, and triglycerides increased by approximately 10%, 13%, and 25%, respectively, in the group receiving olanzapine; all the same measures decreased slightly in the ziprasidone group ( $p$  less than 0.0001;  $p=0.0004$ ;  $p$  less than 0.003, respectively). Fasting serum insulin increased by median 3.3 and 0.25 micro-units/milliliter in the olanzapine and ziprasidone groups, respectively ( $p=0.051$ ). Prolongation of the QTc interval amounted to 0.52 and 6.08 milliseconds for the same 2 groups, respectively ( $p$  less than 0.05) (Simpson et al, 2004).

**b)** A multicenter, randomized, double-blind, parallel-group, 28 week study ( $n=548$ ) found that olanzapine therapy resulted in significantly greater psychopathology improvement and higher response and completion rates compared to ziprasidone, while ziprasidone therapy was superior for weight change and lipid profile. Patients with schizophrenia were randomized to receive olanzapine ( $n=277$ ) 10 to 20 mg/day or ziprasidone ( $n=271$ ) 80 to 160 mg/day. The primary efficacy measure, the Positive and Negative Syndrome Scale total score, showed that the olanzapine group had significantly greater improvement than the ziprasidone group ( $p$  less than 0.001). The olanzapine group also showed significant improvement from baseline to endpoint compared to ziprasidone in the Positive and Negative Syndrome subscales: positive symptoms, negative symptoms, general psychopathology, cognition, and excitability (all  $p$  less than 0.0001 except for negative symptoms  $p=0.003$ ). Patients were allowed to take benzodiazepines or hypnotic monotherapy during the study, but were removed from the study if they required more than two concurrent benzodiazepine hypnotic medications. Significantly more patients in the ziprasidone group required at least one dose of a benzodiazepine compared to the olanzapine group (53.5% versus 40.4%;  $p=0.003$ ). Response was defined as a 30% improvement in the Positive and Negative Syndrome Scale total score at endpoint, and the rate was significantly higher for the olanzapine group compared to the ziprasidone group (58.6% versus 42.5%) ( $p$  less than 0.001). There was no significant difference in exacerbation of symptoms between the two groups, which was defined as a decrease in the Positive and Negative Syndrome Scale total score by 20% or more and a decrease in the Clinical Global Impression severity of illness score of 1 point or more after week 8 (14.6% olanzapine and 25.3% ziprasidone;  $p=0.06$ ). Significantly more patients in the olanzapine group (59.6%) than in the ziprasidone group (42.4%) completed the study ( $p$  less than 0.001). Reasons for discontinuation were only significant for lack of efficacy (olanzapine 7.2% versus ziprasidone 13.7%;  $p=0.02$ ) and aggravation of psychosis (olanzapine 1.4% versus ziprasidone 4.4%;  $p=0.05$ ). There were significantly greater increases in body weight and levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides (all  $p$  less than 0.001) and a significantly greater decrease in high-density lipoprotein cholesterol ( $p=0.001$ ) in the olanzapine group than in the ziprasidone group (Breier et al, 2005).

#### 4.6.D Perphenazine

##### 4.6.D.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

#### 4.6.E Quetiapine

##### 4.6.E.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

#### 4.6.F Risperidone

##### 4.6.F.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

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